Huidelines Sistema nazionale per le Guidelines deli uidel **National Guidelines for Ultrasound in Obstetrics** and Gynaecology



National Guidelines for Ultrasound in Obstetrics and Gynaecology

ORGANIZATIONS THAT PARTICIPATED IN THE CREATION OF THE GUIDELINES

SIGO AOGOI AGUI SIMP SOCIETÀ DI MEDICINA LEGALE SIDIP SIRU









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SECRETARIAL SUPPORT

Caterina Musatti - Congress Planning

The Guidelines are a collection recommendations produced after a systematic assessment of the literature and discussions by a panel of experts and should be used to help clinicians and patients make appropriate choices and carry out treatments under specific conditions. The Guidelines presented here are drawn up on the basis of a standardized methodology.

The recommendations in these Guidelines are not intended to direct clinical management and treatment as mandatory but should be evaluated with reference to each specific clinical condition, available resources and possible limitations, as well as specific population conditions.

METHODOLOGY

OBJECTIVES

The objective of these Guidelines is to provide guidance on the correct use of ultrasound in both obstetric and gynaecological settings: different clinical conditions, to diverse healthcare professionals (specifically to gynaecologists, obstetricians and midwives), general medical doctors, specialists in legal medicine, managers of public and private services, as well as to the general population and to women in particular.

METHODOLOGY USED TO DEVELOP THE GUIDELINES

The process of developing recommendations for the Guidelines on ultrasound during normal pregnancy has been carried out in accordance with the standards defined by the National System of Guidelines (SNLG), described in the Methodology Manual for the Production of Guidelines on Clinical Practice of the National Centre for Clinical Excellence (CNEC, 2019).

STRUCTURE OF THE DEVELOPMENT TEAM

SIEOG, as a scientific society, deals with ultrasound in obstetric and gynaecological fields and periodically publishes its own corporate Guidelines. It has obtained accreditation from the National Institute of Health (Istituto Superiore di Sanità) to propose the new Guidelines on ultrasound in obstetrics and gynaecology to the CNEC.

The organizer appointed a multidisciplinary development team with specialists in obstetrics and gynaecology, midwives, ultrasound experts, lay representatives, legal experts and other stakeholders. All the Scientific Organizations potentially interested in the subject were contacted and adhered to the proposal, appointing a representative who joined the development team (see structure of the development team).

All authors have stated that they have no conflicts of financial, professional or other interest related to the topics covered in the Guidelines. In the event that an author declared that he/she had an interest in the last 10 years that could potentially conflict with the purpose of the Guidelines and that could compromise his/her objectivity of judgement, the author was excluded from the development team.

FORMULATION OF CLINICAL QUESTIONS

Ten subject areas to be addressed in these Guidelines were identified. For each subject area, a work group of 4-5 members and a coordinator were appointed with the task of reviewing, selecting and critically evaluating the contents of the literature identified through systematic research.

The formulation of clinical questions to be answered with recommendations for each subject area was made according to the PICO model (population, intervention, comparison, outcome). The 61 PICO questions were formulated together by the multidisciplinary development team at the initial meeting.

In accordance with the GRADE method, the outcomes identified for each question were voted by the development team using a numerical scale that allowed voters to give a score from 1 to 9. A maximum number of 7 outcomes was set for each question. The average scores received from each outcome resulted in the identification of three categories: "critical outcomes" (mean score 7-9), "important outcomes" (mean score 4-6), and "non-important outcomes" (mean score 1-3) (Annex 1).

SYSTEMATIC REVIEW OF THE LITERATURE

The scientific evidence supporting the recommendations was collected via systematic review of the biomedical literature carried out by the documentalist in June 2020 and updated in June 2021, with sources not dating further back than 2015.

Research and Selection of Guidelines

In order to find the Guidelines of possible interest, bibliographic research was carried out on Medline/PubMed, on Guideline databases and on websites that were considered relevant to the specific scope of interest among those indicated in the CADTH 2019 document.

In Medline/PubMed the research was conducted via MeSH - Medical Subject Heading and by free word searching, using the "Text Word" field to allow for a more sensitive extraction of the results and adoption of the available truncation function. On websites the search was carried out with free terms. The inclusion criteria adopted were: English/Italian language and date of publication after 2015. These criteria were adopted in the subsequent stages of research development for systematic reviews and primary research studies, by adopting research filters specific to each type of publication. Any documents highlighted by members of the work groups and the development team as being worthy of consideration were added to the scientific evidence base.

The details of the search strategy and PRISMA flow chart relating to the PICOs of the individual groups are shown in Annex 2.

Due to the vast scope of the subject matter, it was not possible to identify a single reference Guideline with appropriate qualitative characteristics, therefore the Guideline is considered to have been developed ex novo, according to the CNEC Methodology Manual definition.

Research and selection of systematic reviews and primary research studies

For queries where the answer was not found in an existing high quality Guideline recommendation, a systematic search of systematic reviews was conducted in Medline/PubMed, the Cochrane Library and Epistemonikos. For topics of PICO questions for which no Guidelines or systematic reviews could be found, further research was carried out in the same sources mentioned above, aimed at extracting only primary research studies. The query was carried out via MeSH and free term searching by using appropriate search strings and, in the case of primary research studies, the methodology described in the Cochrane Collaboration manuals was used (de Vet et al., 2008; Higgins et al., 2021) relating to systematic reviews for the treatment and evaluation of the accuracy of diagnostic tests.

A first selection of articles were chosen based on the title and abstract of the study, and then a second selection involved the analysis of full-text articles. Any discrepancies in assessment between the two authors were resolved through discussion, until consensus was reached.

For each PICO outcome, the scientific evidence was summarized in GRADE Evidence Profiles, explaining the level of certainty of the estimates considered (Annex 4).

FROM EVIDENCE TO RECOMMENDATIONS

The 10 work groups prepared a draft of recommendations for each PICO to be submitted to the development team. The development team held an initial methodology meeting, where they identified the topics that should have been covered by recommendations. They also agreed on the PICO outcomes proposed by the work groups and voted on them as described above.

The formulation of the recommendations followed a pre-defined process which was developed at five different meetings, coordinated by the Chair and held via on-line video conferencing in March, April and May 2021:

1) Prior to every meeting each member of the development team received, in addition to the draft recommendation for each PICO outcome, a discussion of the scientific evidence used in relation to the effectiveness and safety of the interventions in question and the reference bibliography.

- 2) After reviewing the material, each member of the development team was asked to give a score using a score card adapted from the GRADE Evidence to Decision Framework (Andrews, 2013) that included the following domains to be evaluated before making the recommendation: women's values, necessary costs/resources, fairness of care, acceptability, and feasibility. For each domain, it was possible to express "complete agreement," "complete disagreement," and "partial agreement". In the event of partial agreement or disagreement, the respondent was asked to add a supporting justification. The layout of the score card can be seen in Annex 5. The scoring of the cards was carried out on-line on the Google Form platform and is shown in Annex 6.
- **3)** During the five meetings, the points where "complete agreement" was not expressed by at least 85% of the members of the development team, were discussed in relation to the issues identified.
- 4) At the end of the meetings, for each question, the development team agreed to the formulation of the recommendations proposed by the work groups. The meetings were recorded.

The meaning of "strength" and "direction" of the recommendations

The development of the recommendations in these Guidelines was carried out by considering the balance between the desirable and undesirable effects of different intervention alternatives, together with other components of context, such as fairness of care, women's values and preferences, use of resources and costs, the acceptability and feasibility of the intervention. In the event of relative uncertainty in the assessment of this balance, the development team expressed a "conditional" recommendation for or against the treatment. If the balance was clearly in favour of or against an intervention, the recommendation was considered to be "strong".

These recommendations are intended as an informative support in a decision-making process that must take place between an individual woman and her doctor and not as a behavioural standard or protocol. In this sense, the recommendations cannot be interpreted as "therapeutic standards", even when they are "strong", because even in this case the unique circumstances and preferences of the individual woman must be considered.

Below is a summary of the meaning of the terms used to define the strength and direction of the GRADE recommendations (Andrews et al., 2013).

EXTERNAL REVISION

The final draft of the Guidelines containing the recommendations voted for by the development team was sent to external auditors in order to get comments and proposals for possible changes or integrations to be made. The comments received from the auditors were considered by the development team and incorporated into the Guidelines (Annex 7).

UPDATING PROCEDURE

An update of the Guidelines is planned for 2024: The Board of SIEOG will be responsible for this by contacting the Scientific Organizations that participated in the formulation of these Guidelines and resubmitting the request for any changes to the panel based on evidence that may emerge in the next few years, taking into account any changes in health regulations.

DISTRIBUTION

After evaluation by the CNEC, the Guidelines will be published on the SIEOG website and on the website of the different Scientific Organizations that collaborated in this project. The Guidelines will also be transcribed in a publishable format and submitted to an international peer-reviewed journal.

Table 1

Terminology used in the Guideline recommendations, implications for different users (women, clinicians, healthcare decision-makers)

	Strong recommendation	Conditional recommendation
Positive recom- mendation	Women Theoretically, if well-informed, almost all women would be in favour of the examination; only a small percentage would not want to undergo it Clinicians In clinical practice, the majority of women would undergo the exam- ination Decision-makers Carrying out the examination may be used as a performance indica- tor	Women The majority of well-informed women would be interested in undergoing the examination, but a substantial proportion would not want to Clinicians In clinical practice, many but not all women would undergo the ex- amination Decision-makers Carrying out the examination is not to be considered for use as a quality criterion for performance indicators
Negative recom- mendation	Women Theoretically, if well-informed, no woman would like to undergo the examination; only a small per- centage would accept it Clinicians In clinical practice, the majority of women would not perform the ex- amination Decision-makers Carrying out the examination may be used as a negative perfor- mance indicator	Women The majority of well-informed women would not be interested in carrying out the examination, but a fair proportion would like to do so Clinicians In clinical practice, many but not all women would undergo the ex- amination Decision-makers Carrying out the examination is not to be considered for use as a quality criterion for performance indicators

REPORTING

The Guidelines were drawn up according to the AGREE Reporting Checklist (https://www.agreetrust.org/resource-centre/agree-reporting-checklist/) and evaluated by means of the AGREE II tool. The completed check-list and the results of the evaluation of AGREE II by two independent evaluators are given in the Appendix (Annex 3).

PRODUCER DECLARATION: the clinical recommendations for medications, health services, organizational or care models and medical devices contained in these Guidelines take into due account the Italian laws, rules and regulations of Italian regulatory agencies and the Ministry of Health, including the Essential Levels of Care and, where relevant, the rules and regulations of public institutions and institutions with healthcare purposes (INAIL).

EDITORIAL INDEPENDENCE

No external funding has been received for the preparation of these Guidelines. All the authors of the Guidelines have completed the Conflict of Interest Statement form adapted from the Methodology Manual for the Production of SNLG clinical practice Guidelines.

All authors have stated that they have no conflicts of financial, professional or other interest related to the topics covered in the Guidelines. In the event that an author declared that he/she had an interest in the last 10 years that could potentially conflict with the purpose of the Guidelines and that could compromise his/her objectivity of judgement, the author was excluded from the development team.

ANNEXES

- Annex 1: PICO and score outcomes
- Annex 2: Database + PRISMA strategies
- Annex 3: Agree 2 Guidelines
- Annex 4: GRADE Evidence Profiles
- Annex 5: Structure of score card
- Annex 6: Panel vote
- Annex 7: External auditors' comments

All the Annexes are available at www.sieog.it.

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ANNEX 1 - PICO AND OUTCOME SCORE

1. FIRST TRIMESTER ULTRASOUND

Questions	Р	I	С	ο	Impor- tance
Q1 Is it useful to	Women in the first	Ultrasound	Ultrasound	1. Perinatal mortality	6
perform an ul- trasound exami- nation in the first trimester for all	trimester of pregnancy	nancies	clinical indi- cation	2. Accurate preg- nancy dating	8
pregnancies?				3. Use of labour in- duction	6
Q2 If the woman wants to perform a screening test for aneuploidies, is it useful to offer first trimester	Pregnant women wishing to perform a screening test for ane- uploidies	First tri- mester ultrasound in accord- ance with a predefined protocol	First tri- mester ultrasound without a predefined protocol	1. Number of inva- sive tests with an aneuploidy out- come compared to the total number of invasive tests per- formed	8
ultrasound in ac- cordance with a pre-defined pro- tocol?				2. Number of in- vasive tests per- formed in the preg- nant population	8
				3. Maternal anxiety	7
				4. Abortion rate	7
Q3 If the woman wants to perform a screening test for aneuploidies that includes the measurement of nuchal translu- cency, is a quality control program of the procedure useful?	Pregnant women wishing to perform a screening test for an- euploidies including the meas- urement of nuchal translucency	Quality control via training and audits	No quality control	1. Number of inva- sive tests with an aneuploidy out- come compared to the total number of invasive tests per- formed	8
				2. Number of in- vasive tests per- formed in the preg- nant population	8
				3. Maternal anxiety	6
				4. Abortion rate	7

Questions	Р	I	с	ο	Impor- tance
Q4 In pregnancies	Pregnancies Fetal with first anato	es Fetal anatomy	Fetal anat- omy evalu-	1. Frequency of fetal malformations	8
with first trimester screening tests at high-risk for aneuploidies, is it	trimester screening tests indica- tive at	in the first trimester in accord-	first trimes- ter without a predefined	2. Implementation of an informed pregnancy	8
useful to evaluate fetal anatomy in accordance with a predefined pro-	high-risk for aneuploidies	ance with a predefined protocol	protocol	3. Maternal anxiety in case of false pos- itives	7
tocol?				4. Maternal mor- bidity	5
Q5 In the first trimes- ter of pregnancy, what is the accu- racy of ultrasound in diagnosing ec- topic pregnancy?	 Vaginal pain or blood loss in pregnant woman of <13 weeks Asympto- matic wom- an with non-diag- nostic ul- trasound or pregnancy of unknown location Woman with previ- ous caesar- ean delivery 	Sonograph- ic signs related to: • uterus • fallopian tubes and ovaries • peritoneal cavity	 Surgical/ histological diagnosis of ectopic pregnancy Confirma- tion of ec- topic preg- nancy at ultrasound follow-up hCG in- crease without chorionic villi found during cu- rettage Suspected/ confirmed ectopic pregnancy resolved af- ter medical treatment 	Accuracy of ectopic pregnancy diag- nosis	8
Q6 In the first trimes- ter of pregnancy, what is the accu- racy of ultrasound in diagnosing spontaneous miscarriage?	 Vaginal pain or blood loss in pregnant woman of <13 weeks Asympto- matic wom- an with non-diag- nostic ul- trasound or pregnancy of unknown location 	Sonograph- ic signs related to: • Gestational sac size and mor- phology • Size of the embryo • Embryonic heart rate	 Clinical/ histological diagnosis of abortion Confir- mation of abortion at ultrasound follow-up 	Accuracy of miscar- riage diagnosis	8

2. SECOND TRIMESTER ULTRASOUND

Questions	Р	I	С	ο	Impor- tance
Q1 Is it useful to per- form a 19-21-week fetal biometry ultrasound in the	General pregnant population Fetal biom- etry 19-21 weeks	Fetal biom- etry 19-21 weeks	Ultrasound performed at other gesta- tional ages	1. Accurate preg- nancy dating	8
general pregnant population to improve maternal and fetal out- comes?				2. Early intrauterine growth restriction	8
Q2 Is it useful to study fetal anato- my at 19-21 weeks gestational age in	General pregnant	Fetal anato- my survey	Not carrying out ultra-	1. Detection of fetal malformations	9
	μομαιαιοτι		amination/ carrying out	2. Perinatal mor- tality	8
ulation of preg- nant women in			examination at other gestational ages	3. Perinatal mor- bidity	8
a pre-defined protocol?				4. Protection of the right to an informed pregnancy	8
Q3 Is it useful to highlight so-	General pregnant population	Search for/ determine so-called "soft mark- ers"	No search/ No determi- nation	1. Identification of fetal malformations/ genetic disorders	6
called "soft markers" during the screening				2. Perinatal mor- tality	5
ultrasound exam- ination at 19-21 weeks gestational				3. Perinatal mor- bidity	5
age in order to improve maternal and fetal out- comes in the gen-				4. Protection of the right to an informed pregnancy	5
eral population of pregnant women?				5. Induction of ma- ternal anxiety	8

3. THIRD TRIMESTER ULTRASOUND

Questions	Р	I	с	0	Impor- tance
Q1 In the low-risk	Low-risk population	Ultrasound 30-32 weeks	No ultra- sound	1. Identification of SGA/FGR	7
population that has already performed an ultrasound at 20				2. Identification of large for gestational age	5
trasound at 30-32 weeks useful for improving preg- nancy outcomes				3. Identification of fetal structural ab- normalities	6
versus no ultra- sound?				4. Reduced perina- tal mortality	6
				5. Reduced perina- tal morbidity	6
Q2 In the low-risk	Low-risk population	Ultrasound 34-36	No ultra- sound	1. Identification of SGA/FGR	8
has already performed an ultrasound at 20 weeks, is an ul-		WEEKS		2. Identification of large for gestational age	7
trasound at 34-36 weeks useful for improving preg- nancy outcomes				3. Identification of fetal structural ab- normalities	6
versus no ultra- sound?				4. Reduced perina- tal mortality	7
				5. Reduced perina- tal morbidity	7
Q3 In the low-risk	Low-risk population	Ultrasound 30-32 weeks	Ultrasound 34-36 weeks	1. Identification of SGA/FGR	5
has already performed an ultrasound at 20 weeks, is an ul-				2. Identification of large for gestational age	5
trasound at 30-32 weeks versus an ultrasound at 34- 36 weeks useful				3. Identification of fetal structural ab- normalities	6
for improving pregnancy out- comes?				4. Reduced perina- tal mortality	5
				5. Reduced perina- tal morbidity	5

Questions	Р	I	с	0	Impor- tance
Q4 In the high-risk	High-risk population	Ultrasound at 30-32	No ultra- sound	1. Identification of SGA/FGR	8
has already performed an ultrasound at 20 weeks, is an ul-		WEEKS		2. Identification of large for gestational age	8
trasound at 30-32 weeks useful for improving preg- nancy outcomes				3. Identification of fetal structural ab- normalities	8
versus no ultra- sound?				4. Reduced perina- tal mortality	8
				5. Reduced perina- tal morbidity	8
Q5 In the high-risk	High-risk population	Ultrasound at 34-36 weeks	No ultra- sound	1. Identification of SGA/FGR	8
has already performed an ultrasound at 20 weeks, is an ul-		WEEKS		2. Identification of large for gestational age	8
trasound at 34-36 weeks useful for improving preg- nancy outcomes				3. Identification of fetal structural ab- normalities	7
versus no ultra- sound?				4. Reduced perina- tal mortality	8
				5. Reduced perina- tal morbidity	8
Q6 In women with	Women with suspected abnormal placental location	Transvaginal ultrasound	Transab- dominal ultrasound	1. Diagnosis of pla- centa praevia	9
normal placental location, does TV				2. Maternal morbid- ity and mortality	8
than TA US in improving clinical outcomes?				3. Fetal and neona- tal morbidity and mortality	8
Q7 In women with an ultrasound diag- nosis of placenta praevia performed before 36 weeks, is transvaginal ultrasound at 36 weeks helpful in improving clinical outcomes versus no ultrasound?	Women with ultrasound diagnosis of placenta praevia at <36 weeks	Transvaginal ultrasound at 36 weeks	No ultra- sound	1. Caesarean sec- tion	8

Questions	Р	I	С	0	Impor- tance
Q8 In women di- agnosed with placenta praevia, does a targeted	Women diagnosed	Targeted ultrasound	Routine ultrasound	1. Maternal morbidi- ty and mortality	9
	with placen- ta praevia	for the as- sessment of suspected		2. Post-partum haemorrhage	9
ultrasound study of the placenta for the assessment of suspected placenta accreta spectrum disor- ders (PAS) help to improve clinical outcomes versus routine ultra- sound?	asound study he placenta for assessment uspected centa accreta ctrum disor- s (PAS) help to prove clinical comes versus tine ultra- nd?	placental accreta spectrum disorders	placental accreta spectrum disorders	3. Duration of hos- pitalization (days)	8
Q9 In pregnancies	Women at risk of vasa praevia	Targeted US for vasa praevia	Routine ul- trasound	1. In utero mortality and morbidity	8
praevia (previous diagnosis of pla-				2. Neonatal mortali- ty and morbidity	9
centa praevia or velamentous cord insertion, etc.), is				3. Rate of elective caesarean sections	8
a targeted ultra- sound for vasa praevia helpful in improving clinical outcomes versus routine ultra- sound?				4. Rate of surgical deliveries (cae- sarean sections, vacuum extraction, forceps)	6

4. ULTRASOUND IN TWIN PREGNANCIES

Questions	Р	I	с	ο	Impor- tance
Q1 What are the op-	Women with twin pregnancies	Ultrasound in twin preg-	Ultra- sound in	1. Accuracy of dating	8
measurements for dating twin preg- pancies?		dating with CRL and/or	pregnan- cies for	2. Perinatal mor- bidity	7
Specific ques- tion: Are the measurements		HC; using dif- ferent biom- etric curves;	with CRL and/or DBP and/	3. Correct identi- fication of growth restriction	8
length, biparietal diameter, head circumference) and the curves of fetal biometric parameters used for singleton preg- nancy dating also effective in twin pregnancies or are there systematic errors when using these curves?		second tri- mester	different biometric curves; in the first or second trimester	4. Planning of delivery or inter- ventions at the appropriate ges- tational age	8
Q1 bis What are the op- timal ultrasound	Women with twin pregnancies	Ultrasound in twin preg- nancies for dating based on the larger foetus	Ultra- sound in twin preg- nancies for dating based on	1. Accuracy of dating	8
measurements for dating twin preg-				2. Neonatal mor- bidity	7
Specific question: Is pregnancy dating based on the larger fetus			the small- er foetus	3. Correct identi- fication of growth restriction	8
more useful than that based on the smaller fetus?				4. Planning of delivery or inter- ventions at the appropriate ges- tational age	8
Q2 In twin preg-	Women with twin pregnancies	Ultrasound in twin preg-	No ultra- sound in	1. Perinatal fetal mortality	9
ultrasonographic determination of		define chori- onicity (mem-	twin preg- nancies to define	2. Neonatal mor- bidity	9
amnionicity useful for fetal and mater- nal health?		ness, number of layers, number of placental masses and lambda and T-signs, sex of the foetus- es, using sev- eral of these parameters together) and amnionicity	ity	3. Avoid carrying out unnecessary diagnostic pro- cedures on the mother	7

Questions	Р	I	С	ο	Impor- tance
Q3 What is the optimal	Women with mon- ochorionic twin	 First-tri- mester ul- trasound 11- 13+6 weeks to assess NT discrepancy, Doppler duc- tus venosus flow ab- normalities (isolated or in combina- tion) Ultrasound after 16 weeks to evaluate growth dis- cordance, amniotic fluid dis- cordance, Doppler ab- normalities (isolated or in combina- tion) First trimes- 	Standard diagnostic criteria for	1. Fetal perinatal mortality	9
gy for identifying twin-to-twin trans- fusion syndrome in monochorionic twin pregnancies?	pregnancies		the diag- nosis of TTTS fol- lowing the Quintero staging system (oligo/ polyhy- dramnios; bladder present, absent in donor; Doppler fetal abnor- malities; hydrops; death of one or both twins)	2. Neonatal mor- bidity	8
				3. Timely referral to a Specialist Centre for treat- ment of structur- al abnormalities that may be eli- gible for in utero treatment	9
				4. Reduction of maternal anxiety	7
Q4 What is the op- timal screening	Women with dichorionic twin pregnancies	 First trimes- ter ultra- sound 11- 13+6 weeks to assess CRL discrep- ancy, of NT Ultrasound from 20 weeks on- 	Ab- dominal circum-	1. Perinatal mor- tality	9
program to identify growth restriction			ference or estimated fetal weight measure- ment in the third	2. Neonatal mor- bidity	8
pregnancies?				3. Timely referral to a Specialist Centre for man- agement	8
		evaluate: - growth dis-	timester	4. Reduction of maternal anxiety	7
	ver wei wai eva - gr cor - at circ enc enc cer eac - fe Do vela (un tery cer tery ver	- abdominal circumfer- ence or es- timated fetal weight <10 th centile of each foetus - fetal Doppler velocimetry (umbilical ar- tery, middle cerebral ar- tery, ductus venosus)		5. Reduction of preterm elective deliveries	7

Questions	Р	I	с	ο	Impor- tance
Q4 bis What is the optimal screening program	Women with mon- ochorionic twin pregnancies	First trimes- ter ultra- sound 11-	Abdo- minal circum-	1. Perinatal mor- tality	9
restriction in mon- ochorionic twin pregnancies?		to assess CRL discrep- ancy, of NT	estimat- ed fetal weight measure- ment in the third trimester	2. Neonatal mor- bidity	8
	Ultrasoun from 16 weeks on wards to evaluate: - growth	 Ultrasound from 16 weeks on- wards to evaluate: - growth dis- 		3. Timely referral to a Specialist Centre for man- agement	9
		cordance - abdominal circumfer- ence and/ or estimated fetal weight <10 th centile - fluid dis- cordance - fetal Doppler velocimetry (umbilical ar- tery, middle cerebral ar- tery, ductus venosus)		4. Reduction of maternal anxiety	7
				5. Reduction of preterm elective deliveries	7
Q5 What is the op- timal screening	is the op- screening pregnancies v		Ultra- sound from 16	1. Fetal perinatal mortality	8
program to iden- tify twin anemia polycythemia se- quence (TAPS) in twins?		wards via Doppler with biometry and peak velocity in the middle cerebral ar-	weeks onwards with bi- ometry	2. Neonatal mortality and morbidity (for anemia/poly- cythemia)	8
		tery		3. Timely referral to a Specialist Centre for man- agement	8

Questions	Р	I	с	0	Impor- tance
Q6 When and how should screening be performed to iden- tify structural ab- normalities in twin pregnancies?	Women with mon- ochorionic twin pregnancies Women with dichorionic twin pregnancies	Ultrasound in the first, sec- ond, and third trimester and fetal echocar- diography	Second trimester ultrasound only	1. Right to an in- formed pregnancy in the case of structural anom- alies and serious disabilities if the foetus survives	8
				2. Correct man- agement of cases with structural ab- normalities for in utero treatment	6
				3. Correct manage- ment of cases with structural abnor- malities for postna- tal treatment	8
				4. Perinatal fetal mortality	8
				5. Neonatal mor- bidity	8
				6. Reduction of maternal anxiety	7
Q7 What is the role of	Women with twin pregnancies	Neurosonog- raphy with/ without MRI	Routine ultrasound	1. Co-twin perina- tal mortality	8
ultrasound in twin pregnancies if one				2. Co-twin perina- tal morbidity	8
utero?				3. Preterm iatro- genic delivery of the co-twin	7
				4. Reduction of maternal anxiety	7
				5. Management of an informed preg- nancy	7
Q8 Is it useful to send	Women with mon- ochorionic twin	Ultrasound and man-	Ultrasound and Man-	1. Perinatal fetal mortality	9
pregnancies to Spe- cialist Centres?	plicated by twin- to-twin transfusion	the Specialist Centre for twin	agement at Level 1 Centres	2. Perinatal mor- bidity	9
	syndrome, growth discordance of ≥20-25% and/or	pregnancies		3. Timeliness of in utero treatment	9
	of both foetuses <10 th centile, death			4. Reduction of maternal anxiety	7
	 In uterus of a twin, structural abnor- malities Women with dicho- rionic twin preg- nancies complicat- ed by growth dis- cordance of ≥25% and/or estimated fetal weight of at least one twin <10th centile, by structur- al abnormalities Women with monochorionic monoamniotic twin pregnancies 			5. Management of an informed preg- nancy	7

5. ULTRASOUND IN THE PREVENTION OF PRETERM DELIVERY

Questions	Р	I	с	0	Impor- tance
Q1 In a singleton	Women with	Cervicome- try at 19-21	No cervi- cometry	1. Premature deliv- ery <37 weeks	6
pregnancy in ab- sence of risk fac-	low-risk singleton	weeks		2. Premature deliv- ery <34 weeks	7
delivery is it useful to measure cervi-	pregnancy			3. Perinatal mor- tality	6
cal length at 19-21 weeks?				4. Perinatal mor- bidity	6
				5. Intraventricular haemorrhage	5
				6. Low birth weight (<2.500 g)	6
				7. Respiratory dis- tress syndrome	6
				8. Duration of hos- pitalization in NICU	6
Q2 Is it useful to	Q2 Is it useful to measure cervical length at 19-21 pregnan-	Cervicome- try at 19-21	No cervi- cometry	1. Premature deliv- ery <37 weeks	8
measure cervical length at 19-21 weeks in singleton		weeks		2. Premature deliv- ery <34 weeks	8
patients with pre- vious premature	previous			3. Perinatal mor- tality	8
births?	birth			4.Perinatal mor- bidity	8
				5. Intraventricular haemorrhage	7
				6. Low birth weight (<2.500 g)	7
				7. Respiratory dis- tress syndrome	8
				8. Duration of hos- pitalization in NICU	7
Q3 Is it useful to	Patients with twin	Cervicome- try at 19-21	No cervi- cometry	1. Premature deliv- ery <37 weeks	6
length in twin	pregnan- cies	weeks		2. Premature deliv- ery <34 weeks	7
19-21 weeks?				3. Perinatal mor- tality	6
				4. Perinatal mor- bidity	6
				5. Intraventricular haemorrhage	6
				6. Low birth weight (<2.500 g)	6
				7. Respiratory dis- tress syndrome	6
				8. Duration of hos- pitalization in NICU	6

Questions	Р	I	с	0	Impor- tance
Q4 Is it useful to	Patients with sin-	Cervicome- try at 16-18	No cervi- cometry	1. Premature deliv- ery <37 weeks	6
measure cervical length at 16-18 weeks in singleton	gleton pregnancy and a	weeks		2. Premature deliv- ery <34 weeks	7
patients with pre- vious premature	history of premature			3. Perinatal mor- tality	6
	delivery			4. Perinatal mor- bidity	6
				5. Intraventricular haemorrhage	6
				6. Low birth weight (<2.500 g)	6
				7. Respiratory dis- tress syndrome	6
				8. Duration of hos- pitalization in NICU	6
Q5 Is ultrasound	Patients with con-	Transvaginal cervicometry	Digital ex- amination	1. Premature deliv- ery <37 weeks	6
measurement of cervical length useful in patients	tractile activity be- fore 37+0			only	2. Premature deliv- ery <34 weeks
with preterm con- tractions?	weeks			3. Perinatal mor- tality	7
				4. Perinatal mor- bidity	7
				5. Intraventricular haemorrhage	6
				6. Low birth weight (<2.500 g)	6
				7. Respiratory dis- tress syndrome	7
				8. Delivery within 7 days	7
				9. Duration of pa- tient hospitalization	7
				10. Treatment with steroids and MgSO4, tocolysis	7

6. DOPPLER ULTRASONOGRAPHY IN OBSTETRICS

Questions	Р	I	с	0	Impor- tance
Q1 In the general pop- ulation undergoing	General population subjected	Umbilical ar- tery Doppler velocimetry performed	Doppler ve- locimetry of the umbilical	1. Intrauterine growth restriction identification	5
ing does evalua- tion with Doppler velocimetry of the	sound	performed	performed	2. Perinatal mor- tality	5
umbilical artery im- prove outcomes?				3. Perinatal mor- bidity	5
Q2 In the population at risk of intrauterine growth restriction	Population at risk of intrauter- ine growth	Umbilical ar- tery Doppler velocimetry performed	Doppler ve- locimetry of the umbilical artery is not	1. Intrauterine growth restriction identification	8
and/or with prior diagnosis of in- trauterine growth	restriction* or with prior di-	performed	performed	2. Perinatal mor- tality	8
restriction does assessment of the umbilical artery	agnosis of intrauter- ine growth			3. Neonatal mor- bidity	8
with Doppler ve- locimetry improve outcomes?	restriction (*complicated pregnancy due to hy- pertensive disorders, pri- or small new- born for ges- tational age or suspected slowing of fetal growth)			4. Early delivery	8
Q3 In the general population does the evaluation with	General population	Doppler ve- locimetry of the uterine arteries in	Doppler velocimetry of uterine ar-	1. Hypertensive disorders of preg- nancy	6
Doppler velocime- try of the uterine arteries in the		the first and second tri- mesters	in the first	2. Intrauterine growth restriction	7
first and second trimesters improve outcomes?			trimesters	3. Fetal morbidity associated with growth restriction	7
				4. Maternal morbid- ity associated with hypertensive disor- ders of pregnancy	6

Questions	Р	I	С	0	Impor- tance
Q4 In high-risk preg- nancies for hyper-	High-risk pregnan- cies for hy-	Doppler ve- locimetry of the uterine	- Doppler f velocimetry of uterine ar-	1. Hypertensive disorders of preg- nancy	7
of pregnancy and intrauterine growth	disorders and in-	the first and second tri-	performed in the first	2. Intrauterine growth restriction	8
the assessment of Doppler velocime- try of the uterine arteries in the first trimester im-	growth re- striction* (*history of previous		trimesters	3. Fetal morbidity associated with intrauterine growth restriction	8
(*history of previous hy- pertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small newborn for gestational age or suspected slow- ing of fetal growth)	hypertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small new- born for ges- tational age or suspected slowing of fetal growth)	Doppler ve- locimetry of Doppler		4. Maternal morbid- ity associated with hypertensive disor- ders of pregnancy	8
Q5 In high-risk preg- nancies for hyper-	High-risk pregnan- cies for hy-	Doppler ve- locimetry of the uterine	Doppler velocime- try of the	1. Hypertensive disorders of preg- nancy	6
of pregnancy and intrauterine growth	disorders and in-	third trimes- ter	third trimes- ter performed	2. Intrauterine growth restriction	7
the evaluation of Doppler velocime- try of the uterine arteries in the sec- ond trimester im-	growth re- striction* (*history of previous		trimester	3. Fetal morbidity associated with intrauterine growth restriction	7
prove outcomes? (*history of previous hy- pertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small newborn for gestational age or suspected slow- ing of fetal growth)	nypertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small new- born for ges- tational age or suspected slowing of fetal growth)			4. Maternal morbid- ity associated with hypertensive disor- ders of pregnancy	6

Questions	Р	I	с	0	Impor- tance
Q6 In pregnancies	In preg- nancies	Doppler ve- locimetry of	Doppler velocimetry	1. Maternal mor- tality	7
complicated by hypertensive disor- ders of pregnancy	ed by hy- pertensive	arteries	of uterine ar- teries is not performed	2. Maternal mor- bidity	7
or intrauterine growth restriction does evaluation	disorders of preg- nancy or			3. Perinatal mor- tality	7
with Doppler ve- locimetry of the uterine arteries in	intrauter- ine growth restriction			4. Perinatal mor- bidity	7
the third trimester improve out- comes?				5. Early delivery	6
Q7 In pregnancies	Complicat- ed preg-	Doppler velocimetry	Doppler velocimetry	1. Fetal intrauterine death	7
intrauterine growth	due to in-	cerebral ar-	dle cerebral	2. Early delivery	7
restriction does the evaluation of Dop- pler velocimetry of the middle cerebral artery improve out- comes?	trauterine growth restriction	tery	artery is not performed	3. Neonatal mor- tality	7
			4. Postnatal out- comes	7	
Q8 In pregnancies at	Pregnan- cies at risk for fetal anemia	Doppler velocimetry of the middle cerebral ar- tery	try ddle ar- dle ar- dle dle cerebral artery is not performed	1. Identification of fetal anemia	9
mia does the eval- uation with Dop-				2. Need for intrau- terine transfusion	9
the middle cerebral				3. Early delivery	8
artery improve out- comes?				4. Perinatal mor- tality	8
				5. Postnatal out- comes	8
Q9 In pregnancies	Complicat- ed preg-	Doppler velocimetry	Doppler velocimetry	1. Fetal intrauterine death	8
intrauterine growth	due to in-	venosus	venosus is	2. Early delivery	8
restriction <32 weeks (severe/ early) does evalu-	trauterine growth restriction		formed	3. Frequency of caesarean sections	6
ation with Doppler velocimetry of the ductus venosus im-	<32 weeks			4. Perinatal mor- tality	9
prove outcomes?				5. Postnatal out- comes	8

7. ULTRASOUND IN THE DELIVERY ROOM

Questions	Р	I	с	ο	Impor- tance
Q1 In women in regu-	Pregnant women in	Transab- dominal and	No ultra- sound	1. Spontaneous vag- inal delivery	3
it useful to perform	active la- bour	transperineal ultrasound		2. Caesarean sec- tion	3
improve the out- come of childbirth?				3. Duration of la- bour	3
				4. Neonatal mor- bidity	4
				5. Maternal mor- bidity	4
Q2 In women with	Pregnant women	Transab- dominal and	No ultra- sound	1. Spontaneous vag- inal delivery	7
extension/arrest of the first stage of labour is it useful	with stage I prolonged/	transperineal ultrasound		2. Caesarean sec- tion	7
to perform an ultra- sound to improve	anest			3. Duration of la- bour	6
the outcome of childbirth?				4. Neonatal mor- bidity	6
				5. Maternal mor- bidity	5
Q3 In women with	Pregnant women	Pregnant women with stage Il pro- longed/ arrest	ransab- ominal and ansperineal ltrasound	1. Spontaneous vag- inal delivery	7
extension/arrest of stage II labour, is an	with stage II pro-			2. Caesarean sec- tion	7
improving delivery outcomes?	arrest			3. Duration of la- bour	6
				4. Neonatal mor- bidity	7
				5. Maternal mor- bidity	6
				6. Empowerment of the parturient	6
Q4 In women in stage II of labour, where	Pregnant women in stage II of	Transabdomi- nal ultrasound for fetal	Clinical eval- uation (no ultrasound)	1. Probability of suc- cess of the vaginal operative delivery	7
there are indica- tions for an urgent operative delivery, is it useful to perform	labour with indications for urgent	position/atti- tude and/or transperineal		2. Duration of vaginal operative delivery	7
an ultrasound prior to the application of the obstetric vacu- um extractor to im- prove maternal and perinatal outcome?	delivery	(at push)		3. Maternal mor- bidity	7
Q5 In women with baemorrhage after	Patients with haem-	Transabdomi- nal ultrasound	No ultra- sound	1. Need for invasive surgical procedures	8
vaginal delivery, is it useful to perform	ter vaginal delivery	uterine cavity		2. Need for uterine cavity tamponade	8
a transabdominal ultrasound to im- prove outcomes?				3. Incidence of ma- jor haemorrhage (>2000 ml)	7
				4. Maternal mor- bidity	8

8. ULTRASOUND IN GYNAECOLOGY

Questions	Р	I	С	0	Impor- tance
Q1 In women with	Women with acute	Transvaginal ultrasound	Clinical ex- amination	1. Reduction of hos- pitalizations	8
performing a transvaginal ultra- sound lead to an	pelvic pain			2. Reduction of duration of hospi- talization	7
the outcomes that are important to women?				3. Identification of emergency or ur- gent surgical cases	8
				4. Identification of patients eligible for medical treatment	7
Q2 In women with	Women with atyp-	Transvaginal ultrasound	Clinical ex- amination	1. Reduction of hos- pitalizations	8
abnormal uterine bleeding, does transvaginal ultra- sound lead to an	loss			2. Reduction of surgical diagnostic procedures	8
the outcomes that are important to women?				3. Identification of patients eligible for medical treatment	7
Q3 In women with	Patients with adnexal masses	Transvaginal ultrasound	Clinical ex- amination/ markers	1. Reduction of sur- gical procedures	8
a transvaginal ul- trasound lead to				2. Identification of emergency or ur- gent surgical cases	9
an improvement in the outcomes that are important to				3. Reduction of hospitalizations	8
women?				4. Correct identifi- cation of the nature of the mass and its consequent clinical management	8
Q4 In asymptomatic women on hor- mone replacement therapy, does	Asymp- tomatic women undergo- ing hor-	Transvaginal ultrasound	Clinical ex- amination	1. Improvement of specific diagnoses of pre-malignant or malignant endome- trial disease	7
transvaginal ultra- sound lead to an improvement in the outcomes that are important to women?	placement therapy			2. Increase in num- ber of diagnostic/ invasive procedures	7

Questions	Р	I	с	0	Impor- tance
Q5 In the general asymptomatic population does performing a transvaginal ultra-	General asympto-	Transvaginal ultrasound	No examina- tion/clinical	1. Reduction of mortality	6
	ulation		markers	2. Early diagnosis of ovarian cancer	6
sound lead to an improvement in the outcomes that are important to				3. Early diagnosis of endometrial cancer	5
women?	portant to n?			4. Reduction in the number of requests for further imaging investigations	6
Q6 In the population	Population with higher	Transvaginal ultrasound	No examina- tion/clinical	1. Reduction of mortality	7
higher-risk of de- veloping cancer	oncologi- cal risk		markers	2. Early diagnosis of ovarian cancer	7
factors, does per- forming a transvag- inal ultrasound lead to an improvement				3. Early diagnosis of endometrial cancer	7
in the outcomes that are important to women?				4. Reduction in the number of requests for further imaging investigations	7

9. POINT OF CARE ULTRASOUND

Questions	Р	I	с	ο	Impor- tance							
Q1 In emergency/ urgent obstetric and gynecological	Patients who ac- cess the gynaeco-	Pelvic ultra- sound	Clinical ex- amination	1. Reduction in the number of inappro- priate hospitaliza- tions	8							
improve the out- comes that are im-	for emer- gencies/			2. Identification of organic diseases	8							
portant to women?	care			3. Maternal mortality	7							
				4. Reduction in duration of hospi- talization	7							
				5. Reduction of ad- missions to Inten- sive Care	8							
Q2 When the gyneco-	Patients who	Pelvic ultra- sound	Clinical ex- amination	1. Identification of organic diseases	8							
logical examination does not allow a satisfactory clinical evaluation, can a complementary clinic and	a gynae- cological outpatient clinic and	access a gynae- cological outpatient clinic and cannot be assessed accurately at the clin- ical exami- nation	t - -		2. Reduction in the number of biochemical tests requested	8						
an improvement in the outcomes that are important to women?	assessed accurately at the clin- ical exami- nation								ssessed ccurately t the clin- cal exami- nation	issed irately e clin- exami- on		3. Reduction in the number of requests for imaging tests (CT MRI level II ul- trasound)
				4. Reduction of hospitalizations	8							
				5. Reduction of mortality	8							
				6. Patient satisfaction	8							
Q3 In post-term	Post-term pregnan-	Ultrasound evaluation	Clinical ex- amination without ul- trasound	1. Fetal intrauterine death	7							
pregnancy, does performing an ul- trasound to assess the single deepest	cies	deepest pool		2. Reduction in the number of inappro- priate inductions	6							
improve perinatal outcome?	amniotic fluid pool improve perinatal outcome?			3. Identification of intrauterine growth restriction	5							
				4. Neonatal aci- dosis	6							
				5. Hospitalizations in neonatal inten- sive care	6							
				6. Neonatal mortality	6							

Questions	Р	I	с	0	Impor- tance
Q4 Is the ultrasound assessment of fetal presentation in addition to the obstetrical exam- ination, at patient admission or in advanced third tri- mester, associated with an improve- ment in outcomes that are important to the women?	Pregnant women who are first ad- mitted or are in the advanced stages of the third trimester	Ultrasound evaluation of fetal pres- entation	Clinical ex- amination	1. Number of wom- en undergoing external cephalic version	7
				2. Reduction in the frequency of cae- sarean sections	8
Q5 Does ultrasound evaluation of fetal heart beat improve maternal-fetal out- come in doubtful cardiotocography cases?	Pregnant women in which the fetal heart beat is not clearly identifiable at CTG ex- amination	Ultrasound evaluation of fetal heart beat	Cardiotoco- graphic ex- amination	1. Reduced mater- nal stress	8
				2. Identification of fetal bradycardia	8
Q6 In patients evaluat- ed in the ER for an- tenatal bleeding in the third trimester does an ultrasound assessment of pla- cental localization improve maternal and fetal out- comes?	Pregnant women who ar- rive at the emergen- cy room during the third tri- mester of pregnancy with metr- orrhagia	Ultrasound evaluation of placental localization	Clinical ex- amination	1. Fetal intrauterine death	8
				2. Maternal mor- tality	8
				3. Need for mater- nal transfusions	7
				4. Intensive care admissions	8
				5. Reduction in the rate of caesarean sections	7
				6. Reduction of hospitalizations	6

10. REFERRAL SCAN

Questions	Р	I	с	о	Impor- tance
Q1 In a pregnant pa- tient at risk* for fetal malformations, is it useful to perform a referral scan in order to study fetal anat- omy in a detailed manner? *At least one maternal risk factor: •Diabetes •Debsity •ART •Family history of malfor- mations •Maternal infections (TORCH) •Consumption of/Expo-	Pregnant women at risk for fe- tal malfor- mations	Referral scan	Screening scan	1. Perinatal mor- tality	9
				2. Perinatal mor- bidity	8
				3. Identification of major malforma- tions	8
				4. Identification of malformations	8
				5. Possibility of pa- tient self-determi- nation regarding an informed pregnan- cy (interruption of pregnancy, psycho- logical preparation)	8
Aliek of fetal anemia (Parvovirus B19 infec- tion or high titre positive indirect Coombs test) At least one fetal risk factor: • Abnormal ultrasound as- pects at screening • Increased NT				6. Adverse psy- chological reper- cussions for the mother in case of diagnostic errors (false positives)	8
Q2 In pregnant patients at risk* for fetal heart disease, is fetal echo- cardiography useful? *At least one maternal risk factor: •Heart disease in a first-de- gree relative •Hereditary diseases associ- ated with heart diseases (Ro/SSA or La/SSB) •ART (TPT) •Maternal infections (TORCH) •Consumption of/Exposure to teratogens	Pregnant women at risk for fetal heart disease	Echocardiog- raphy	Screening scan	1. Perinatal mor- tality	9
				2. Perinatal mor- bidity	9
				3. Identification of major malformations	9
				4. Identification of malformations	8
				5. Possibility of pa- tient self-determi- nation regarding an informed pregnan- cy (interruption of pregnancy, psycho- logical preparation)	8
At least one fetal risk factor: • Major extracardiac malfor- mations • Suspected fetal heart dis- ease at screening • Fetal arrhythmia • Increased NT • Velocimetry defect of the ductus venosus (RF) or tri- cuspid regurgitation detect- ed in the first trimester • Early fetal hypo-develop- ment • Fetal hydrops • Monochorionic twin preg- nancy				6. Adverse psy- chological reper- cussions for the mother in case of diagnostic errors (false positives)	7

EXECUTIVE SUMMARY

1. FIRST TRIMESTER ULTRASOUND

Recommendation 1

It is recommended to offer a screening ultrasound to all pregnant women during the first trimester.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Recommendation 2

For women wishing to perform a screening test for fetal aneuploidies, it is recommended to apply a pre-defined protocol for performing the first trimester ultrasound.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Recommendation 3

A quality control program for the measurement of nuchal translucency is recommended as this increases the accuracy of screening tests for aneuploidies.

- **STRONG POSITIVE RECOMMENDATION**
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Recommendation 4

A pre-defined protocol is recommended for evaluating fetal anatomy as this may help recognize fetal structural abnormalities in the first trimester.

This investigative protocol is differentiated between the general population and high-risk aneuploidy pregnancies.

The possibility of applying this protocol in the first trimester may be limited by technical factors.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 5

In symptomatic pregnant women of <13 weeks with pelvic pain or vaginal blood loss, and those with non-diagnostic ultrasound or pregnancy of unknown location, a transvaginal ultrasound is recommended. It is considered the diagnostic tool of choice for the diagnosis of ectopic tubal pregnancy with a sensitivity of 87-99% and a specificity of 94-99.9%.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 6

In case of vaginal blood loss or pain in pregnant women of <13 weeks, or with non-diagnostic ultrasound or pregnancy with unknown location, it is recommended to inform the woman of the accuracy limitations of diagnosing spontaneous miscarriage with a single ultrasound, particularly at early gestational ages.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

2. SECOND TRIMESTER ULTRASOUND

Recommendation 1

Assessment of fetal biometry is recommended for all women in order to improve pregnancy outcomes during the second trimester screening examination.

In the event that an ultrasound has not been performed in the first trimester, it is recommended that pregnancy dating be carried out during the second trimester screening ultrasound.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 2

Evaluation of fetal anatomy in accordance with a pre-defined protocol for the detection of major fetal malformations is recommended for all women during the second trimester pregnancy screening examination.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 3

In order to carry out a screening for aneuploidies, searching for so-called "soft markers" is not recommended in the general population of pregnant women during the second trimester pregnancy screening examination.

- STRONG NEGATIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

3. THIRD TRIMESTER ULTRASOUND

Recommendation 1-3

The literature data are insufficient to respond separately to PICOs 1-3. Therefore, the three PICOs were considered together.

In the low-risk population, ultrasound in the third trimester at 34-36 weeks may identify alterations in fetal growth and congenital abnormalities.

The panel wants to point out that an ultrasound performs better in identifying fetal growth restriction and fetal macrosomia compared than the symphysis-fundus height measurement. The panel recommends clinical studies specifically aimed at assessing the impact of third-trimester ultrasound on perinatal mortality and morbidity.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND SYSTEM-ATIC REVIEWS OF MODERATE QUALITY, ONLY ONE OF LOW QUALITY

Recommendation 4-5

Ultrasound is recommended in the third trimester in the high-risk population.

The panel points out that there is insufficient evidence for comparison of ultrasound at 30-32 weeks versus 34-36 weeks.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A HIGH QUALI-TY SYSTEMATIC REVIEW

Recommendation 6

Transvaginal ultrasound is recommended for the diagnosis of placenta praevia or low-lying placenta because the transvaginal approach is superior compared to transabdominal and transperineal approaches.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 7

In women with placenta praevia (i.e., with a placental margin less than 20 mm from the internal uterine os) at 32 weeks gestation and who are asymptomatic, additional transvaginal ultrasound at approximately 36 weeks gestation is recommended in order to discuss the mode of delivery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 8

Prenatal assessment of women at risk for PAS (Placenta Accreta Spectrum) is recommended in a Referral Centre in order to plan clinical management and delivery and reduce maternal morbidity and mortality.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF LOW QUALITY

Recommendation 9

There is insufficient evidence to support universal screening for vasa praevia at the time of routine ultrasound in the general population.

The panel wants to point out that although targeted ultrasound assessment of pregnancies at higher risk for vasa praevia has been studied, the balance between benefits and risks remains undetermined, and further research in this area is needed.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

4. ULTRASOUND IN TWIN PREGNANCIES

Recommendation 1 and 1bis

In the first trimester, an ultrasound must be offered for dating the pregnancy.

In order to date spontaneous conception pregnancies, in case of discordant CRLs, the dating should be carried out by referring to the twin with greater CRL.

In the case of pregnancies resulting from in vitro fertilization, the date of oocyte retrieval or the date of transfer and the age of the embryo at transfer must be used for dating.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 2

During the first trimester of pregnancy, ultrasound should be offered to all women with twin pregnancies to determine the chorionicity and amnionicity.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES
In the first trimester of monochorionic twin pregnancies no screening procedure is recommended to identify TTTS.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 3bis

In monochorionic twin pregnancies in the second and third trimesters, periodic measurement at regular intervals (approximately every 15 days) of the single deepest pool of amniotic fluid is recommended.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 4

In dichorionic twin pregnancies, periodic monitoring of fetal biometry and the single deepest pool of amniotic fluid, and assessment of the fetal weight discordance is recommended from 24 weeks onwards.

Note: The panel believes that these indications should consider the problems related to local resources and, on the basis of these considerations, proposes that the checks be carried out every 4-6 weeks.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF MOD-ERATE QUALITY

Recommendation 4bis

In uncomplicated monochorionic twin pregnancies, it is recommended to carry out a screening program with frequent periodic ultrasound assessments, approximately every 2 weeks, starting at 16 weeks, with evaluation of: fetal biometry, single deepest pool of amniotic fluid, estimated fetal weight discordance and Doppler of the umbilical artery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF MOD-ERATE QUALITY

Recommendation 5

Early diagnosis of TAPS is recommended in monochorionic twin pregnancies that are complicated by TTTS or sIUGR, i.e. in cases of heart failure in a twin, or polyhydramnios or Doppler alterations in the umbilical artery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 6

In twin pregnancies, ultrasound screening for structural abnormalities should be offered in the same manner and timing as in singleton pregnancies.

STRONG POSITIVE RECOMMENDATION

▶ RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 7

In Specialist Centres with experience in twin pregnancies, sampling of the middle cerebral artery peak systolic velocity value (MCA-PSV) is recommended in monochorionic twin preg-

nancies with death of a fetus in utero, in order to identify the presence of anemia in the surviving fetus. The panel suggests performing customized monitoring based on the cause of death of the co-twin, gestational age, and fetal well-being at the time of diagnosis, and performing an MRI of the fetal brain.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A LOW QUALITY LITERATURE SYSTEMATIC REVIEW

Recommendation 8

The panel recommends requesting the opinion of a Specialist Centre in the case of:

- Women with monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome, growth discordance of >25% and estimated weight of one or both fetuses <10th centile, death of a twin in utero, structural abnormalities, suspected TRAPS or TAPS.
- Women with dichorionic twin pregnancies complicated by growth discordance of >25% and estimated fetal weight of at least one twin <10th centile, structural abnormalities, death of a twin in utero.
- Women with monochorionic monoamniotic twin pregnancies.
- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

5. ULTRASOUND IN THE PREVENTION OF PRETERM DELIVERY

Recommendation 1

Cervicometry screening in singleton pregnancy patients, in the absence of clinical or anamnestic risk factors for premature delivery, cannot currently be universally recommended. The panel wants to point out that universal screening has proven to be cost-effective only in some countries (e.g. in the United States and the United Kingdom) and that the implementation of such a screening method in Italy needs more research in order to assess its clinical impact. The panel also stresses the need for adequate training for operators performing such ultrasound evaluation.

Research recommendation: the panel highlights the importance of Italian studies regarding the effectiveness of such on the general population.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONE LOW QUALITY

Recommendation 2

In patients with singleton pregnancies and a history of premature delivery, the measurement of cervical length is recommended at 19-21 weeks.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONE WAS OF LOW QUALITY

Recommendation 3

In twin pregnancies, it is not recommended to measure routinely the cervical length cervicometry for risk prevention of preterm delivery.

Note: The panel believes that, although twin pregnancies are at increased risk of preterm birth, there is currently no evidence that such implementation can translate into effective preventative strategies to reduce preterm delivery and that it therefore is associated with

health improvement in women and children. The panel believes that the clinical data currently available on preterm delivery prevention in twin pregnancies are not sufficient to justify using resources to implement this screening universally.

Recommendations for research: the panel recommends the implementation of clinical studies on this topic.

- NEGATIVE CONDITIONAL RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE WAS LOW QUALITY

Recommendation 4

In patients with singleton pregnancies at high-risk for premature delivery, measurements of the cervical length starting from 16-18 weeks are recommended.

- POSITIVE CONDITIONAL RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE WAS LOW QUALITY

Recommendation 5

Ultrasound measurement of the cervix is recommended in patients >24 weeks with symptoms of preterm delivery.

The panel highlights the role of this method in choosing the most appropriate clinical management and optimization of resources.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, LOW QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

6. DOPPLER ULTRASONOGRAPHY IN OBSTETRICS

Recommendation 1

Doppler ultrasonography of the umbilical artery is not recommended for screening in the general population.

- STRONG NEGATIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

Recommendation 2

Doppler ultrasonography of the umbilical artery is recommended in the high-population for the identification of fetal growth restriction and for monitoring pregnancies complicated by fetal growth restriction.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

Recommendation 3a

Doppler ultrasonography of the uterine arteries in the first trimester can be used together with biochemical markers as part of a multi-parameter test for the screening of hypertensive disorders of pregnancy and fetal growth restriction in the general population.

Further studies evaluating possibilities of implementation in all regions, with particular attention to the costs and the benefits, are needed before such screening strategy is routinely implemented in the Italian population.

- POSITIVE CONDITIONAL RECOMMENDATION
- RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY AND A PRIMARY STUDY OF HIGH QUALITY

Doppler ultrasonography of the uterine arteries in the second trimester is not recommended for the screening of hypertensive disorders of the pregnancy and fetal growth restriction in low-risk women.

A strong association between a pathological Doppler ultrasonography of the uterine arteries in the second trimester and pre-eclampsia, however there is no evidence on the effectiveness of drugs or strategies for the prevention of pre-eclampsia and fetal growth restriction. On this basis, the panel does not recommend the implementation of the test in the second trimester in low-risk patients.

STRONG NEGATIVE RECOMMENDATION

IDENTIFY RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 4

Doppler ultrasonography of the uterine arteries in the first trimester can be used together with bio-chemical markers as part of a multi-parameter test for the screening of hypertensive disorders of the pregnancy and fetal growth restriction in a population at high-risk. According to the existing guidelines, maternal and obstetric history represent the first line screening for hypertensive disorders of the pregnancy and fetal growth restriction.

The panel emphasizes, however, that the multi-parameter test has a greater sensitivity and specificity than maternal and obstetric history and may help in identifying the best preventive strategy. The panel also highlights that further cost-effectiveness studies are needed to evaluate the applicability of such screening strategy before its routine implementation.

▶ POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON A HIGH QUALITY GUIDELINE AND A MODERATE QUALITY PRIMARY STUDY

Recommendation 5

Doppler ultrasonography of the uterine arteries in the second trimester is recommended for the prediction of pre-eclampsia and fetal growth restriction in high-risk patients.

Albeit in the absence of preventive strategies, the detection of changes of the Doppler ultrasonography in high-risk patients may allow clinical surveillance aimed and improve clinical outcomes.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 6

Doppler ultrasonography of the uterine arteries in the third trimester may be performed in patients with hypertensive disorders of pregnancy or fetal growth restriction.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES FOR INTRAUTERINE GROWTH RESTRICTION, ONLY ON PRIMARY STUDIES OF MODERATE QUALITY FOR HYPERTENSIVE DISORDERS OF PREGNANCY

Recommendation 7

Doppler ultrasonography of the middle cerebral artery is recommended in pregnancies complicated by fetal growth restriction.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON A HIGH OR MODERATE QUALITY GUIDELINE AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Doppler ultrasonography of the middle cerebral artery is recommended in pregnancies at risk for fetal anemia.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON A LOW QUALITY GUIDELINE

Recommendation 9

Doppler ultrasonography of the ductus venosus is recommended in pregnancies complicated by fetal growth restriction <32 weeks.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A HIGH QUALITY PRIMARY STUDY

7. ULTRASOUND IN THE DELIVERY ROOM

Recommendation 1

Routine ultrasound is not recommended to improve delivery outcomes in active labour.

- STRONG NEGATIVE RECOMMENDATION
- RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES

Recommendation 2

It is recommended that ultrasound should not be routinely performed to improve delivery outcomes in all women with stage I labour extension/arrest.

Note: The lack of available data does not allow for a positive recommendation to be made in any case for the use of ultrasound in stage I labour extension/arrest. However, if the delivery room is equipped with an ultrasound system and healthcare workers are specifically trained in the use of ultrasound during labour, its execution can help the clinician in the management of labour and in the formulation of a prognosis for delivery.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies on the use of ultrasound in the delivery room and enhancing the specific training of doctors and midwives working in the delivery room.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES

Recommendation 3

It is recommended that ultrasound should not be routinely performed to improve delivery outcomes in all women with stage II labour extension/arrest.

Note: However, data are scarce and therefore do not allow for a positive recommendation to be made on the use of ultrasound to improve delivery outcomes in the case of a prolonged stage II labour. Its execution can be of assistance to the clinician, both for greater accuracy in defining fetal position and station, and in formulating a prognosis for delivery in cases where the delivery room is equipped with an ultrasound system and healthcare workers are specifically trained in the use of ultrasound during labour.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies on the use of ultrasound in the delivery room and enhancing the specific training of doctors and midwives working in the delivery room.

- NEGATIVE CONDITIONAL RECOMMENDATION
- RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND SYSTEM-ATIC REVIEWS AND LOW QUALITY PRIMARY STUDIES

In women in stage II of labour where indication is given for an operative delivery, the panel suggests performing an ultrasound check when the operator is unsure of the position of the fetal occiput after clinical evaluation and there are no emergency conditions.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies and enhancing the training of doctors and midwives working in the delivery room for a broader use of ultrasound in the delivery room.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND MODER-ATE QUALITY PRIMARY STUDIES

Recommendation 5

Routine ultrasound evaluation to improve outcomes is not recommended in women with bleeding after vaginal delivery.

- STRONG NEGATIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND MODERATE QUALITY PRIMARY STUDIES

8. ULTRASOUND IN GYNAECOLOGY

Recommendation 1

Transvaginal ultrasound is recommended in all cases of pelvic pain as it allows for a differential diagnosis and adequate management.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH OR MODERATE QUALITY GUIDELINES

Recommendation 2

A pelvic ultrasound is recommended in women with abnormal uterine bleeding, both in fertile and postmenopausal age, because: it allows for a differential diagnosis, it identifies patients at high-risk for endometrial cancer and contributes to appropriate management.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH OR MODERATE QUALITY GUIDELINES

Recommendation 3

The panel recommends the use of transvaginal and possibly transabdominal ultrasound as the first choice imaging method in women with an adnexal mass.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 4

In asymptomatic women on hormone replacement therapy, the panel suggests that routine transvaginal ultrasound should not be performed.

Note: However, the panel believes that, although there is no evidence in the literature of the usefulness of ultrasound during hormone replacement therapy, such an examination may be recommended as a baseline assessment prior to the initiation of hormone replacement therapy and suggests that a periodic assessment may lead to a better customization of dosages and treatment plans.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Routine transvaginal ultrasound is not indicated in the general asymptomatic population. **Note:** While highlighting that there are no elements in the literature in favour of routine ultrasound examinations, the panel notes that the use of gynaecological ultrasound is very widespread as a complementary assessment to a gynaecological examination.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 6

In the asymptomatic hereditary cancer risk population (BRCA1 and 2; mutations of genes involved in DNA mismatch repair [MMR] with diagnosis of Lynch syndrome II) the panel recommends performing prophylactic surgery. However, ultrasound monitoring may be considered in women aged 30-35 onwards only if the patient does not accept surgery or wishes to postpone the surgical procedure. The literature does not define the exact time interval, the panel suggests an ultrasound every 6 months associated with CA125 testing.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

9. POINT OF CARE ULTRASOUND

Recommendation 1

A point of care ultrasound is recommended in emergency/urgent cases in order to facilitate the identification of some medical conditions and to reduce the length of stay in hospital. POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON LOW QUALITY PRIMARY STUDIES AND SYSTEM-ATIC REVIEWS

Recommendation 2

When the gynaecological examination does not allow a satisfactory clinical assessment, the use of a complementary ultrasound to improve the outcomes that are important to women is not supported by evidence. However, the panel of experts believes that a complementary ultrasound by trained gynecologists may reduce the need for further instrumental examinations and should therefore be considered.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF LOW QUALITY

Recommendation 3

The panel recommends ultrasound assessment of the single deepest amniotic fluid pool as part of the clinical monitoring of post-term pregnancies.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF LOW QUALITY

Recommendation 4

Ultrasound examination is recommended to assess fetal presentation in doubtful cases or when breech presentation is suspected at the obstetric examination carried out at the admission or in advanced third trimester.

- POSITIVE CONDITIONAL RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

The panel opinion is that in all cases of difficult identification of the fetal heart beat by the use of cardiotocography, the ultrasound evaluation can help in identifying the correct positioning of the cardiotocographic sensor on the maternal abdomen, and allows for a rapid and accurate evaluation of the fetal heart rate. This recommendation is based on the opinion of the panel as there is no scientific evidence available on this issue.

POSITIVE CONDITIONAL RECOMMENDATION

▶ QUALITY OF SCIENTIFIC EVIDENCE: THERE IS NO SCIENTIFIC EVIDENCE

Recommendation 6

In women with antenatal bleeding in the third trimester an ultrasound assessment of placental localization can be performed as a POCUS in the when an adequately trained obstetrical medical staff is not available for a diagnostic ultrasound. This recommendation is based on the panel's opinion that this ultrasound cannot be classified as a POCUS.

POSITIVE CONDITIONAL RECOMMENDATION

▶ QUALITY OF SCIENTIFIC EVIDENCE: THERE IS NO SCIENTIFIC EVIDENCE

10. REFERRAL SCAN

Recommendation 1

In all women with at least one significant maternal or fetal risk factor for congenital fetal malformations, a referral scan is recommended for the detailed evaluation of the fetal anatomy. STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Recommendation 2

In all women with at least one significant maternal or fetal risk factor for congenital fetal heart disease, fetal echocardiography is recommended to improve pregnancy outcomes.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND ONLY ONE OF MODERATE QUALITY, AND SYSTEMATIC REVIEWS AND PRIMARY STUDIES OF MODERATE QUALITY

RECOMMENDATIONS, LITERATURE ANALYSIS AND EVIDENCE INTERPRETATION

1. FIRST TRIMESTER ULTRASOUND

Introduction

Ultrasound in the early stages of pregnancy has been part of a gynaecologist's clinical knowledge for many years. The technological evolution of ultrasound equipment and the implementation of prenatal screening by means of different assessments, including nuchal translucency, has broadened its potential for clinical use.

The protocol for performing this examination is dependent on the gestational age (in weeks) during the first trimester at which it is performed and is different whether it applies to a screening examination or to a more in-depth one for abnormalities found at screening. The protocol for carrying out the examination is part of the Supplement proposed by SIEOG.

Recommendations

Question 1

Is it useful to perform an ultrasound examination in the first trimester for all pregnancies?

Recommendation 1

It is recommended to offer a screening ultrasound to all pregnant women during the first trimester.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Literature Analysis and Evidence Interpretation

Evidence from the literature demonstrates that ultrasound is the most accurate method for predicting gestational age, compared to the last menstrual period. The delivery date estimate based on the last menstrual period is subject to significant error and may be affected by maternal age, parity, body mass index and possible smoking habit (NICE, 2019a).

The crown-rump length should be used for accurate dating of pregnancy with ultrasound: if this measurement is greater than 84 mm, the gestational age should be calculated by measuring the head circumference (ISUOG, 2013; NICE, 2019a; Australian Government - Department of Health - **Recommendation Level B**).

The screening ultrasound for the first trimester should be performed between 10+0 and 13+6 weeks of gestation in order to establish the correct pregnancy dating (NICE, 2019a). This gestational age range partly overlaps with that for assessing the thickness of nuchal translucency as part of screening tests for fetal chromosomal abnormalities (11+0 weeks to 13 weeks 6 days), this may allow some women to perform both assessments with a single ultrasound examination.

Accurate pregnancy dating allows a reduction of labour inductions in post-term pregnancy (NICE, 2019a) and allows for better management of certain pathological conditions such as preterm delivery, pre-eclampsia and fetal growth restriction (WHO, 2016).

Performing screening ultrasound in the first trimester to all pregnant women allows the early detection of multiple pregnancies, and a more accurate programming of second-trimester screening ultrasound (NICE, 2019a; WHO, 2016).

Question 2

If the woman wants to perform a screening test for aneuploidies, is it useful to offer first trimester ultrasound in accordance with a pre-defined protocol?

Recommendation 2

For women wishing to perform a screening test for fetal aneuploidies, it is recommended to apply a pre-defined protocol for performing the first trimester ultrasound.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Literature Analysis and Evidence Interpretation

Screening tests for fetal aneuploid should be offered to all pregnant women regardless of age, after careful informational counselling (IIA Recommendation Level) (SOGC, 2017). The screening test for fetal aneuploidies in the first trimester should include the measurement of nuchal translucency and maternal serum biochemistry of free beta human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) (Recommendation level II-2B) (SOGC, 2017; ISUOG, 2013; RCOG 2016; RANZCOG, 2018; ISS, 2014). The examination should be carried out at a gestational age ranging from 11+0-13+6 weeks (ISUOG; SOCG) and for fetal crown-rump length (CRL) values ranging from 45 to 84 mm.

Applying a defined protocol for the evaluation of nuchal translucency by experienced operators who have undergone appropriate training is an essential criterion for including nuchal translucency in the risk assessment for fetal aneuploidies (Recommendation Level II-2A) (SOGC, 2017; ISUOG, 2013).

The addition of other biomarkers, such as the evaluation of fetal nasal bone, tricuspid valve regurgitation and ductus venosus flow, can be considered according to the experience of the operator and the internal clinical protocols of the facility where the screening test is performed (ISUOG, 2013).

The use of maternal age alone as a risk factor for fetal aneuploidies is an inaccurate indicator that should not be used as a criterion for access to invasive prenatal diagnosis when a prenatal screening test can be offered (Recommendation Level II-2D) (SOGC, 2017; ISS, 2014).

Regardless of the screening test result, it is recommended that the presence of nuchal translucency \geq 3.5 mm should be considered a marker for chromosomal abnormalities and structural defects. This should entail the offer of genetic counselling and an invasive prenatal diagnosis procedure with chromosomal microarray analysis, and an obstetric referral scan in the second trimester (Recommendation Level II-2A) (SOGC, 2017).

The application of a pre-defined protocol for performing ultrasound in the first trimester affects: the number of invasive tests to be performed in the pregnant population; the rate of diagnosed aneuploidies and, indirectly, the rate of fetal loss due to invasive procedures. Women's anxiety is reduced by the systematic application of an effective screening program, and it is hypothesized that offering a qualitatively controlled test will reduce it further, even if there is no scientific evidence to demonstrate this.

Question 3

If the woman wants to perform a screening test for aneuploidies that includes the measurement of nuchal translucency, is a quality control program of the procedure useful?

Recommendation 3

A quality control program for the measurement of nuchal translucency is recommended as this increases the accuracy of screening tests for aneuploidies.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF LOW QUALITY

Literature Analysis and Evidence Interpretation

The healthcare professional who performs screening in the first trimester with nuchal translucency must comply with the specific ultrasound protocol for the investigation he/she is undertaking. Reliable and reproducible measurement of nuchal translucency requires appropriate training. All ultrasound operators that measure nuchal translucency should be certified (RANZCOG, 2018; SOGC, 2017) and all women, regardless of their age, should have access to high-quality screening for common trisomies. Even if a woman does not wish to be screened for common trisomies by choice, she must be offered an ultrasound assessment at 11th-14th weeks that includes the early study of fetal anatomy and nuchal translucency (SOGC, 2017).

Operators who also assess additional markers (nasal bone, tricuspid, ductus venosus) should in any case receive specific training and be certified to perform such a investigations (RANZCOG, 2018).

In order to ensure this, there are annual education, accreditation and audit programs. Indeed, many countries have established certified operator registers and rigorous audit programs, which should be considered essential for all operators participating in these screening programs (ISUOG, 2013).

In summary, the operator who performs the first trimester ultrasound screening examination must:

- 1) have received specific training (ISUOG, 2013; RANZCOG, 2018);
- participate in ongoing education activities to keep up-to-date with the development of screening options and procedures, as well as possible implementation strategies (ISUOG, 2013; RANZCOG, 2018);
- 3) participate in quality control programs (audits) (ISUOG, 2013);
- 4) be able to offer adequate information and counselling before and after the examination (RANZCOG, 2018), as well as provide assistance via appropriate programs in case of pathological or suspect findings (ISUOG, 2013; RANZCOG, 2018).

These recommendations represent an international benchmark for first-trimester ultrasound. If the examination cannot be performed in accordance with these recommendations, it is appropriate to document the reasons why and refer these women elsewhere, minimizing the amount of time that could prevent them from undergoing the screening examination and possibly increase maternal anxiety (ISUOG, 2013).

A "quality control" of the ultrasound examination affects: the number of invasive tests that are performed in the pregnant population, the rate of diagnosed aneuploidies and, indirectly, the rate of fetal loss due to invasive procedures. Women's anxiety is reduced by the systematic application of an effective screening program, and it is assumed that providing a qualitatively controlled examination will reduce it further, even if there is no scientific evidence in this regard.

Question 4

In pregnancies with first trimester screening tests at high-risk for aneuploidies, is it useful to evaluate fetal anatomy in accordance with a predefined protocol?

Recommendation 4

A pre-defined protocol is recommended for evaluating fetal anatomy as this may help recognize fetal structural abnormalities in the first trimester.

This investigative protocol is differentiated between the general population and high-risk aneuploidy pregnancies.

The possibility of applying this protocol in the first trimester may be limited by technical factors.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

In a recent meta-analysis of 19 cohort studies (Karim et al., 2017) on a total of 115,731 unselected fetuses (general population screening) with an incidence of 1% for structural abnormalities (single or multiple), a sensitivity of 32% (95% CI 22.45-43.12%) was found for fetal anomalies in general during the first trimester ultrasound and 45% (95% CI 38.44-52.14%) for major fetal anomalies. Data from 6 studies in high-risk populations (2,841 fetuses with an incidence of anomalies of 6.5%) found a doubled first-trimester ultrasound sensitivity for all anomalies (61.18%; 95% CI 37.71-82.19%) (Karim et al., 2017). The use of a standardized protocol for the study of fetal anatomy in the first trimester was found to be the factor most associated with the sensitivity of the examination (p<0.0001), with a tendency to increase sensitivity of diagnosing fetal structural abnormalities with a first trimester ultrasound may be limited by factors such as maternal obesity, the presence of myomas, retroverted uterus, and gestational age at the time of examination (Karim et al., 2017). The second trimester screening ultrasound is more accurate and is the recommended screening ultrasound examination in order to find fetal structural anomalies.

Every woman has the right to know about the possibility of screening for different fetal diseases and must be informed in detail (NICE, 2019a). In all cases, it is recommended that the woman who undergoes the prenatal screening process should be adequately informed of: the objectives and methods of screening, the possibilities of false positives and false negatives, and the available diagnostic tests, so that she can make a decision on whether or not to perform the screening test being offered. It is therefore recommended that the informed consent principle be utilized as enshrined by Law no. 219/2017.

Despite the qualitative evidence demonstrating women's satisfaction in relation to receiving information during screening and their willingness to undergo tests for different pathologies, they are not always aware of the anxiety that may be generated by an abnormal or suspect finding (WHO, 2016). In a systematic review (Lou et al., 2015) of studies using quantitative and validated measures to quantify the levels of anxiety (STAI: Spielberger's State-Trait Anxiety Inventory) in pregnant women in relation to screening for Down Syndrome (with 7 out of 383 studies meeting PICO and inclusion criteria), a reduction in anxiety was demonstrated if screening results were negative and vice versa, a significant increase in anxiety was found in parturients who received an increased risk outcome. Since in screening for common trisomies with combined testing, the majority of high-risk tests are false positives, screening increases anxiety in about 5% of the population with a euploid fetus. However, the same study shows a reduction in anxiety after a normal diagnostic test result; it returns to the same levels as the negative screening population. Therefore, no association between screening and residual anxiety has been demonstrated.

There are no studies that show an increase in maternal morbidity, other than the psychological risks related to ultrasound examination. On the other hand, a diagnosis carried out close to the deadline for possible termination of pregnancy may adversely affect the option of termination itself, as the time to understand and process the information received is very limited, as opposed to a possible early diagnosis.

Question 5

In the first trimester of pregnancy, what is the accuracy of ultrasound in diagnosing ectopic pregnancy?

Recommendation 5

In symptomatic pregnant women of <13 weeks with pelvic pain or vaginal blood loss, and those with non-diagnostic ultrasound or pregnancy of unknown location, a transvaginal ultrasound is recommended. It is considered the diagnostic tool of choice for the diagnosis of ectopic tubal pregnancy with a sensitivity of 87-99% and a specificity of 94-99.9%.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

It should be noted that the 2019 NICE Guidelines cite the previous RCOG 2016 Guidelines in which the evaluation of evidence attributed to the EBM system did not show evidence levels of Grade A or B for any of the proposed indications (cited again in NICE). Transvaginal ultrasound is considered to be the diagnostic tool of choice for the diagnosis of ectopic tubal pregnancy with a sensitivity of 87-99% and a specificity of 94-99.9% (RCOG, 2016).

However, the following recommendations are reported with regard to the possibility of diagnosing ectopic tubal pregnancy. In detail, during transvaginal ultrasound they consider:

- indicative signs of diagnosis: the presence of an adnexal mass, separate from the ovary, containing a gestational sac with the yolk sac inside, or an adnexal mass, separate from the ovary, containing a gestational sac with a fetal pole inside (with or without cardiac activity);
- 2) the probability of ectopic tubal pregnancy when an adnexal mass, separate from the ovary, containing an empty gestational sac (sometimes described as a "tubal ring sign" or "bagel sign") is detected, or when a complex and inhomogeneous adnexal mass, separate from the ovary is detected;
- suspected signs of an empty uterus, or fluid collection within the uterine cavity (sometimes described as a pseudogestational sac);

4) a moderate to large amount of free fluid in the peritoneal cavity or pouch of Douglas, may represent a hemoperitoneum and demonstrates the usefulness of assessing the following before making a diagnosis: the ultrasound characteristics of the uterus and its adenxa, the clinical presentation of the woman and serum hCG levels.

It is important to scan both the uterus and its adenxa to exclude heterotopic pregnancy, and to consider the possibility that a pregnancy with unknown location may be an ectopic pregnancy until the location of pregnancy is determined. Greater importance should be given to clinical symptoms rather than to serum hCG levels. In addition, regardless of serum hCG levels, women with an unknown pregnancy location should be provided with written information on what to do if they experience new or worsening symptoms.

In cases where an ultrasound does not give a certain diagnosis, NICE also gives precise indications with reference to the use of hCG levels for diagnosis.

Specifically:

- 1) 2 measurements of serum hCG should be taken as close to 48 hours apart (but not earlier) as possible to determine the subsequent management of a pregnancy with unknown location;
- 2) if there is an increase in serum hCG of more than 63% after 48 hours: there is likely to be an evolving intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded); however, transvaginal ultrasound should be offered to determine the pregnancy location between 7 and 14 days later. This assessment may be anticipated in women with serum hCG concentrations greater than or equal to 1,500 IU/litre;
- **3)** a decrease in serum hCG by more than 50% after 48 hours indicates that pregnancy is unlikely to continue, but the recommendation is to prescribe a urine pregnancy test 14 days after the second serum hCG test and to explain that:
 - (a) if the test is negative, no further action is necessary;
 - (b) if the test is positive, it must be re-evaluated in the short term;
- **4)** a decrease in serum hCG of less than 50% or an increase of less than 63% requires short-term clinical re-evaluation.

The criteria for an ultrasound diagnosis of caesarean scar pregnancy, interstitial pregnancy, cornual pregnancy and abdominal pregnancy have also been proposed in the RCOG Guidelines, which are given below.

Caesarean scar pregnancy:

- empty uterine cavity;
- gestational sac or solid trophoblast mass situated at the scar site of a previous caesarean section on the lower uterine segment;
- thin or absent myometrium between the gestational sac and bladder;
- evidence of prominent trophoblastic/placental circulation at Doppler examination;
- empty endocervical canal.

Interstitial pregnancy:

- empty uterine cavity;
- products of conception/gestational sac located laterally in the interstitial part (intramural) of the fallopian tube and surrounded by less than 5 mm of myometrium in all scan planes;
- the "interstitial line" sign, i.e. a thin echogenic line extending from the uterine cavity to the periphery of the interstitial mass.

Cornual pregnancy:

- visualization of a single interstitial portion of the fallopian tube in the main uterine body;
- a gestational sac/mobile products of conception, separate from the uterus and surrounded completely by myometrium;
- presence of a vascular pedicle connecting the gestational sac to the unicornuate uterus.

Abdominal pregnancy:

- empty uterine cavity;
- absence of both a dilated tube and a complex adnexal mass;
- gestational sac surrounded by intestinal loops and separated from them by the peritoneum;
- mobile and floating gestational sac, particularly evident with the pressure of the transvaginal probe toward the posterior cul-de-sac.

There are no specifically recognized criteria for the ultrasound diagnosis of ovarian ectopic pregnancy.

Question 6

In the first trimester of pregnancy, what is the accuracy of ultrasound in diagnosing spontaneous miscarriage?

Recommendation 6

In case of vaginal blood loss or pain in pregnant women of <13 weeks, or with non-diagnostic ultrasound or pregnancy with unknown location, it is recommended to inform the woman of the accuracy limitations of diagnosing spontaneous miscarriage with a single ultrasound, particularly at early gestational ages.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

The NICE 2019b Guidelines recommend that in case of non-visualization of the embryo heart beat, the crown-rump length should be measured, and if the embryo/fetal pole is not visible the average diameter of the gestational sac should be measured only.

If the crown-rump length is less than 7.0 mm with transvaginal ultrasound and no heart beat is visible, or the average diameter of the gestational sac is less than 25.0 mm with transvaginal ultrasound and no visible embryo/fetal pole is present, the recommendation is to perform a second ultrasound at a minimum interval of 7 days from the first.

Diagnosis of internal abortion can be made if:

- cardiac activity in an embryo with a crown-rump length of 7.0 mm or more is not seen on transvaginal ultrasound, or
- cardiac activity is not seen in an embryo with a crown-rump length of 10.0 mm or more on transabdominal ultrasound, or
- the embryo is not seen in a gestational sac with an average diameter of 25.0 mm or more.

The panel of experts considered the fact that in Italy ultrasound examinations (with the only exception of certain scans to support the clinical assessment) are carried out by medical doctors and not by non-medical operators as in the United Kingdom. Therefore, the need to have the diagnosis confirmed by a second operator in case of missed miscarriage, as suggested by NICE, is not considered applicable to the Italian healthcare context.

According to the indications given by NICE (2019b), a diagnosis of complete miscarriage can be made if no trophoblastic tissue is detected within the uterine cavity in a patient in which a previous ultrasound examination had demonstrated the presence of an intrauterine gestational sac. In the absence of a previously well-documented ultrasound, the pregnancy should be described as pregnancy with unknown location. These women should be offered follow up (hCG, ultrasound) until a definitive diagnosis is achieved.

In patients in which a previous ultrasound examination demonstrated the presence of an intrauterine gestational sac, a diagnosis of incomplete miscarriage can be made if well-defined hyperechogenic echoes are present within the uterine cavity, which can be traced back to trophoblastic tissue, often with evidence of vascularization (not clots, which are poorly defined and avascular).

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2. SECOND TRIMESTER ULTRASOUND

Introduction

Obstetric ultrasound in the second trimester are currently offered as a screening test to the entire pregnant population. It is important to remember that the purpose of a screening examination is to identify, in a population of apparently healthy subjects, those who are at risk of pathological conditions in order to offer them precise diagnoses and suitable treatment methods.

In the case of prenatal screening tests, in which the second-trimester ultrasound can be included, the main aim is to provide women with complete information and, if necessary, to send them for a referral scan, in order to provide appropriate material for an informed decision on the possibilities of treatment.

The screening examination must therefore be clearly distinguished from the diagnostic examination, which has the fundamental purpose of excluding or diagnosing a certain pathological condition.

As with any screening examination, the second trimester screening ultrasound, even if it is carried out in accordance with appropriate protocols, it is inevitably burdened by false positives and negatives. In addition to causing severe mental conditions such as anxiety, sadness, etc., false positives also have an impact on healthcare organization which must make in-depth diagnostic tests available; as far as false negatives are concerned, they are the cause of missed diagnoses or diagnostic delays of relevant pathological conditions and can be followed up by legal medical disputes, which in turn only increase the direct and indirect costs of a screening program.

The screening ultrasound examination in the second trimester, like all screening methods, should be based on its functioning on the best available scientific evidence, on a rigorous feasibility assessment, on a balance between costs and benefits, on the threshold of sensitivity and specificity, on positive and negative predictive values, as well as on the identification and availability of diagnostic procedures that should follow the screening test if a condition needs to be investigated further. It is necessary to establish ways of monitoring and ensuring the quality of the screening ultrasound examination offered to allow for regular evaluations of the functioning of the screening program within established parameters. The verification and quality assurance of a screening examination/program is the process of verifying its compliance with national standards, which helps to ensure the safety and effectiveness of a screening program and encourages continuous improvements.

Recommendations

Question 1

Is it useful to perform a 19-21-week fetal biometry ultrasound in the general pregnant population to improve maternal and fetal outcomes?

Recommendation 1

Assessment of fetal biometry is recommended for all women in order to improve pregnancy outcomes during the second trimester screening examination.

In the event that an ultrasound has not been performed in the first trimester, it is recommended that pregnancy dating be carried out during the second trimester screening ultrasound. STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

WHO high quality Guidelines (2016) recommend that ultrasound imaging should be performed in all women within the first 24 weeks in order to obtain correct pregnancy dating as this has a large impact on the management of the subsequent stages of pregnancy itself.

A 2015 Cochrane systematic review analysed the results of 8 studies, for a total of 25,516 patients, and demonstrated a significant benefit in terms of reducing post-term delivery inductions in the patient group subjected to ultrasound at \leq 24 weeks compared to those not offered this ultrasound assessment (mean RR of 0.59 [CI 0.42-0.83]).

The Australian Government produced high quality guidelines in 2019 that reported that, although ultrasound determination of gestational age is more accurate when carried out in the first trimester, in view of the fact that some pregnant women perform their first ultrasound evaluation at more advanced gestational ages, it is recommended in these cases to estimate the gestational age during the second trimester ultrasound. These guidelines also recommend that all pregnant women should be offered a screening ultrasound examination in the second trimester to assess not only fetal anatomy but also fetal development.

The 2015 Guidelines of the French College of Gynaecologists and Obstetricians suggest that fetal biometry should be interpreted with regard to the pregnancy's clinical context.

As recommended by the 2013 SOGC Guidelines in cases where a fetal growth restriction is suspected, the patient should undergo further assessments and be sent to a Specialist Centre for a 19-23-week velocimetry Doppler assessment of the uterine arteries.

A recent meta-analysis (D'Ambrosio, 2019) reported the result of 6 studies including 3,078 cases of fetuses with short femur (study group) and 222,303 fetuses with normal femur (control group). Analysis of the data showed that a femur length below the 5th centile or of -2 standard deviations is associated with a high incidence of unfavourable perinatal outcomes compared to the control population: low birth weight (22.1% vs 8.57%), Apgar score <7 at 5 minutes (3.9% vs 1.79%), preterm delivery (12.16% vs 8.16%), intrauterine death (1.83% vs 0.44%), and need for hospitalization in neonatal intensive care units (15.3% vs 14.8%).

Question 2

Is it useful to study fetal anatomy at 19-21 weeks gestational age in the general population of pregnant women in accordance with a pre-defined protocol?

Recommendation 2

Evaluation of fetal anatomy in accordance with a pre-defined protocol for the detection of major fetal malformations is recommended for all women during the second trimester pregnancy screening examination.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

Two high-quality Guidelines, those of the WHO (2016) and those of the Australian Government (2019), recommend to perform a routine ultrasound second trimester for all pregnancies women in order to improve prenatal detection rate of congenital fetal malformations. The prevalence of congenital malformations in the general population reported in academic literature is of 2.09% (ranging from 0.76% to 2.45%), including major and minor malformations. This percentage is in line with Italian data on the prevalence of malformations obtained from EUROCAT (European Surveillance of Congenital Anomalies and Twins) https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en reported in Tables 1 and 2.

There is no evidence in the literature regarding the real impact of the second trimester screening ultrasound on the detection rate of congenital fetal anomalies.

However, a 2015 Cochrane systematic review included in its primary outcomes the detection rate of congenital abnormalities prior to 24 weeks in women who underwent screening and those who remained unscreened. The results of the 2 trials reported a total of 17,158 pregnancies with 387 fetal abnormalities, most of which (346 = 89%) were not detected within 24 weeks. However, it was more likely for the second trimester screening group to receive a prenatal diagnosis than the unscreened group of women (16% *versus* 4%; RR 3.46 [Cl 1.67-7.14]).

Data analysis of the two trials in the 2015 Cochrane review reveals another important concept: the 1990 Helsinki trial recorded a considerable difference in the detection rate percentages between the two diagnostic Centres involved in the study. This highlighted how the difference in operator expertise can have an impact on the performance and effectiveness of the screening program, highlighting the need for training, quality control and audit programs. This is why the 2018 RANZCOG Guidelines recommend that operators involved in second trimester screening undergo appropriate training and ongoing professional development in this field of interest.

However, the two trials in the 2015 Cochrane review date back to the 1990s and therefore do not take into account the improvement of ultrasound equipment or the increase in operator expertise in carrying out second trimester screening ultrasound, and this has undoubtedly taken place in recent years.

In order to get the most up-to-date data, Italian data was extracted from EUROCAT (Tables 3, 4) on the percentage of cases with congenital anomalies reported in the prenatal period between 2014 and 2018, on all cases of children who received a diagnosis of congenital anomaly within the first year of life.

Meta-analyses conducted to verify the ability of the screening ultrasound to detect fetal malformations are not available for all apparatuses. However, a recent meta-analysis (Van Velzen et al., 2017) carried out on studies with an unselected population, aimed at determining the detection rate of cardiac malformations showed a difference in the percentage of cardiac defects diagnosed in the prenatal period, depending on the type of malformation: a higher rate of prenatal diagnosis (85%) was reported in cases of univentricular and heterotaxy heart disease and a lower rate in cases of aortic coarctation, transposition of the great vessels and ventricular septal defects. Table 5 shows the prenatal detection rate for a single heart defect. The meta-analysis also reports that prenatal detection rate of heart defects shows a strong correlation with the severity of the heart defect and that the detection rate of conotruncal heart diseases still has room for improvement.

A Cochrane 2015 review also analysed the impact of performing ultrasound before 24 weeks on perinatal mortality among the primary outcomes. Data from these 10 studies, which included 35,735 participants, did not show a significant difference between the screened women and the control group in terms of perinatal mortality (0.73% *versus* 0.82%; RR 0.89; 95% CI 0.70-1.12).

Table 1

Prevalence per 10,000 pregnancies. All anomalies - from 2014 to 2018 Emilia-Romagna, Milan Area, Tuscany, Campania, North East Italy, Sicily (Italy)

Type of anomalies	Includes genetic anomalies	Excludes genetic anomalies	
Years Average years 2014-2018		Average years 2014-2018	
(range)		(range)	
All cases 258.14		216.71	
(235.9-275.1)		(211.62-226.57)	
Born alive 209.00		195.25	
(194.21-225.62)		(191.1-206.09)	
ТОР	47.98 (39.93-56.97)	20.70 (19.33-22.17)	
FID/SA	1.15 (0.84-1.76)	0.75 (0.44-1.58)	

From https://eu-rd-platform.jrc.ec.europa.eu/eurocat-eurocat-data/prevalence/ accessed on 10/1/2021 Uploaded on 10/12/2019.

TOP: Termination of pregnancy due to fetal anomalies; FID: Fetal intrauterine deaths; SA: Spontaneous abortions from 20 weeks of pregnancy.

Table 2

Prevalence per 10,000 pregnancies per congenital group of abnormalities. From 2014 to 2018 - Emilia-Romagna, Area of Milan, Tuscany, Campania, North East Italy, Sicily (Italy) - includes genetic anomalies

Type of anomalies	CNS	CHDs	CL/P	GI	Abdominal wall defects	Urinary	Limbs
Years	Mean	Mean	Mean	Mean	Mean	Mean	Mean
	2014-2018	2014-2018	2014-2018	2014-2018	2014-2018	2014-2018	2014-2018
	(range)	(range)	(range)	(range)	(range)	(range)	(range)
All cases	5.61	94.63	6.37	16.92	3.67	31	31
	(4.2-7.56)	(92.33-98.34)	(4.72-8.09)	(12.84-18.91)	(2.64-4.54)	(29.2-33.09)	(29.2-31.64)
Born alive	0.99	86.34	5.54	15.65	1.69	27.65	27.65
	(0.74-1)	(83.92-90.95)	(3.91-7.25)	(12.14-17.86)	(0.88-2.1)	(26.02-29.94)	(26.02-29.94)
ТОР	4.41	7.82	0.77	1.17	1.96	3.28	3.28
	(3.1-5.81)	(6.3-10.29)	(0.65-0.88)	(0.7-1.73)	(1.74-2.43)	(2.81-3.15)	(2.81-3.58)
FID/SA	0.22	0.46	0.05	0.09	0.02	0.06	0.11
	(0-0.88)	(0.35-0.58)	(0-0.18)	(0-0.23)	(0-0.11)	(0-0.12)	(0-0.12)

From https://eu-rd-platform.jrc.ec.europa.eu/eurocat-eurocat-data/prevalence/ accessed on 10/1/2021 Data uploaded 10/1212019

TOP: Termination of pregnancy due to fetal anomalies; FID: Fetal intrauterine deaths; SA: Spontaneous abortions from 20 weeks of pregnancy. CNS: Central nervous system (includes neural tube defects, hydrocephaly, microcephaly, holoprosencephaly). CHDs: Congenital heart diseases (includes all major heart diseases + interventricular defects + interatrial defects + patent ductus arteriosus in full-term births). CL/P (cleft lips with or without palate involvement). GI: Gastro-intestinal abnormalities (includes oesophageal atresia, intestinal stenosis/atresias, anus-rectal atresia, Hirschsprung's disease, bile duct atresia, annular pancreas, diaphragmatic hernia). Urinary tract (includes bilateral renal agenesis, multicystic kidney, hydronephrosis, bladder exstrophy, posterior urethral valves, Prune Belly). Limbs (includes club foot, limb reduction, syndactyly, polydactyly, hip dysplasia).

Table 3

Percentage of congenital anomalies diagnosed in the prenatal period. All the anomalies - from 2014 to 2018 - Emilia-Romagna, Area of Milan, Tuscany (Italy). Excludes genetic anomalies

Regions	Total number of cases	Number of cases diag- nosed in the prenatal period	Percentage of all cases (95% CI)	
Tuscany	2,301	950	41.29% (39.29%-43.31%)	
Milan area	Milan area 2,677		31.83% (30.09%-33.62%)	
Emilia-Romagna	nagna 4,165 1,146		27.52% (26.18%-28.89%)	
All Italian data	talian data 9,143 2,948		32%	

From https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prenatal-screening-and-diagnosis_en acessed on 25/1/2021. Uploaded on 21/01/2021

Table 4Percentage by type of congenital anomaly diagnosed in the prenatal period.From 2014 to 2018 - Emilia-Romagna, Area of Milan, Tuscany (Italy).Excludes genetic anomalies

Congenital anomalies	Total number of cases	No. of cases diagnosed in the prenatal period (% of total cases)
Anencephaly	75	72 (96%)
Spina bifida	117	101 (86%)
Hydrocephaly	113	90 (80%)
TGA	140	93 (66%)
HLHS	89	75 (84%)
Diaphragmatic hernia	103	67 (65%)
CL/P	259	152 (59%)
Omphalocele	73	56 (77%)
Gastroschisis	43	39 (91%)
Bilateral renal agenesis and Potter sequence	28	37 (96%)
Posterior Urethral Valve and Prune Belly	22	15 (68%)
Club foot	388	190 (49%)
Limb reduction	175	90 (51%)

From https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prenatal-screening-and-diagnosis_en acessed on 25/1/2021. Uploaded on 21/01/2021

N: Number. TGA: Transposition of the great arteries; HLHS: Hypoplastic left heart syndrome; CL/P: cleft lip with or without palate involvement.

Once lethal malformations were excluded, perinatal mortality rates were very similar between the 2 groups (0.53% vs 0.56%, RR 0.96%; CI 0.72-1.27). The low detection rate of malformations reported in the analysed studies is likely to affect perinatal mortality results. The 1990 Helsinki trial showed that an improvement in detection rate, with a consequent increase in pregnancy terminations, was associated with a reduction in perinatal mortality. Whereas the low detection rate reported by the 1993 RADIUS trial (only 17% of fetuses with malformations were detected in prenatally before 24 weeks) together with the 24-week limit for pregnancy termination produced a minimal impact on perinatal mortality, unlike the first study mentioned (Helsinki, 1990). Moreover, for some diseases, such as congenital heart diseases, their prenatal detection would appear to have an impact on the reduction of perinatal mortality of death prior to surgery was significantly lower in patients with critical congenital heart diseases that had been identified in prenatal age than in those with a post-natal diagnosis in whom the diagnosis of heart disease had occurred only after birth, for the same cardiac defect and with homogeneous risk factors (pooled odds ratio 0.26; 95% CI, 0.08-0.84).

Cochrane's 2015 systematic review of secondary outcomes analysed the impact of second-trimester ultrasound on the reduction of perinatal morbidity. There were no significant differences in terms of infants with low birth weight (<2.5 kg) (RR 1.04; 95% CI 0.82-1.33) or differences in Apgar scores 5 minutes after birth (RR 0.76; 95% CI 0.33-1.72) between the group of women undergoing ultrasound prior to 24 weeks and the group of women who had not undertaken it.

There are high-quality studies that show that women generally appreciate the information acquired during screening tests and are willing to perform screening tests to assess their specific risk for a variety of pathological conditions.

However, there is evidence that pregnant women are not always aware that ultrasound is a diagnostic tool and that abnormal findings may emerge during ultrasound examination, which may increase maternal anxiety and stress. Australian Guidelines reported that studies aimed at assessing potential maternal psychological benefits or risks related to ultrasound examination are not yet available (Australian Government - Department of Health, 2020). There is currently a clear lack of trials that have examined women's views on the screening ultrasound examination in the second trimester.

Although ultrasound examination is generally regarded as a non-harmful investigative methodology and is very popular among the pregnant population and their families, an important point reported in certain studies is an insufficient level of information regarding the purpose of the ultrasound examination. The Australian Government Guidelines underline the importance of counselling regarding the ultrasound examination in the second trimester and in particular the fact that it cannot reveal every fetal abnormality. In all cases, it is recommended that the women undergoing a prenatal screening test (and this also concerns the second trimester ultrasound examination) receives adequate information on the objectives and methods of screening, on the possibilities of false positives and false negatives, and on the available diagnostic tests, before making a decision regarding the planning and execution of the screening test offered (Australian Government - Department of Health, 2020; NICE, 2019).

Several Guidelines report that if a congenital abnormality is suspected during the second trimester screening ultrasound, the mother should be sent to a Specialist Centre to exclude or confirm fetal disease and if the abnormality is confirmed, the woman must be informed in detail about it so that she can potentially request access to pregnancy termination (RAN-ZCOG, 2018; NICE, 2019; Belgian Health Care, 2015).

Question 3

Is it useful to highlight so-called "soft markers" during the screening ultrasound examination at 19-21 weeks gestational age in order to improve maternal and fetal outcomes in the general population of pregnant women?

Recommendation 3

In order to carry out a screening for aneuploidies, searching for so-called "soft markers" is not recommended in the general population of pregnant women during the second trimester pregnancy screening examination.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

So-called soft markers that are detectable during the screening ultrasound examination of the second trimester are not fetal structural abnormalities, but findings of uncertain significance proposed in the 1980s for their correlation with the risk of aneuploidies, in particular trisomy 21, but also with trisomies 13 and 18, Turner's syndrome and triploidy. The list of these markers has been modified over the years and historically includes: isolated lateral ventriculomegaly, nasal bone absence or hypoplasia, thickening of the nuchal fold, hyperechogenic intracardiac focus, hyperechogenic bowel, pyelectasia and short femur length. The use of such markers was initially proposed in the population of high-risk women, and the appropriateness of their use in the population of low-risk women has always been heavily debated and has been considered by many as inappropriate for some time now (Smith-Bindman et al., 2001).

Currently, the nationwide use of the screening test for aneuploidies via the measurement of nuchal translucency and biochemical tests has shifted the risk calculation for these abnormalities predominantly to the first trimester of pregnancy, with the achievement of high sensitivity and a low percentage of false positives. To date, cfree DNA is increasingly being used on a large scale as an alternative or additional test to traditional screening tests. These screening methods have removed all rationale behind using "soft markers" in the second trimester for a calculation/recalculation of the risk of aneuploidies; their low positive predictive value and high rate of false positives in a population that is already being screened with much more powerful screening methods , means their main effect would be to increase maternal anxiety and the possible use of invasive procedures unjustifiably, with both increased social and fetal loss costs.

For these reasons, some high-quality Guidelines (NICE, 2019) state that the search for so-called soft markers should not be used to screen aneuploidies during the second trimester screening ultrasound.

Some of the ultrasound findings included in the previous list of soft markers are in fact useful conditions that should be reported during the second trimester ultrasound to select women at risk for pathologies other than aneuploidies, such as certain structural anomalies or fetal development anomalies as highlighted in a narrative review on the subject (Mi Sun et al., 2018). Therefore, detecting some of these ultrasound patterns should bring about dedicated diagnostic investigations and accurate ultrasound follow-up. Regarding this, meta-analyses are available on some of these ultrasound findings (for example regarding hyperechogenic bowel and short femur), which demonstrate the association of these findings with an unfavourable perinatal outcome (D'Ambrosio et al., 2019; D'Amico et al., 2020).

Table 6 shows the conditions for which an association with diseases other than aneuploidies has been described and which therefore are useful to be reported during a second trimester ultrasound.

Table 5

Prenatal detection rate of specific types of heart disease (isolated and non-isolated cases)

Type of heart disease	Number of studies included	Total number of cases	Prenatal detection rate, % (95% CI)
Significant VSD	3	308	36.1 (30.7-41.7)
Atrioventricular canal	8	542	60.4 (47.0-73.0)
Ebstein anomaly	4	57	80.1 (45.6-99.9)
Aortic coarctation	6	609	22.3 (18.0-27.0)
Tetralogy of Fallot	8	503	42.0 (30.9-53.6)
DORV, Fallot type	4	111	71.5 (59.5-82.3)
TGA	8	361	36.4 (21.0-53.3)
DORV, Taussig Bing	2	49	61.3 (46.9-74.8)
Truncus arteriosus	6	133	69.1 (43.1-90.6)
Pulmonary atresia with VSD	5	58	59.8 (45.6-73.2)
cTGA	5	49	72.3 (49.8-90.9)
Hypoplastic left heart	8	549	87.3 (78.3-94.2)
Tricuspid atresia	3	37	90.8 (77.9-99.1)
Pulmonary atresia with intact ventricular septum	4	59	41.3 (25.5-57.9)
Heterotaxic syndromes	3	99	89.1 (66.6-100)

VSD: Ventricular septal defect; DORV: Double outlet right ventricle; cTGA: Corrected transposition of great arteries.

Table 6

Conditions for which an association with anomalies other than aneuploidies is described: incidence, associated conditions and management

Markers	Incidence (%)	Associated conditions	Management	
Ventriculomegaly (≥10 mm)	3.0-15	Associated brain malformations Congenital infections (CMV, toxoplasma)	Diagnostic ultrasound (fetal neurosonogram) TORCH	
Hyperechogenic bowel (echogenicity ≥ that of bone)	0.2-1.8	Cystic fibrosis Congenital infections (CMV) Fetal growth restriction Gas- trointestinal anomalies	Search for cystic fibrosis mutations TORCH Diagnostic ultrasound	
Short humerus and/or femur (<5 th centile or <-2SD)	0.4-3.9	Skeletal anomalies Fetal growth restriction	Diagnostic ultrasound	
Renal pyelectasis (Renal pelvis A-P diameter >7 mm in transverse scan)	0.1-2.4	Vesicoureteral obstruction/ reflux	Diagnostic ultrasound	

Amended by: Mi Sun Kim, Sukho Kang, Hee Young Cho. Clinical significance of sonographic soft markers: A review. J Genet Med 2018; 15 (1): 1-7. (SD: Standard deviation).

There is no evidence available from the academic literature that demonstrates the impact of the detection of soft markers in the second trimester on the reduction of perinatal mortality.

There is no evidence in the academic literature that demonstrates an impact of the detection of soft markers in the second trimester on the reduction of perinatal morbidity.

The purpose of ultrasound is to identify particular fetal conditions and provide parents with sufficient information on the aetiology, on the associations and implications of the diagnosis during pregnancy and the perinatal period.

Identifying markers of uncertain interpretation, which may be associated with potentially serious diseases, but at the same time can be variants of standard, certainly increases maternal anxiety. Feedback and communication of the presence of soft marketers are controversial, because this information is a cause for anxiety in parents, it takes a long time to counsel, and could lead to unnecessary invasive procedures.

In order to avoid inducing maternal anxiety, soft markers that do not significantly increase the risk of malformations, and do not alter obstetric behaviour, should no longer be reported.

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3. THIRD TRIMESTER ULTRASOUND

Introduction

The main goals of obstetric ultrasound performed in the third trimester of pregnancy are the evaluation of fetal growth, amniotic fluid quantity and placental insertion. Ultrasound examination in the third trimester of pregnancy is used to diagnose conditions that are associated with increased perinatal morbidity such as small for gestational age fetus, large for gestational age fetus and breech presentation. However, it is still not clear how much third-trimester ultrasound actually improves maternal or perinatal outcomes in a low-risk population. In addition, not all fetal abnormalities are diagnosed with the second trimester ultrasound because they may develop or become evident later in pregnancy, or because maternal habitus or fetal position they could not be identified during second trimester screening. In about one case per 300 pregnancies, the third trimester ultrasound will identify fetal structural abnormalities that were not diagnosed by the second trimester screening ultrasound. Most frequently, these are urogenital abnormalities, central nervous system abnormalities, or cardiac defects, predominantly ventricular septal defects.

The purpose of this chapter is to provide clinical recommendations based on the available scientific evidence to guide operators during the third trimester ultrasound examination in women at high- or low-risk.

Recommendations

Question 1

In the low-risk population that has already performed an ultrasound at 20 weeks, is an ultrasound at 30-32 weeks useful for improving pregnancy outcomes *versus* no ultrasound?

Question 2

In the low-risk population that has already performed an ultrasound at 20 weeks, is an ultrasound at 34-36 weeks useful for improving pregnancy outcomes *versus* no ultrasound?

Question 3

In the low-risk population that has already performed an ultrasound at 20 weeks, is an ultrasound at 30-32 weeks *versus* an ultrasound at 34-36 weeks useful for improving pregnancy outcomes?

Recommendation 1-3

The literature data are insufficient to respond separately to PICOs 1-3. Therefore, the three PICOs were considered together.

In the low-risk population, ultrasound in the third trimester at 34-36 weeks may identify alterations in fetal growth and congenital abnormalities.

The panel wants to point out that an ultrasound performs better in identifying fetal growth restriction and fetal macrosomia compared than the symphysis-fundus height measurement.

The panel recommends clinical studies specifically aimed at assessing the impact of third-trimester ultrasound on perinatal mortality and morbidity.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND SYSTEM-ATIC REVIEWS OF MODERATE QUALITY, ONLY ONE OF LOW QUALITY

Literature analysis (systematic reviews and meta-analyses) of the last 5 years and evidence interpretation

A recent systematic review and meta-analysis examined the diagnostic performance of the third trimester ultrasound in predicting late-onset small for gestational age fetus and/or fetal growth restriction (Caradeux et al., 2019). The literature search was conducted between 2007 and 31st May 2018. The research included observational cohort studies in the low-risk or unselected population with ultrasound screening performed at ≥32 weeks. Twenty-one studies were included, for a total of 80,663 fetuses. Thirteen studies reported estimated fetal weight <10th centile and birth weight <10th centile, with a sensitivity of 38% (95% CI 31-46) and a specificity of 95% (95% CI 93-97). The positive and negative likelihood ratios were 8.7 (95% CI 6.2-11.8) and 0.65 (95% CI 0.51-0.71), respectively, with a diagnostic odds ratio of 13.6 (95% CI 9.2-19.0). Six studies reported information regarding abdominal circumference <10th centile and birth weight <10th centile, with a sensitivity of 35% (95% CI 20-52) and a specificity of 97% (95% CI 95-98). The positive and negative likelihood ratios were 11.3 (95% CI 7.0-16.7) and 0.67 (95% CI 0.53-0.80), respectively, with a diagnostic odds ratio of 17.4 (95% CI 9.2-29.1). For a 10% false positive rate, the sensitivity of AC <10th centile was 78% (95% CI 61-95) versus 54% (95% CI 46-62) of the estimated fetal weight <10th centile. Three studies reported information about the estimated fetal weight <10th centile and fetal growth restriction, with a sensitivity of 70% (95% CI 55-82) and a specificity of 95% (95% CI 93-99). The positive and negative likelihood ratios were 8.7 (95% CI 6.2-11.8) and 0.65 (95% CI 0.58-0.71), respectively, with a diagnostic odds ratio of 13.6 (95% CI 9.2-19.0). For a 10% false positive rate, the sensitivity of the estimated fetal weight <10th centile to identify the fetal growth restriction was 83% (95% CI 71.3-94.5), while it was 54% (95% CI 46-62) for the small for gestational age (SGA, birth weight <10th centile). Furthermore, the influence of the gestational age in which the ultrasound was performed was analysed and a significant trend toward better sensitivity was found if the ultrasound was performed later in pregnancy (coefficient 0.148 [95% CI 0.066-0.229]), while there was no statistical significance for the specificity.

Another recent systematic review and meta-analysis of randomized studies on routine third trimester ultrasound *versus* serial measurements of symphysis-fundus height in low-risk women (Al-Hafez, 2020) examined the identification of fetal growth restriction as a secondary outcome. The literature search was conducted until October 2019 and 7 randomized studies were identified for a total of 23,643 women. The rate of fetal growth restriction (estimated fetal weight <10th centile) was higher in the ultrasound group (763/10,388 [7%] compared to the serial measurements of the symphysis-fundus height group (337/9,021 [4%]), with a relative risk of 2.11 (95% CI 1.86-2.39), while there were no statistically significant differences in the detection rate of small for gestational age (SGA) at birth, 801/12,311 (7%) *vs* 712/11,280 (6%), relative risk 0.94 (95% CI 0.77-1.14).

A third systematic review and meta-analysis published by Cochrane examined the diagnostic performance of the ultrasound estimated fetal weight *versus* placental markers after the 24th week of gestation for the identification of small for gestational age infants in highand low-risk women and in the unselected population (Heazell et al., 2019). Using 86 studies, 159,490 pregnancies with 15,471 small for gestational age infants, it was found that the ultrasound estimated fetal weight is the most accurate test for identifying small for gestational age infants with a diagnostic odds ratio of 21.3 (95% CI 13.1-34.5).

A recent systematic review and meta-analysis of cohort and cross-sectional studies on the role of universal ultrasound screening to predict pregnancy outcomes (Smith, 2021) reported that the suspicion of a fetal macrosomia at ultrasound examination (estimated fetal weight >4.000 g or >90th centile) is highly predictive of giving birth to a newborn with birth weight >4.000 g or >90th centile; diagnostic odds ratio 17.11 [95% CI 13.32-21.96]. This meta-analysis included 40 studies with 66,187 women (literature search conducted until the 22^{nd} of October, 2018).

A second systematic review and meta-analysis by the same group (Moraitis et al., 2020) with literature search conducted until May 2020 identified 41 studies for a total of 112,034 women. The estimated fetal weight >4.000 g (or >90th centile) and the abdominal circumference >36 cm (or >90th centile) showed a sensitivity of >50% in predicting macrosomia (birth weight >4.000 g or >90th centile) and a positive likelihood ratio of 8.74 (95% CI 6.84-11.17) and 7.56 (95% CI 5.85-9.77) respectively.

Another recent systematic review and meta-analysis of randomized controlled studies on routine third trimester ultrasound *versus* serial measurements of symphysis-fundus height (al-Hafez, 2020) in low-risk women examined the identification of large for gestational age fetuses as a secondary outcome. The literature search was conducted until October 2019 and 7 randomized studies were identified for a total of 23,643 women. The rate of large for gestational age (estimated fetal weight >90th centile) was higher in the ultrasound group (1,060/3,513 [30%] compared to the serial measurements of symphysis-fundus height group (375/3,558 [11%]), with a relative risk of 2.84 (2.55-3.16), while no significant differences for large for gestational age at birth were identified, 901/10,411 (9%) vs 815/9,372 (9%), relative risk 0.97 (95% CI 0.89-1.06).

A secondary analysis of a randomized controlled study on selective versus universal ultrasound screening in nulliparous women (Sovio, 2018), showed that universally performed ultrasound at 36 weeks had a diagnostic odds ratio of 17.1 (95% CI 12.0-24.3) in identifying macrosomia at birth.

The EUROCAT register, beside reporting the percentage of cases of congenital abnormalities diagnosed in the prenatal period between 2014 and 2018 on over the total number of children diagnosed with congenital abnormalities by the first year of life (overall detection rate 42.2%, excluding genetic conditions), also specifies the percentage of anomalies diagnosed after 23 weeks, which in Europe corresponds to 8.9% of congenital anomalies (and between 6 and 8% from data available in three Italian regions). According to the register, 25% of congenital anomalies are diagnosed before 23 weeks, while the gestational age at diagnosis is not known in 8.09% of congenital anomalies.

A systematic review and meta-analysis published in 2021 (Drukker et al., 2021) determined the prevalence and the type of fetal abnormalities seen for the first time by the third trimester screening ultrasound, in women already screened in the second trimester. Thirteen studies were included for a total of 141,717 women, of which 643 were diagnosed with abnormalities that had not been previously identified, with an overall prevalence of 3.68 (95% CI 2.72-4.78) per 1,000 women undergoing ultrasound (approximately 1 in 300 women). Prevalence increased when only studies where the ultrasound protocol included repetition of the fetal anatomy study in addition to fetal growth assessment were analised (4.20 for 1,000, 95% CI 3.81-4.61). The gestational age period of ultrasound varied greatly among these studies. The most frequent abnormalities were urogenital (55%), of the central nervous system (18%, half of which were mild/moderate ventriculomegalies), and cardiac (14%). However, this meta-analysis did not aim to compare the prenatal detection rate of abnormalities between routine ultrasound in the third trimester and the referral scan, nor to evaluate the performance of the ultrasound screening in the third trimester. A recent systematic review and meta-analysis of randomized controlled studies examined whether, in low-risk women, routine third trimester ultrasound reduces perinatal mortality compared to serial measurements of symphysis-fundus height (Al-Hafez, 2020). The literature search was conducted until October 2019 and 7 randomized studies were identified for a total of 23,643 women. The perinatal mortality rate was not significantly different between the two groups: ultrasound group 41/11,322 (0.4%) *vs* symphysis-fundus group 34/10,285 (0.3%); relative risk 1.14 (95% CI 0.68-1.89). No significant differences were found in the rate of in utero deaths or neonatal deaths between the two groups. However, it should be noted that the meta-analysis did not have sufficient power to find statistically significant differences in perinatal mortality.

A recent systematic review and meta-analysis of randomized controlled studies of third trimester ultrasound performed routinely *versus* measurement of symphysis-fundus height (Al-Hafez, 2020) in low-risk women examined, as a secondary outcome, the need for resuscitation, hospitalization in neonatal intensive care, the rate of neonatal respiratory distress, Grade III or IV intraventricular haemorrhage and neonatal sepsis. The literature search was conducted until October 2019 and 7 randomized studies were identified for a total of 23,643 women. No statistically significant differences were identified for the outcomes considered between the ultrasound and the serial measurement of symphysis-fundus height group: need for resuscitation 386/12,062 (3%) vs 405/11,022 (3%), relative risk 0.94 (0.83-1.07); hospitalization in NICU 482/5,236 (9%) vs 458/5,295 (8%), relative risk 1.07 (0.94-1.20); neonatal RDS 5/175 (3%) vs 4/175 (2%), relative risk 1.25 (0.22-7.11); intraventricular haemorrhage Grade III or IV 0/7,216 vs 2/6,129 (0.03%); relative risk 0.30 (0.03-2.89); neonatal sepsis 7/7,216 (0.1% 9 vs 4/6,131) (0.07%), relative risk 1.48 (0.43-5.05).

Another recent systematic review and meta-analysis of cohort and cross-sectional studies on the role of universal ultrasound screening to predict pregnancy outcomes (Smith, 2021) reported that suspicion of fetal macrosomia at ultrasound examination (estimated fetal weight >4.000 g or >90th centile) is weakly, but with statistical significance, predictive of the risk of shoulder dystocia; diagnostic odds ratio 2.64 (95% Cl 1.65-4.24). This meta-analysis included 40 studies with 66,187 women (literature search conducted until the 22nd of October, 2018). A second systematic review and meta-analysis by the same group (Moraitis et al., 2020) with literature search conducted until May 2020 identified 41 studies for a total of 112,034 women. The estimated fetal weight >4.000 g (or >90th centile) had a sensitivity in predicting shoulder dystocia with a positive likelihood ratio of 2.12 (95% Cl 1.34-3.35). For both meta-analyses, data were insufficient to calculate other neonatal morbidity outcomes in relation to fetal macrosomia.

In conclusion, the most recent available scientific evidence would suggest that: O-1: ultrasound is the best method for identifying fetal growth restriction/small for gestational age fetus compared to the serial measurements of symphysis-fundus height or the dosage of placental biomarkers. It would appear that the abdominal circumference measurement has a better performance in identifying fetal growth restriction than the estimated fetal weight and that the sensitivity is better if ultrasound is performed later in pregnancy. O-2: ultrasound is strongly predictive of the risk of giving birth to a large for gestational age newborn. The diagnostic performance is better for ultrasound than for serial measurements of symphysis-fundus height.

O-3: The third trimester ultrasound allows for the identification of certain congenital structural anomalies not diagnosed during the second trimester ultrasound, or because they manifest only in the third trimester. O-4: Performing ultrasound would not appear to significantly reduce the risk of perinatal mortality compared to the serial measurements of symphysis-fundus height. O-5: Performing ultrasound and identifying a large for gestational age fetus seems to be a weak, but statistically significant, predictor of shoulder dystocia. For other perinatal morbidity outcomes, there would appear to be no statistically significant difference in performing ultrasound compared to the serial measurements of symphysis-fundus height.

Comparison with other Guidelines: Most of the guidelines do not recommend ultrasound in the third trimester in the low-risk population (FIGO, 2021; NICE, 2019), except for the French guidelines. This recommendation is based entirely on a Cochrane systematic review and meta-analysis (Bricker, 2015), last revised in 2015, which did not find a significant association between ultrasound examination conducted >24 weeks of gestation and perinatal mortality (risk ratio 1.01, 95% Cl 0.67-1.54; 8 studies, 30,675 participants). Of the 8 included studies, only two were published after 2000, while 3 were published in the 1980s. One study considered only elements of placental maturity, while for the others there was a significant heterogeneity in the considered biometric measures. Finally, the meta-analvsis had insufficient power to demonstrate a statistically significant difference in perinatal mortality it was estimated that a sample of women >200,000 would be required to have a 90% power to identify this effect (Smith, 2021). Finally, the effectiveness of a screening test depends not only on its diagnostic performance, but also on the efficacy of the intervention that is applied once the risk condition has been identified. The outcome of pregnancy in term so perinatal mortality and morbidity will depend greatly on this last point, which is why the so-called "treatment paradox" should also be considered in data interpretation.

The identification of fetal malformations was part of the secondary outcomes of the same 2015 Cochrane systematic review (Bricker, Medley, Pratt, 2015). For this outcome, two randomized studies were analysed comparing the third trimester universal screening approach vs the referral scan approach, for a total of 21,550 pregnancies (Skråstad et al., 2013; Crane et al., 1994). Cochrane authors point out that, in the face of a higher detection rate of abnormalities in the universal screening group in both trials, there was no increase in neonatal survival in this group compared to the group in which the third trimester ultrasound was performed on clinical indication. The two trials were conducted at the beginning of the 1990s and, therefore, it should be that there has been considerable improvement in ultrasound equipment and operator expertise over the last 30 years, which likely in improved diagnostic ability to diagnose prenatal structural abnormalities, better definition of intervention protocols and improvement of neonatal care. Taken together, all these factors could impact perinatal outcomes. Moreover, the RADIUS trial, was not specific for the third trimester ultrasound, but was intended to determine the usefulness of routine obstetric ultrasound in pregnancy in improving perinatal outcomes by comparing pregnancies that have undergone two screening ultrasound (at 18-20 and 31-33 weeks) and those undergoing ultrasound only on clinical indication. Possible benefits of a third trimester diagnosis of previously unknown abnormalities include preparing parents for the birth of a child with a malformation, planning for birth in a Centre with an appropriate level of care that is to the type of malformation, and planning for neonatal follow-up.

In conclusion, given that in the low-risk or unselected population:

 ultrasound in the third trimester is good at identifying fetal growth restriction and large for gestational age fetuses and may identify congenital structural anomalies not previously diagnosed;

- the data available are insufficient to demonstrate whether routine ultrasound in the third trimester significantly increases the prenatal detection rate of abnormalities compared to the selective use in a high-risk population;
- data from the literature are insufficient to demonstrate whether performing an ultrasound has or does not have a significant effect on perinatal mortality;
- this effect is also usually associated with an intervention, that is generally not included or not specified in the third trimester ultrasound study protocols, and therefore does not depend solely on the execution of the ultrasound;
- these considerations are also applicable to perinatal morbidity outcomes;
- the clinical value of routine ultrasound in the third trimester should be measured not only by the actual reduction of adverse perinatal outcomes, but also by its ability to increase prenatal diagnosis of congenital anomalies, with possible benefits resulting for the unborn child and his/her family.

Question 4

In the high-risk population that has already performed an ultrasound at 20 weeks, is an ultrasound at 30-32 weeks useful for improving pregnancy outcomes *versus* no ultrasound?

Question 5

In the high-risk population that has already performed an ultrasound at 20 weeks, is an ultrasound at 34-36 weeks useful for improving pregnancy outcomes *versus* no ultrasound?

Recommendation 4-5

Ultrasound is recommended in the third trimester in the high-risk population.

The panel points out that there is insufficient evidence for comparison of ultrasound at 30-32 weeks *versus* 34-36 weeks.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A HIGH QUALI-TY SYSTEMATIC REVIEW

Literature Analysis and Evidence Interpretation

The literature data are insufficient to answer to PICOs 4 and 5 separately. Therefore, the two PICOs were considered together.

The Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2014) recommend that patients with risk factors and a more than double overall risk of fetal growth restriction (*odds ratio* >2.0) compared to that of the general population should be referred for fetal biometry evaluation and umbilical artery Doppler assessment from 26-28 weeks gestation. In addition, the RCOG Guidelines recommend serial evaluation of fetal biometry and Doppler velocimetry whenever an abdominal circumference or estimated fetal weight are <10th centile or when a reduced fetal growth occurs.

The systematic review and meta-analysis published by Cochrane (Heazell et al., 2019) showed that even in the high-risk population, ultrasound estimated fetal weight is the most accurate test for identifying small for gestational age fetuses with a diagnostic odds ratio of 21.3 (95% CI 13.1-34.5).

In the population at risk of macrosomia these guidelines do not recommend ultrasound in the third trimester. A recent systematic review and meta-analysis (Smith, 2021) reports that the suspicion of a fetal macrosomia on the ultrasound examination (estimated fetal weight >4.000 g or >90th centile) is highly predictive of the risk of giving birth to a newborn with birth weight >4.000 g or >90th centile; diagnostic odds ratio 17.11 [95% Cl 13.32-21.96].

A secondary analysis of a randomized study on referral scans versus universal third trimester ultrasound screening in nulliparous women (Sovio et al., 2018) showed that in LGA fetuses, ultrasound performed at 36 weeks, combined with assessment of the abdominal circumference growth trend, has a positive predictive value for macrosomia at birth. This evaluation also allows for the identification of fetuses who are more at risk of associated complications.

There are currently no data in the literature to support greater predictive value of ultrasound at 30-32 or 34-36 weeks with regard to fetal structural abnormalities in the high-risk population for growth problems.

The Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2014) point out that the assessment of fetal biometry in growth-restricted fetuses can identify cases most at risk of perinatal complications. In detail, the construction of an individual growth curve resulting from serial fetal biometry assessments allows for a better identification of cases at risk of adverse perinatal outcomes.

Question 6

In women with suspected abnormal placental location, does TV US perform better than TA US in improving clinical outcomes?

Recommendation 6

Transvaginal ultrasound is recommended for the diagnosis of placenta praevia or lowlying placenta because the transvaginal approach is superior compared to transabdominal and transperineal approaches.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Transvaginal ultrasound increases the accuracy of placental localization, especially when the placenta is in a posterior location or the transabdominal ultrasound is limited by maternal obesity or uterine fibroids. The Guidelines of the Royal College of Obstetricians and Gynaecologists (2019a) cite a study by Sherman S.J. and colleagues, which although small (n=38), it is the only randomized controlled study comparing transabdominal to transvaginal ultrasound and demonstrates the safety of the procedure and its superior diagnostic performances, especially when the placenta is in a posterior location. According to the Royal College of Obstetricians and Gynaecologists Guidelines transvaginal ultrasound reclassifies 26-60% of low-lying placentas diagnosed during the second trimester screening ultrasound. Overall, transvaginal ultrasound has a high accuracy (positive predictive value 93.3%, negative predictive value 97.6%, false negative rate 2.33%) for the diagnosis of placenta praevia in women with suspected placenta praevia at transabdominal ultrasound performed in the second or early third trimester, with 87.5% sensitivity and 98.8% specificity (RCOG, 2019a).

The Royal College of Obstetricians and Gynaecologists Guidelines also cite a prospective cohort study on 59 women with placenta praevia, covering the internal cervical os, in which Ghi T. and colleagues showed that the best *cut-off* to identify women at risk of bleeding requiring caesarean section before 34 weeks is a cervical length less than or equal to 31 mm (sensitivity 83.3% and specificity 76.6%). Women with a cervical length of less than or equal to 31 mm have a 16-fold higher-risk (OR 16.4; 95% CI 3.4-75.9) of undergoing emergency caesarean section due to massive haemorrhage. Similarly, Zaitoun M.M.'s prospective study on 54 women with placenta praevia covering the internal uterine os, which is included in the Royal College of Obstetricians and Gynaecologists Guidelines, showed that combining a cervical length of <30 mm and a lower placental margin thickness >10 mm gives a sensitivity of 83.3% and a specificity of 78.4%. However, multiple prospective studies using a standardized definition of lower placental margin thickness are required before this sign can be used in clinical practice.

Women with a cervical length <25 mm compared to women with normal cervical length have a relative risk of 7.2 (95% CI 2.3-22.3) for massive haemorrhage during caesarean section for placenta praevia (RCOG, 2019a).

Repeated transvaginal ultrasound scans for cervical length measurement have shown that when it decreases quickly to 35 mm or less from 26 weeks onwards, there is an increased risk of preterm caesarean delivery due to massive haemorrhage (RCOG, 2019a).

Cohort studies with a low-risk of bias have shown that cervical length, as measured by transvaginal ultrasound, is a predictive factor for antepartum bleeding, massive haemorrhage during the caesarean section, and emergency caesarean section in women with placenta praevia. Moreover, a short cervix found during a transvaginal ultrasound performed before 34 weeks increases the risk of preterm delivery with emergency caesarean section (RCOG, 2019a).

Question 7

In women with an ultrasound diagnosis of placenta praevia performed before 36 weeks, is transvaginal ultrasound at 36 weeks helpful in improving clinical outcomes *versus* no ultrasound?

Recommendation 7

In women with placenta praevia (i.e., with a placental margin less than 20 mm from the internal uterine os) at 32 weeks gestation and who are asymptomatic, additional transvaginal ultrasound at approximately 36 weeks gestation is recommended in order to discuss the mode of delivery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

The recommendations for delivery cannot be based on ultrasound alone, but must be based on past medical history and women's preferences, supplemented with data from the transvaginal ultrasound. Women with a placental margin of less than 20 mm from the internal uterine orifice in the third trimester have a higher-risk of having a caesarean section when the placental margin is thick (>10 mm) and/or contains the marginal sinus or have "sponge" like appearance at ultrasound. These additional signs are poorly defined and unsought in routine ultrasound imaging during clinical practice. Delivery can occur via the vaginal route even when the distance between the lower placental margin and the internal uterine orifice is between 10 and 20 mm at 36 weeks.

The chance of successfull vaginal delivery when the placental edge is between 10 and 20 mm from the internal uterine os ranges from 56% to 93%. These studies are small, observational and retrospective (RCOG, 2019a).

Question 8

In women diagnosed with placenta praevia, does a targeted ultrasound study of the placenta for the assessment of suspected placenta accreta spectrum disorders (PAS) help to improve clinical outcomes *versus* routine ultrasound?

Recommendation 8

Prenatal assessment of women at risk for PAS (Placenta Accreta Spectrum) is recommended in a Referral Centre in order to plan clinical management and delivery and reduce maternal morbidity and mortality.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF LOW QUALITY

Literature Analysis and Evidence Interpretation

Several ultrasound imaging techniques have been studied over the years, including grayscale imaging and colour Doppler imaging (CDI) and/or three-dimensional power Doppler sonography.

In a systematic review and a meta-analysis of 23 ultrasound studies cited in the Guidelines of the Royal College of Obstetricians and Gynaecologists including 3,707 pregnancies at risk of placenta accreta, D'Antonio F. and colleagues found that the overall performance of ultrasound, when carried out by qualified operators, was very good with a sensitivity of 90.72% (95% CI 87.2-93.6), a specificity of 96.94% (95% CI 96.3-97.5) and a diagnostic Odds Ratio (OR) of 98.59 (95% CI 48.8-199.0) (RCOG, 2019a).

Among the different ultrasound signs, the uterine-bladder interface abnormality had the best specificity at 99.75% (95% CI 99.5-99.9) for the prediction of placenta accreta. Abnormal vascularization with CDI had the best predictive accuracy with a sensitivity of 90.74% (95% CI 85.2-94.7), a specificity of 87.68% (95% CI 84.6-90.4) and diagnostic OR of 69.02 (RCOG, 2019a).

According to the Royal College of Obstetricians and Gynaecologists Guidelines, which report on a systematic review and meta-analysis of standardized ultrasound signs by Jauniaux (2019a) and colleagues in women with placenta praevia and history of previous caesarean section, ultrasound diagnostic performance for prenatal detection of the placenta accreta spectrum disorders (PAS) is even higher in prospective studies with a sensitivity of 97.0% (95% CI 93.0-99.0), a specificity of 97.0% (95% CI 97.0-98.0) and diagnostic OR of 228.5 (95% CI 67.2-776.9). Placental lacunae that give the placenta a "moth-eaten" appearance in grayscale images and increased vascularization of the placental bed with large afferent vessels entering the lacunae are the most common ultrasound signs associated with placenta accreta spectrum disorders (RCOG, 2019a).

According to the Society of Obstetricians and Gynaecologists of Canada, in women with placenta praevia and risk factors for PAS (Placenta Accreta Spectrum disorders), the diagnostic accuracy of ultrasound for the diagnosis of PAS is reported as: sensitivity 90.7% (confidence interval 95% (CI) 87.2-93.6), and specificity 96.9% (95% CI 96.3-97.5). Ultrasound can be used for screening and for diagnosing PAS in pregnancies with anterior placenta praevia. The effectiveness of ultrasound in this context depends on the awareness of clinical risk factors: image quality, operator experience, gestational age, imaging methods and adequate bladder filling.

Pregnant women with clinical risk factors for placenta accreta spectrum disorders and anterior placenta praevia at the second trimester screening ultrasound should be referred to a second level examination to diagnose or rule out this disorder. Placenta accreta spectrum disorders are potentially life-threatening disorders that require interdisciplinary treatment at Specialist Centres to achieve the safest results for the mother and newborn.

According to a joint paper by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, prenatal diagnosis of placenta accreta spectrum disorders is desirable because the results are optimized when delivery occurs in a second-level maternal care facility prior to the onset of labour or bleeding and thus avoiding rupture of the placenta. The primary diagnostic method for prenatal diagnosis is a obstetric ultrasound. Although visualization of the ultrasound signs of PAS may be useful in diagnosis, none of the signs (or combinations of signs) associated with placenta accreta spectrum reliably predicts the depth of invasion or the type of placenta accreta spectrum disorder. The absence of ultrasound findings does not preclude a diagnosis of PAS; therefore, clinical risk factors remain equally important as predictors of PAS (ACOG-SMFM, 2018).

A systematic review and meta-analysis by Buca D. and colleagues (Buca, 2018) included 13 studies and 971 pregnancies affected by PAS; of these, 53.0% (95% CI 50.8-57.3; 514/971) were diagnosed in prenatal age by ultrasound or magnetic resonance imaging, while 47.0% (95% CI 44.8-51.3; 457/971) were detected at the time of delivery. The prevalence of placenta praevia was 91.4% (95% CI 83.4-96.9; I² = 82%) in the prenatally-diagnosed PAS group, while it was 57.9% (95% CI 39.0-75.6; I² = 90.4%) in the intrapartum diagnosis group, with an OR of 12.0 (95% CI 5.9-24.6; I² = 51%).

Women with a prenatal diagnosis of PAS had less blood loss during surgery (mean difference (MD) -0.87L; 95% CI -1.5 to -0.23L; p=0.008). Similarly, units of packed red blood cells (MD -1.45; 95% CI -2.9 to -0.04; p=0.04) and fresh frozen plasma (MD -1.73; 95% CI -3.3 to -0.2; p=0.03) were transfused less in women with a prenatal diagnosis of PAS than those with an intrapartum diagnosis, while there was no difference in the number of units of platelets transfused during surgery between the two study groups. The risk of hospitalization in intensive care and the median length of stay in hospital (MD 0.77; 95% CI -0.40 to 1.94; p=0.20) and in intensive care (MD -0.70 95% CI -2.32 to 0.92; p=0.4) were not different between women with a prenatal diagnosis and those with an intrapartum diagnosis of PAS.

Ultrasound is very accurate in at risk women with previous caesarean section and low anterior placenta or placenta praevia when performed by experienced operators (RCOG, 2014; SOGC, 2019; ACOG-SMFM, 2018).

The results of a systematic literature review (Buca, Liberati, Cali, 2018) show that prenatal diagnosis of PAS is associated with reduced haemorrhagic morbidity compared to diagnosis during delivery. Women with prenatal diagnosis of PAS had lower mean blood loss and fewer units of packed red blood cells and fresh frozen plasma transfusions than controls, suggesting a beneficial effect of prenatal imaging on maternal outcome in PAS cases.

The same systematic review (Buca, Liberati, Calì, 2018) showed that the risk of hospitalization in intensive care and the median length of stay in hospital and intensive care unit are not different between women with a prenatal diagnosis and those with an intrapartum diagnosis of PAS.

Question 9

In pregnancies at risk of vasa praevia (previous diagnosis of placenta praevia or velamentous cord insertion, etc.), is a targeted ultrasound for vasa praevia helpful in improving clinical outcomes versus routine ultrasound?

Recommendation 9

There is insufficient evidence to support universal screening for vasa praevia at the time of routine ultrasound in the general population.

The panel wants to point out that although targeted ultrasound assessment of pregnancies at higher risk for vasa praevia has been studied, the balance between benefits and risks remains undetermined, and further research in this area is needed.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Targeted search for vasa praevia during the second-trimester screening ultrasound has high diagnostic accuracy with low false positives. A combination of both transabdominal and transvaginal colour Doppler imaging (CDI) provides the best diagnostic accuracy for vasa praevia. Neonatal survival is 97% in women with antenatally diagnosed vasa praevia and 44% in cases not diagnosed prior to delivery. The probability of neonatal blood transfusion is 3.4% in cases diagnosed prior to delivery and 58.5% in previously undiagnosed cases, respectively. However, there is insufficient evidence to support universal screening for vasa praevia during pregnancy in the general population (SOGC, 2019).

Overall, the recommendation of the United Kingdom's National Screening Committee (NSC) on screening for vasa praevia is that screening for velamentous cord insertion as a means of identifying vasa praevia should not be implemented. Moreover, due to the limited number of prospective studies it is not possible to assess the benefits and risks of universal screening, compared to a more limited or targeted approach, in order to identify vasa praevia in currently identified risk groups, such as women with low-lying placenta during the mid-pregnancy screening ultrasound. A 2016 systematic review by Ruiter L. and colleagues, cited in the Royal College of Obstetricians and Gynaecologists Guidelines (2019b), evaluated the incidence and risk factors of vasa praevia, including 13 studies (two prospective cohort studies, 10 retrospective cohort studies and a case-control study) and 569,410 women. It found that 83% of the 325 cases examined had one or more risk factors, including placenta praevia, bilobed placenta, succenturiate placental lobes, conception by assisted reproductive technology and velamentous cord insertion (RCOG, 2019b).

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4. ULTRASOUND IN TWIN PREGNANCIES

Introduction

Twin pregnancies, defined as a gestation with the simultaneous presence of two fetuses, occurs in about 1-2% of pregnancies and presents a higher-risk of maternal complications, mortality and perinatal morbidity than a singleton pregnancy. Preterm childbirth, which takes place in more than 50% of such pregnancies, is a major culprit for the increased risks associated with this type of pregnancy, but it is not the only one: growth restriction and congenital anomalies are frequent fetal complications in these pregnancies, and so are certain maternal diseases such as hypertension disorders and bleeding events. Monochorionic placentation, with its specific features (single placenta, circulatory anastomosis), is also responsible for the possible appearance of conditions that are exclusive to these pregnancies such as twin-to-twin transfusion syndrome, TRAP sequence and sequelae in the surviving fetus after an in utero death of a twin.

Additional complications, such as cord entanglement, can be seen in monochorionic monamniotic pregnancies, which have an even higher mortality rate.

In light of the increased risk of complications, women pregnant with twins require frequent monitoring. Ultrasound has an important prognostic role, starting from the first trimester of pregnancy, in defining chorionicity, amnionicity and correct dating; it is also a potential means of screening and diagnosing complications such as growth restriction, congenital anomalies and twin-to-twin transfusion syndrome in monochorionic pregnancies.

Recommendations

Question 1

What are the optimal ultrasound measurements for dating twin pregnancies? Specific question: Are the measurements (crown-rump length, biparietal diameter, head circumference) and the curves of fetal biometric parameters used for singleton pregnancy dating also effective in twin pregnancies or are there systematic errors when using these curves?

Question 1bis

What are the optimal ultrasound measurements for dating twin pregnancies? Specific question: Is pregnancy dating based on the larger fetus more useful than that based on the smaller fetus?

Recommendation 1 and 1bis

In the first trimester, an ultrasound must be offered for dating the pregnancy. In order to date spontaneous conception pregnancies, in case of discordant CRLs, the dating should be carried out by referring to the twin with greater CRL.

In the case of pregnancies resulting from in vitro fertilization, the date of oocyte retrieval or the date of transfer and the age of the embryo at transfer must be used for dating.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Accuracy of dating

The 2019 NICE Guidelines refer to the data analysis and recommendations made in the previous 2011 version; all the studies considered show low or very low quality evidence. THE NICE and ISUOG Guidelines indicate that CRL (crown-rump length) between 45 mm and 84 mm is used for embryo dating (11 weeks and 0 days and 13 weeks and 6 days). ISUOG Guidelines suggest using head circumference after 14 weeks or above 84 mm CRL, as for singleton pregnancies. The 2017 SOGC Guidelines suggest using a combination of parameters, rather than a single one, to confirm dating after the first trimester.

The literature analysed by NICE concerning the accuracy of singleton pregnancy measurements, when applied to twin pregnancies, showed no statistically significant differences in size between twin and singleton pregnancies using CRL (very low quality evidence) or biparietal diameter (low quality evidence). There was no statistically significant difference in dating based on day of oocyte retrieval between twin and singleton pregnancies (low quality evidence). Likewise, there was no evidence that any fetal measurement specific to twin pregnancies was more effective than another in estimating gestational age. Furthermore, there is insufficient evidence from the analysis performed to recommend the use of specific curves for twin pregnancies.

As for the fetus to be used to estimate the gestational age in twin pregnancies, NICE states that using the smaller twin could lead to an underestimation of the gestational age. ISUOG Guidelines also consider other studies that recommend re-dating either based on the CRL of the smallest fetus or on the average of the two CRLs, but they conclude that the more common practice is to use the CRL of the largest fetus. Using the CRL of the smallest fetus to date a pregnancy can give a false reassurance.

The ISUOG Guidelines state that IVF pregnancies must be dated using the date of the oocyte retrieval date or the embryonic age from fertilization.

Perinatal morbidity

The diagnostic accuracy of the gestational age is a fundamental indirect parameter for predicting, identifying, and managing potential complications in twin pregnancies.

Correct identification of growth restriction

According to NICE, no evidence is available for predicting fetal growth restriction, and using the growth curves used in singleton pregnancies also for the smaller fetus in twin pregnancies, which are characterised by a reduced growth potential, does not lead to evaluation errors in the clinical practice (very low evidence).

No evidence was available for the prediction of other complications in twin pregnancies or congenital anomalies.

Planning of delivery or interventions at the appropriate gestational age

Twin pregnancies are at high-risk of preterm delivery. The accuracy of the gestational age estimate is critical because it is the basis for managing these pregnancies, their complications, and for planning delivery.

Question 2

In twin pregnancies is the ultrasonographic determination of chorionicity and amnionicity useful for fetal and maternal health?

Recommendation 2

During the first trimester of pregnancy, ultrasound should be offered to all women with twin pregnancies to determine the chorionicity and amnionicity.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

The pregnancy risks, clinical management and subsequent outcomes differ significantly based on the chorionicity and amnionicity. Therefore, the early determination of chorionicity and amnionicity is fundamental in the management of twin pregnancies and has been taken into account in all the most recent Guidelines.

The chorionicity must be reported and documented with appropriate images.

When chorionicity is carried out between 11+0 and 13+6 weeks of amenorrhoea, it should be determined by using:

- the thickness of the membranes at the insertion site of the amniotic membranes at a placental level;
- identifying the "T-sign" or "lambda-sign";
- identifying the number of placental masses.

In patients performing the first ultrasound examination after 14 weeks of gestation, the chorionicity should be determined using the same ultrasound signs as in the first trimester, specifically by counting the layers of the amniotic membranes and noting the presence or absence of fetal sex discordance.

If chorionicity or amnionicity cannot be determined by transabdominal ultrasound assessment (e.g. due to an elevated BMI or retroverted uterus), a transvaginal ultrasound assessment is recommended. If, despite transvaginal ultrasound, it is not possible to determine the chorionicity, a second opinion should be requested from a tertiary Specialist Centre. If the third-level Centre is also uncertain as to chorionicity, it is safer to classify the pregnancy as monochorionic and plan for proper follow-up.

Amnionicity must also be assessed and documented when chorionicity is determined. In case of doubt, the presence or absence of the amniotic membrane between the two fetuses is more easily assessed during the first trimester by transvaginal ultrasound.

The 2019 NICE Guidelines on the determination of chorionicity confirm the recommendations previously given in 2011 as valid. Specifically, the Guidelines set the objective of evaluating the optimal method for determining chorionicity on the basis of the diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratio) of the membrane thickness, the number of membrane layers, the number of placental sites, lambda/T-sign and the composite evaluation based on different ultrasound parameters, at different gestational ages. On the basis of the studies analysed, the sensitivity and specificity of the ultrasound parameters used are generally high, especially when evaluated in association with each other. The authors recommend that the examination should be carried out in the first trimester because it is simpler and allows for an early identification of the risks of pregnancy on the basis of the chorionicity. Monochorionic pregnancies are at increased risk of complications (including twin-to-twin transfusion syndrome, fetal growth disorders, structural abnormalities) and perinatal death compared to dichorionic ones. The advantage of correctly identifying monochorionic pregnancies (real positive pregnancies) allows them to undergo greater surveillance, appropriate risk counselling and appropriate management. Identifying dichorionic pregnancies (true negatives) avoids unnecessary tests and interventions; false positives undergo avoidable monitoring and maternal anxiety. False negatives are those most penalized for inadequate monitoring and the risk of not identifying serious complications. In 2019 the diagnosis of amnionicity was added to the recommendations (without revising the evidence), as monoamnionicity is to be considered an additional complication that requires an informed and dedicated management.

The 2016 ISUOG, the 2016 RCOG and the 2017 RANZCOG Guidelines give the same recommendations as NICE.

Another characteristic cited by the ISUOG Guidelines, which may be useful for the assessment of amnionicity, is using pulsed wave Doppler ultrasound to search for cord-entanglement, which is almost universally present in monochorionic monamniotic twin pregnancies (MCMA).

Similarly, the 2017 SOGC Guidelines emphasize that early determination of chorionicity and amnionicity in the first trimester is fundamental in prenatal management of twin pregnancies. The management of structural abnormalities, the screening for chromosomal abnormalities and the identification of aneuploidies, the determination of the aetiology underlying the discordance in fetal growth and/or amniotic fluid volume, and the early diagnosis of twin-to-twin transfusion syndrome all depend on chorionicity. High mortality and morbidity in MCMA pregnancies is well documented in the literature, and early diagnosis and intensive monitoring could improve pregnancy outcomes. There are separate sonographic criteria to be used before 10 weeks of gestational age (number of gestational sacs, number of amniotic sacs in the chorion, number of yolk sacs) and beyond this gestational age (discordant sex, number of placental masses, presence or absence of "lambda sign" and characteristics of the membrane separating the twins). In case of non-visualization of the membrane, stuck twin syndrome oligo-/anhydramnios or a misdiagnosis of a present membrane should be both excluded; in these cases the presence of "cord entanglement" or the lack of membrane visualization between the cord insertions may be useful for diagnosing monoamnionicity. The use of the transvaginal ultrasound should also be considered in doubtful cases.

The accuracy of the diagnosis of chorionicity is higher before 14 weeks; in the second trimester the "lambda sign" may no longer be visible and the use of multiple ultrasound parameters seems to increase the sensitivity and specificity of the ultrasound instrument in the diagnosis of chorionicity.

Question 3

What is the optimal screening strategy for identifying twin-to-twin transfusion syndrome in monochorionic twin pregnancies?

Recommendation 3

In the first trimester of monochorionic twin pregnancies no screening procedure is recommended to identify TTTS.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Recommendation 3bis

In monochorionic twin pregnancies in the second and third trimesters, periodic measurement at regular intervals (approximately every 15 days) of the single deepest pool of amniotic fluid is recommended.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Screening in the first trimester

Monochorionic pregnancy makes up about 20-25% of twin pregnancies. About 10-15% of these are complicated by twin-to-twin transfusion. The associated outcome is severe, with 60-90% of pregnancies resulting in perinatal death or disability.

Early diagnosis, staging and laser ablation therapy significantly improve outcomes, with 70-85% of at least one live newborn and a low incidence of neurobehavioural disability.

In the NICE Guidelines, the following parameters were studied during first trimester screening for the development of twin-to-twin transfusion in line with the Quintero classification:

- Ratio between the nuchal translucencies (NT) of the two twins: one study with 99 patients, no significant association;
- a ratio of CRLs of the two twins: one study with 99 patients, no significant association;
- abnormal ductus venosus in at least one fetus: one study with 99 patients, significant association;
- NT >95th centile: seven studies with 689 patients, low sensitivity and high specificity;
- NT discordance >31%: a study with 89 patients area under the curve (AUC) <70, poor screening capacity;
- NT discrepancy >20%: five studies, 938 patients, low accuracy (sensitivity 53%, specificity 69%);
- NT discordance >0,6 mm: a study with 99 patients, low sensitivity (50%) and high specificity (92%);
- CRL discordance >20%: a study with 177 patients, very low screening capacity;
- CRL discordance >12%: a study with 200 patients, low accuracy;
- amniotic fluid discordance: a study with 200 patients, low sensitivity (22%) and high specificity (96%);
- reverse flow in ductus venosus: a low-quality trial with 179 patients, low sensitivity (38%) and high specificity (85%), a very low-quality trial with 99 patients reported moderate accuracy;
- membrane folding: a study with low quality evidence from 187 patients, low sensitivity and high specificity.

Screening in the second trimester

In the NICE Guidelines the following parameters were studied during second trimester screening for the development of twin-to-twin transfusion in line with the Quintero classification:

- Abdominal circumference discordance >20%: a study with very low quality evidence on 177 patients, low screening capacity;
- head circumference discordance >20%: a study with very low quality evidence on 177 patients, low screening capacity;
- femur length discordance >20%: a study with very low quality evidence on 177 patients, low screening capacity;
- fetal weight discordance >20%: a study with very low quality evidence on 177 patients, with little screening capacity.

Diagnostic monitoring in the second and third trimesters

The recommendation is to increase the frequency of check ups in the second and third trimesters, to at least once a week, in the event of a 4 cm or greater liquid discrepancy between the two amniotic sacs, and to include the assessment of umbilical artery Doppler velocimetry.

Refer the patient to a Specialist Centre if the single deepest pool is <2 cm and >8 cm before 20 weeks or >10 cm after 20 weeks in the other sac.

There is little evidence on the accuracy of second and third trimester tests and only one study reported different parameters, but with very low quality evidence.

Experts agree that the amount of amniotic fluid must be sufficiently increased to be able to perceive ultrasound differences, and for this reason the advice is to carry out a measurement of the single deepest pool of amniotic fluid with the amniotic membrane visible, every fifteen days from 16 weeks until birth, and classifying it according to the Quintero criteria for the definition of stage 1. In cases where fetal growth discordance and amniotic fluid discordance are detected, monitoring is intensified and performed weekly. In suspected cases, the evaluation of umbilical artery Doppler velocimetry may demonstrate a deviation of blood from one fetus to another.

When the single deepest pool of amniotic fluid reaches the threshold values required for the diagnosis of TTTS, the patient should be sent to a Specialist Centre for further management.

Question 4

What is the optimal screening program to identify growth restriction in dichorionic twin pregnancies?

Recommendation 4

In dichorionic twin pregnancies, periodic monitoring of fetal biometry and the single deepest pool of amniotic fluid, and assessment of the fetal weight discordance is recommended from 24 weeks onwards.

Note: The panel believes that these indications should consider the problems related to local resources and, on the basis of these considerations, proposes that the checks be carried out every 4-6 weeks.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF MOD-ERATE QUALITY

Literature Analysis and Evidence Interpretation

According to NICE and ISUOG Guidelines, screening for growth restriction in twin pregnancies is not recommended in the first trimester because the crown-rump length and nuchal translucency are not accurate predictors of growth discordance in the second and third trimesters of pregnancy.

Abdominal palpation or the symphysis-fundus measurement are also not indicated because not accurate for monitoring fetal growth.

Both these guidelines (NICE and ISUOG) recommend calculating measurements of the head circumference, abdominal circumference and femur length and evaluating amniotic fluid by measuring the single deepest pool in both amniotic sacs.

Estimated fetal weight (EFW) discordance should be calculated using the following formula.

(larger twin EFW - smaller twin EFW) x 100 EFW larger twin

The growth curves used for monitoring fetal growth in twin pregnancies are generally the same as those used in singleton pregnancies. However, in twin pregnancies, particularly in the third trimester, slower fetal growth is more frequent. Thus, the use of specific growth curves for twin pregnancies has been suggested. There is currently no agreement on their use, because it has not been clarified whether or not this growth slowing down is due to some degree to placental insufficiency that would require closer monitoring. The 2021 FIGO Guidelines on the intrauterine growth restriction suggest using growth curves for twin pregnancies to avoid over diagnosing growth restriction in this population which results in increased resource use and maternal anxiety, although the strength of the recommendation is weak.

In the event of a discordance in EFW of \geq 20% and/or estimated fetal weight of at least one twin < 10th centile for gestational age in the second and third trimesters of pregnancy, the interval between check ups should be increased to at least one per week.

Referral to a Specialist Centre for the management of complicated twin pregnancies with fetal growth restriction is indicated if the discordance in EFW is \geq 25% and if the EFW of one or both twins is <10th centile.

The data in the literature differ when it comes to both the screening and the optimal ultrasound monitoring of pregnancies with diagnosed growth restriction.

According to the ISUOG Guidelines for dichorionic twin pregnancies an optimal screening program would involve ultrasound monitoring in the first trimester and then from the 20th week serial assessment should be carried out every 4 weeks, while according to the NICE Guidelines, the assessment of growth should be started at 24 weeks.

Complicated dichorionic pregnancies should be monitored more frequently depending on the condition and its severity.

According to the NICE Guidelines, an optimal screening program would include ultrasound serial assessment starting from the 24th week of gestation, evaluating two or more biometric parameters for the calculation of the estimated fetal weight and the amniotic fluid index. According to NICE, starting before the 24th week would result in additional costs and could cause maternal anxiety and the benefits are not significant to motivate such clinical conduct. Amniotic fluid evaluation should be performed by measuring the single deepest pool of both amniotic sacs.

It is important to monitor the EFW discordance at intervals of no more than 28 days between checks because the interval presents the best benefit/risk ratio in terms of identifying fetal growth restriction, increasing maternal anxiety, and increasing costs for the healthcare system.

The SOGC Guidelines suggest that although there is insufficient evidence to recommend specific ultrasound screening for dichorionic twin pregnancies, the recommendation is to initiate serial ultrasound assessment every 3-4 weeks starting from the 18th-22th week. According to the same Guidelines, Doppler assessment of the umbilical artery may be useful in monitoring fetal growth in multiple pregnancies when complications involve placental circulation or the physiology of fetal haemodynamics, such as in fetal growth restriction. However,

routine Doppler assessment of the umbilical artery in uncomplicated twin pregnancies is not recommended (the ISUOG Guidelines differ on this: these Guidelines recommend Doppler assessment of the umbilical artery at each check up from the 24th-26th week gestational age, even in uncomplicated twins).

Perinatal mortality and perinatal morbidity

Twin pregnancies have an increased risk of developing complications and perinatal mortality and perinatal morbidity are higher, therefore, all Guidelines agree that an appropriate method of screening and ultrasound monitoring must be identified in order to detect complications early and to manage pregnancies optimally and improve fetal and neonatal outcome.

A false negative result may increase the risk of perinatal mortality just as a false positive result may potentially increase the risk of perinatal morbidity secondary to iatrogenic prematurity.

If we take into account perinatal mortality, neonatal morbidity, and the preterm birth risk associated with the fetal growth restriction, it is considered appropriate to identify this condition in order to be able to monitor patients and reduce the risk of adverse outcomes. No unique threshold was found to define weight discordance in twin pregnancies. The literature data suggest that the odds ratio for neonatal mortality is statistically significant when the discordance is 25% for the smaller fetus and 30% for the larger fetus. According to ISUOG Guidelines, a 20% discrepancy in EFW represents the threshold above which the risk of adverse outcomes increased and if the discordance in EFW is \geq 25% the hazard ratio for perinatal death risk is 7.3. The SOGC suggests that a weight discordance threshold of 20% should be considered, and according to the NICE Guidelines, in the second and third trimesters of pregnancy, the monitoring interval should be reduced and Doppler assessment of the umbilical artery for each twin should be included in the event of a discordance in fetal EFW of \geq 20% and/or estimated fetal weight of at least one twin <10th centile per gestational age.

Timely referral to a Specialist Centre

According to the NICE Guidelines, referral to a Specialist Centre for the Management of dichorionic pregnancies complicated by fetal growth restriction is indicated if the discordance in EFW is of \geq 25% and if the estimated fetal weight of one or both twins is <10th centile for gestational age as the risk of mortality and perinatal morbidity is significantly increased in these cases. The ISUOG Guidelines suggest referring to a third-level Specialist Centre if the discrepancy in EFW is \geq by 25%.

Reduction of maternal anxiety

The recommendation is to explain to patients in an empathetic and professional manner about the clinical management of the pregnancy and possible outcomes of screening and diagnostic tests to minimize any anxious and depressive reactions. The recommendation is to offer women with multiple pregnancies the possibility of being monitored by a multidisciplinary team that includes psychotherapists (only if they feel the need to do so).

Healthcare professionals must provide emotional support to patients, and at the first contact, it would be advisable to propose the opportunity of giving advice and discussing certain aspects of the pregnancy, such as increased risk and symptoms and signs of premature delivery.

Question 4bis

What is the optimal screening program to identify growth restriction in monochorionic twin pregnancies?

Recommendation 4bis

In uncomplicated monochorionic twin pregnancies, it is recommended to carry out a screening program with frequent periodic ultrasound assessments, approximately every 2 weeks, starting at 16 weeks, with evaluation of: fetal biometry, single deepest pool of amniotic fluid, estimated fetal weight discordance and Doppler of the umbilical artery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE OF MOD-ERATE QUALITY

Literature Analysis and Evidence Interpretation

According to the NICE and ISUOG Guidelines, screening for growth restriction in twin pregnancies is not recommended in the first trimester. Abdominal palpation or the symphysis-fundus measurement are also not indicated because they are not an accurate method for monitoring fetal growth.

Fetal biometry must be calculated from the measurements of head circumference, abdominal circumference and the length of the femur. Amniotic fluid assessment should be performed by measuring the single deepest pool of both amniotic sacs in monochorionic diamniotic pregnancies.

Just as for dichorionic twin pregnancies, discordance in estimated fetal weight (EFW) must be calculated with the following formula:

(larger twin EFW - smaller twin EFW) x 100

EFW larger twin

The growth curves used for monitoring fetal growth in twin pregnancies are the same as those used in singleton pregnancies, even though in twin pregnancies, particularly in the third trimester, slower fetal growth is more common. Even for monochorionic twin pregnancies, the FIGO 2021 Guidelines on intrauterine growth restriction suggest using growth curves for twin pregnancies to avoid overdiagnosing growth restriction in this population, which would mean increased resource use and maternal anxiety, even though the strength of the recommendation is weak.

In the second and third trimesters of pregnancy, the interval between check ups should be increased to at least one per week if there is a discrepancy in EFW \geq 20% and/or estimated fetal weight of at least one twin <10th centile for gestational age.

Referral to a Specialist Centre for the management of complex fetal growth-restriction in twin pregnancies is indicated if the EFW discordance is \geq 25% and the estimated fetal weight of one or both twins is <10th centile.

Perinatal mortality and perinatal morbidity

Twin pregnancies, especially monochorionic pregnancies in which fetuses share the placenta, have an increased risk of fetal growth restriction, preterm delivery, and pre-eclampsia and postpartum haemorrhage. Fetal growth restriction is a specific complication of monochorionic pregnancies characterized by unequal placental sharing between the two fetuses, intraplacental anastomosis, marginal or velamentous cord insertion and altered fetus-placental flows. Monochorionic pregnancies also have a higher rate of intrauterine death than dichorionic pregnancies, particularly during the second trimester, and have a higher-risk of neurocognitive morbidity (up to seven times higher in monochorionic pregnancies than in dichorionic pregnancies), of co-existing complications such as twinto-twin transfusion syndrome (TTTS), sFGR and intrauterine death.

Ultrasound monitoring is critical for identifying patients at high-risk for complications and although the evidence is limited regarding the frequency of ultrasound monitoring, the recommendation is that in monochorionic pregnancies it should be more frequent.

The data in the literature differ in certain aspects regarding optimal screening and ultrasound monitoring of growth-restricted pregnancies. According to the ISUOG guidelines for uncomplicated monochorionic twin pregnancies, an optimal screening program includes serial assessment every 2 weeks from the 16th week with evaluation of fetal biometry, amniotic fluid index, estimated fetal weight discordance, and Doppler of the umbilical artery. Amniotic fluid assessment should be performed by measuring the single deepest pool of both amniotic sacs in monochorionic diamniotic pregnancies.

According to the 2011 NICE Guidelines, updated in 2019, an optimal screening program includes ultrasound monitoring starting at the 16th week of gestation, every two weeks, and two or more biometric parameters should be evaluated for the calculation of the estimated fetal weight and amniotic fluid index. Amniotic fluid evaluation should be performed by measuring the single deepest pool of both amniotic sacs. The recommendation is to reduce the interval between check ups to at least one per week in the event of:

- EFW discordance ≥20% and/or
- estimated fetal weight of at least one twin <10th centile per gestational age.

The EFW discordance is an independent risk factor for adverse perinatal outcomes associated with a substantial increase in mortality and perinatal morbidity for both twins. According to ISUOG Guidelines, a 20% discrepancy in EFW represents the threshold above which the risk of adverse outcomes increased and if the discordance in EFW is \geq 25% the hazard ratio for perinatal death risk is 7.3. According to the Royal College of Obstetricians and Gynaecologists - RCOG (2016), an EFW discordance of > 20% identifies selective fetal growth restriction.

In some cases, the magnitude of growth discordance is similar to that of dichorionic pregnancies, but managing this complication in monochorionic pregnancies is more complex because of the presence of placental anastomoses connecting the circulation of the two twins.

A significant fetal weight discordance, called selective fetal growth restriction, is seen in 15% of monochorionic pregnancies in the absence of twin-to-twin transfusion Syndrome (TTTS) and in 50% of TTTS-complicated pregnancies.

Initially, a clinical picture of sFGR can be differentially diagnosed with TTTS whereby in isolated growth restriction, the amniotic fluid can be less in one amniotic sac and normal in the other one, in contrast in TTTS there is a clinical picture of polyhydramnios in one twin and oligohydramnios in the second.

The classification of fetal growth restriction in monochorionic pregnancies depends on the Doppler pattern of the umbilical artery, on the basis of which the following types of sFGR can be distinguished:

- Type I: End diastolic flow positive,
- Type II: End diastolic flow absent or reversed,
- Type III: Intermittent pattern.

Doppler assessment of the umbilical artery in monochorionic pregnancies that are complicated by fetal growth restriction allows healthcare workers to classify, define and evaluate prognosis and potential morbidity. Specifically, cases with absent or reversed diastolic flow or intermittent pattern (TYPE II or III) are at increased risk of perinatal mortality and morbidity. Type I sFGR is associated with relatively good outcomes (more than 90% perinatal survival), type II sFGR is at increased risk (up to 29%) of smaller fetus intrauterine death and/or premature delivery. sFGR type III is associated with a 10-20% risk of sudden intrauterine death of the smaller fetus (despite regular cardiotocographic traces hours or days before) and 10-20% risk of neurological damage in the larger twin.

Timely referral to a Specialist Centre

Referral to a Specialist Centre for the management of dichorionic pregnancies complicated by fetal growth restriction or growth delay is indicated if the EFW discordance is \geq 25% and if the estimated fetal weight of one or both twins is <10th centile for gestational age because the risk of death and perinatal morbidity is significantly increased in these cases.

According to the ISUOG guidelines, the indication is to refer to a Specialist Centre when the EFW discordance is \geq by 25%. According to the Royal College of Obstetricians and Gynaecologists - RCOG 2016, monochorionic twin pregnancies complicated by fetal growth restriction (EFW discordance >20%) must be sent to a Specialist Centre with experienced operators. Specialist Centres should have at least two experienced operators and more than 15 cases per year to maximize perinatal outcomes and minimize long-term morbidity.

Reduction of maternal anxiety

The recommendation is to explain to patients in an empathetic and professional manner about the clinical management of the pregnancy and possible outcomes of screening and diagnostic tests to minimize any anxious and depressive reactions. The recommendation is to offer women with multiple pregnancies the possibility of being monitored by a multidisciplinary team.

Since complications of monochorionic pregnancies such as selective fetal growth restriction or twin-to-twin transfusion syndrome may occur, being able to communicate comprehensively, professionally and in an empathetic manner with the couple is of fundamental importance in reducing unnecessary fears and in making them understand the central role and need for more prenatal monitoring. Healthcare professionals must provide emotional support to patients, and at the first contact, it would be advisable to propose the opportunity of giving advice and discussing certain aspects of the pregnancy, such as increased risk and symptoms and signs of premature delivery.

Question 5

What is the optimal screening program to identify twin anemia polycythemia sequence (TAPS) in twins?

Recommendation 5

Early diagnosis of TAPS is recommended in monochorionic twin pregnancies that are complicated by TTTS or sIUGR, i.e. in cases of heart failure in a twin, or polyhydramnios or Doppler alterations in the umbilical artery.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Screening for TAPS in uncomplicated monochorionic twin pregnancies has not been shown to be beneficial, whereas such an assessment is recommended in complicated monochorionic pregnancies. The possibility of obtaining an adequate diagnosis and potential treatment means it is highly recommended to refer these patients to Specialist Centres.

Fetal perinatal mortality

Twin anemia polycythemia sequence (TAPS) is a complication whose rate of spontaneous onset is reported to be 3-5% in uncomplicated monochorionic twins. Diagnosis is based on finding a severe discrepancy in peak systolic velocity values in the middle cerebral artery, a method that has limited reproducibility and a high rate of false positives in diagnosing anemia (17%). Therefore, it cannot be considered for screening in monochorionic twins. The early diagnosis of TAPS is highly recommended in monochorionic pregnancies which are already complicated by TTTS or sIUGR, that is, in cases where a diagnosis of heart failure, or polyhydramnios or alterations of Doppler in umbilical artery in one twin has been made.

Neonatal mortality and morbidity (for anemia/polycythemia)

Screening for TAPS in pregnancies that are not otherwise complicated is not recommended because the method used to diagnose it, i.e., the measurement of peak systolic velocity in the middle cerebral artery, has a false positive rate of 17% and may therefore result in iatrogenic prematurity which may be responsible for neonatal mortality and morbidity. In contrast, in pregnancies already complicated by TTTS or sIUGR, screening for TAPS is highly recommended because preterm uterine treatment or delivery may be a way of preventing neonatal morbidity and mortality from anemia or polycythemia.

Timely referral to a Specialist Centre for management

In case of suspicion of the development of TAPS, referral to a Specialist Centre is beneficial in terms of reducing mortality and perinatal morbidity, with a disadvantage in economic terms or of travel to areas far from residence. The possibility of obtaining an adequate diagnosis and potential treatment means it is highly recommended to refer these patients to Specialist Centres.

Question 6

When and how should screening be performed to identify structural abnormalities in twin pregnancies?

Recommendation 6

In twin pregnancies, ultrasound screening for structural abnormalities should be offered in the same manner and timing as in singleton pregnancies.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Structural abnormalities are more frequent in twin pregnancies than in singleton pregnancies, and the management of cases with discordant structural abnormalities is more complex. The rate of fetal abnormalities in dizygotic twins is probably the same as in singleton pregnancies, while in monochorionic twins it is 2-3 times higher. In about 1 in 25 dichorionic twin pregnancies, 1 in 15 monochorionic twin pregnancies and 1 in 6 monoamniotic twin pregnancies, there is a major congenital anomaly that typically affects a twin. Early diagnosis gives the couple and professionals a wider choice of options to manage the pregnancy, it allows: parents to prepare for the birth of an infant with a problem, professionals to offer the option of abortion, transfer to a Specialist Birth Centre, and potentially facilitates intrauterine therapy.

The performance of a screening ultrasound for structural abnormalities in twin pregnancies is recommended by all major Scientific Organizations, although the overall quality of evidence in favour of the examination is low.

The 2011 NICE Guidelines, updated in 2019, recommend that a screening ultrasound should be offered for structural abnormalities between 18+0 and 20+6 weeks. The 2017 SOGC Guidelines also recommend detailed ultrasound screening for malformations, preferably between 18 and 22 weeks, in all twin pregnancies. The 2016 ISUOG Guidelines recommend that twin pregnancies should be assessed for major structural abnormalities in the second trimester of pregnancy and that the examination should be performed at approximately 20 weeks (18-22) by an experienced operator. The same guidelines suggest that fetal abnormalities should also be assessed in the first trimester of pregnancy. However, the literature review published by NICE in 2011, and updated in 2019, shows that a strategy based on second or third trimester ultrasound has a greater sensitivity and +LR than the combination of second or third trimester ultrasound, or first trimester ultrasound with fetal echocardiography, for the same specificity and -LR.

An analysis of the literature concerning the evaluation of the usefulness of a screening anomaly scan aimed at identifying structural anomalies shows that this type of examination is characterized by:

- diagnostic accuracy with high specificity and moderate sensitivity to detect all fetal structural abnormalities;
- diagnostic accuracy with high sensitivity and specificity to detect all cardiac abnormalities;
- diagnostic accuracy with high sensitivity and specificity to detect lethal structural abnormalities (fetal-perinatal mortality);
- diagnostic accuracy with high sensitivity and specificity to diagnose abnormalities that can lead to survival with long-term morbidity (right to an informed pregnancy in case of structural abnormalities when survival entails severe disability);
- diagnostic accuracy with high sensitivity and specificity to diagnose abnormalities that can undergo intrauterine therapy (correct management of cases of structural abnormalities for in utero treatment);
- diagnostic accuracy with low sensitivity but high specificity to diagnose associated abnormalities with possible short-term or immediate morbidity (neonatal morbidity).

The abnormalities most associated with twin pregnancies include neural tube defects, anterior abdominal wall defects, facial defects, gastrointestinal defects, and cardiac malformations.

Such defects are much more common in monochorionic twin pregnancies, and for this reason the Royal College of Obstetricians and Gynaecologists - RCOG, recommends that these pregnancies routinely perform not only an ultrasound between 18+0 and 20+6 weeks for malformation screening, but also a detailed assessment of the fetal heart. The 2016 ISUOG Guidelines also recommend a detailed examination of the fetal heart, specifying that the assessment should include the situs, the four chamber view, aortic and pulmonary flow, and the aortic arch.

Management of a monochorionic twin pregnancy in which a fetus has an abnormality is complex due to monochorionic placentation. For this reason, a timely diagnosis in these cases is particularly important and referral to a third-level Centre should be discussed with the patient.

According to the SOGC, regarding the reassessment of fetal anatomy during the various ultrasound examinations performed during pregnancy, there are no data to determine whether this is valuable in the diagnosis of structural abnormalities. For this reason, reassessment of anatomy is not recommended at each ultrasound examination and a detailed examination of fetal anatomy should only be offered in the second trimester.

The trade-off between clinical benefits and possible harm from performing ultrasound screening for abnormalities in twin pregnancies is not unlike that of singleton pregnancies (reducing maternal anxiety), and the anxiety in parents generated by the presumed diagnosis of malformation is considerable. This, however, can be further amplified in twin pregnancies where invasive diagnostic procedures or therapeutic procedures pose a risk of harm to the healthy fetus. Moreover, failure to diagnose malformations may also increase the risk to the healthy fetus.

As in singleton pregnancies, women should be informed of the limitations of the screening ultrasound for morphological abnormalities and that the detection rate varies according to the type of abnormality, the body mass index and fetal position at the time of examination. In twin pregnancies, ultrasound may be more difficult to perform due to the presence of the second fetus, and therefore the diagnostic accuracy of the examination may be reduced compared to singleton pregnancies. Due to these factors, it is important to allocate sufficient time to perform the examination (at least 45 minutes). The NICE Guidelines also suggest that the examination should be performed around 20+6 weeks (and not earlier) due to its specific complexity.

Question 7

What is the role of ultrasound in twin pregnancies if one of the fetuses dies in utero?

Recommendation 7

In Specialist Centres with experience in twin pregnancies, sampling of the middle cerebral artery peak systolic velocity value (MCA-PSV) is recommended in monochorionic twin pregnancies with death of a fetus in utero, in order to identify the presence of anemia in the surviving fetus. The panel suggests performing customized monitoring based on the cause of death of the co-twin, gestational age, and fetal well-being at the time of diagnosis, and performing an MRI of the fetal brain.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A LOW QUALITY LITERATURE SYSTEMATIC REVIEW

Literature Analysis and Evidence Interpretation

In monochorionic pregnancies, the 2016 ISUOG Guidelines suggest sampling peak velocity in the middle cerebral artery of the living twin for signs of anemia (or alternatively carrying out CTG). However, there is no evidence that immediate iatrogenic delivery can prevent the risk of brain damage in the co-twin, which generally has already occurred when the diagnosis of the twin's death is made. There are reported cases of anemic twins being treated with intrauterine transfusion, but this procedure has not been demonstrated to prevent death or neurological injury from further on. If the gestational age is at full-term, it seems sensible not to postpone delivery, but in preterm cases, it is recommended that the pregnancy should be extended to reduce the risks of premature birth. In the case of a conservative approach, a serial ultrasound monitoring (every 2-4 weeks) of biometrics and Doppler velocimetry of the umbilical and middle cerebral artery is recommended by the authors; if the average middle cerebral artery peak velocity is not indicative of fetal anemia in the living twin in the first days after the death of the co-twin, it is unlikely to occur later on. A fetal brain imaging survey is recommended at 4-6 weeks after the death to identify severe brain damage; in cases where there is evidence that the co-twin may have suffered neurological damage, discontinuation of pregnancy should be considered as a possible option. For dichorionic pregnancies, no indication is given on ultrasound monitoring. However, the authors recommend that all twins with an intrauterine death of a twin should be sent to Specialist Centres with experience in the management of such pregnancies.

The 2016 RCOG Guidelines provide guidance for monochorionic pregnancies only and report of the possibility of carrying out an evaluation of the peak velocity of the middle cerebral artery, via Doppler velocimetry, in order to identify the presence of fetal anemia in the living twin. In addition, they suggest that an MRI of the fetal brain should be performed 4 weeks after intrauterine death, to identify possible brain lesions, in case this information may be useful for planning pregnancy management. Like the ISUOG Guidelines, they indicate that monochorionic pregnancies complicated by the death of a twin in utero should be referred to Specialist Centres with multidisciplinary experience in the management of these pregnancies.

The 2017 RANZCOG Guidelines suggest that in monochorionic pregnancies, ultrasound or MRI examination of the CNS of the surviving fetus should be considered to assess the presence of neurological lesions. In addition, ultrasound monitoring with PSV assessment in MCA should be offered to the patient and a transfusion in case of severe anemia in the surviving twin. There is, however, no evidence to recommend this practice in order to prevent death and/or neurological injury of the surviving twin.

A recent systematic review and meta-analysis published by Mackie et al. in 2019 on 42 studies, confirms an increased risk of intrauterine death of the co-twin in monochorionic twin pregnancies compared to dichorionic ones [41% (95% CI 33.7-49.9) vs 22.4% (95% CI 16.2-30.9); or 2.06 (95% CI 1.14-3.7)] (p=0.016). On the other hand, the preterm birth risk <34 weeks remains high for both monochorionic and dichorionic pregnancies [58.5% (95% CI 48.2-70.9) vs 53.7% (95% CI 40.8-70.6) p=0.356] and the risk of neonatal death [27.9% (95% CI 21.1-36.9) vs 21,2% (95% CI 14.5-31.2) p=0.051], is at the limits of statistical significance. Six studies investigated the presence of brain damage in the MRI examination of the fetal brain in monochorionic pregnancies and in 20% of cases lesions were present; the ultrasound examination did not identify 31.5% of lesions in three studies, and another three studies showed consistency between ultrasound and fetal MRI. There are no studies investigating the findings of intrauterine brain lesions in dichorionic pregnancies to compare with these data. On the other hand, in seven studies on monochorionic pregnancies, cerebral abnormalities on postnatal imaging were more frequent than in dichorionic ones [43% (95% CI 32.8-56.3) vs 21.2% (95% CI 10.6-42.4); OR 5.41 (95% CI 1.03-28.58) p=0.047]. On the basis of this review, the role of fetal brain MRI in monochorionic pregnancies is particularly important, although the extreme heterogeneity of the timing of the examination does not allow conclusions to be drawn on the optimal time in these cases. In the absence of evidence on the monitoring of dichorionic twin pregnancies with intrauterine death of a twin, it is the authors' opinion that customized monitoring based on the causes of death of the twin, gestational age, and fetal well-being at the time of diagnosis be carried out.

Question 8

Is it useful to send complicated twin pregnancies to Specialist Centres?

Recommendation 8

The panel recommends requesting the opinion of a Specialist Centre in the case of:

- Women with monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome, growth discordance of >25% and estimated weight of one or both fetuses <10th centile, death of a twin in utero, structural abnormalities, suspected TRAPS or TAPS.
- Women with dichorionic twin pregnancies complicated by growth discordance of >25% and estimated fetal weight of at least one twin <10th centile, structural abnormalities, death of a twin in utero.
- Women with monochorionic monoamniotic twin pregnancies.
- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Complicated twin pregnancies are difficult to manage, both because they are relatively less frequent, and because they have peculiar differences compared to singleton pregnancies. Management requires special experience in dealing with these pregnancies.

The 2019 NICE Guidelines recommend that a consultation should be requested from a Specialist Centre when the aforementioned conditions are identified. The quality of evidence of this recommendation is very low for all outcomes considered (intrauterine death, neonatal mortality, neonatal morbidity, neonatal intensive care admission, maternal satisfaction and the impact of the referral to the Specialist Centre, maternal morbidity, emergency caesarean section, Apgar score, birth weight, maternal anxiety, depression, quality of life and breast-feeding), due to the lack of studies that have considered this topic. The recommendation is based on the collective experience of the authors of the NICE Guidelines and is shared by our work group. There are no recent publications providing further additional information to those formulated by NICE.

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5. ULTRASOUND IN THE PREVENTION OF PRETERM DELIVERY

Introduction

Premature delivery, which is considered as delivery before 37+0 weeks of gestation, is one of the main causes of perinatal mortality and morbidity with about 15 million premature infants every year, and more than 1 million neonatal deaths due to premature birth. About one third of premature deliveries are due to severe obstetric conditions, but in the remaining cases it is due to spontaneous premature labour with spontaneous onset.

However, the spontaneous onset of uterine contractions results in premature delivery in a minority of cases.

The correct diagnosis of premature labour is based on the concurrence of significant changes in the uterine cervix (dilation at digital evaluation or shortening at transvaginal ultrasound), and/or findings related to an inflammatory reaction of the amniochorionic membranes (positive fibronectin test on vaginal secretions). However, even in case of a correct diagnosis, treatments (e.g., tocolysis) have been more effective in procrastinating labour than in preventing it. Therefore, there is great interest in the identification of reliable predictive factors of premature delivery, in order to identify high-risk patients could benefit from a targeted management. Finally, the ultrasound measurement of the cervix has been proven to be very useful, not only for the diagnosis of premature labour, but also for the prediction of premature delivery.

Recommendations

Question 1

In a singleton pregnancy in absence of risk factors for premature delivery is it useful to measure cervical length at 19-21 weeks?

Recommendation 1

Cervicometry screening in singleton pregnancy patients, in the absence of clinical or anamnestic risk factors for premature delivery, cannot currently be universally recommended.

The panel wants to point out that universal screening has proven to be cost-effective only in some countries (e.g. in the United States and the United Kingdom) and that the implementation of such a screening method in Italy needs more research in order to assess its clinical impact. The panel also stresses the need for adequate training for operators performing such ultrasound evaluation.

Research recommendation: the panel highlights the importance of Italian studies regarding the effectiveness of such on the general population.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONE LOW QUALITY

Literature Analysis and Evidence Interpretation

Most available Guidelines report that transvaginal cervicometry can identify patients at high-risk for premature delivery (<37 weeks and <34 weeks of gestation) (ACR, 2019; Australian Gov, 2019; Australian Gov, 2018; RANZCOG, 2017b; SIGO, 2020; SOCG, 2020a), giving the possibility to provide a targeted prophylactic treatment and reduce the incidence of premature delivery in these patients (KCE, 2015b; SIGO, 2020; SOCG, 2020a; SOCG, 2020b). However, there is no agreement between the recently published Guide-

lines on the cervicometry screening in the general population. Recent good quality guidelines (SOGC, 2019; SOGC, 2020a; Australian, 2019) do not recommend universal screening and emphasize the need to evaluate it cost effectiveness.

Several Guidelines point out that, in case of a cervix <25 mm, administration of vaginal progesterone reduces the incidence of birth at <37 and <34 weeks of gestation, leading to an improvement of the perinatal outcome including perinatal mortality and morbidity, low birth weight (<2.500 g), neonatal respiratory distress syndrome and need for neonatal intensive care (Australian Gov, 2018; KCE, 2015b; SOCG, 2019; SOCG, 2020b). The most recent meta-analyses, edited by Romero et al., cited in the Guidelines (Romero, 2018 in SOCG, 2019) show how this approach can reduce the risk of delivery <34 weeks by about 34% (relative risk reduction - RRR), respiratory distress syndrome (53% RRR), neonatal intensive care admission (32% RRR), and composite neonatal mortality and morbidity (41% RRR), reporting a number-needed-to-treat of approximately 11 patients to prevent delivery at <34 weeks (general population).

Son et al. (cited by ACR, 2019) reported that the implementation of universal screening by transvaginal cervicometry results in a significant reduction in the incidence of delivery <37 weeks (4.8% *versus* 4.0%, AOR 0.82; 95% confidence interval [CI] 0.76-0.88) and <34 weeks (1.3% *versus* 1.0%, AOR 0.74; 95% CI 0.64-0.85) (Son, 2016 in ACR, 2019).

No relevant data were found on the effect of cervicometry on the incidence of intraventricular haemorrhage of the newborn. However, this complication is considered comparable to the other perinatal outcomes mentioned, which are associated with prematurity (SIGO, 2020).

The literature agrees that adequate training is necessary for operators performing such ultrasound examination, favouring the transvaginal approach in most cases (ACR, 2019; Australian Gov, 2018; SMFM, 2016; RANZCOG, 2017b; SIGO, 2020; SOGC, 2020a).

Question 2

Is it useful to measure cervical length at 19-21 weeks in singleton patients with previous premature births?

Recommendation 2

In patients with singleton pregnancies and a history of premature delivery, the measurement of cervical length is recommended at 19-21 weeks.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONE WAS OF LOW QUALITY

Literature Analysis and Evidence Interpretation

A history of previous premature birth significantly increases the risk of premature birth in the current pregnancy (SIGO, 2020; SOGC, 2019). Transvaginal cervicometry at 19-21 weeks showed greater sensitivity in the identification of the population at risk for premature delivery in this group of patients than those without a prior premature birth history (SIGO, 2020; SOGC, 2020a).

In particular, the availability of preventive interventions effective in reducing the rate of premature delivery in these patients, such as vaginal progesterone or cervical cerclage, in addition to the best performance of cervical screening, justifies their clinical use (SIGO, 2020; RANZCOG, 2017b). It has been calculated that the number of patients needed to be screened

to prevent premature delivery at <34 weeks (cut-off: 20 mm cervicometry) would be 97 with prior premature delivery, compared to 221 nulliparas and 802 low-risk patients (Facco, 2013 in Australian Gov, 2019).

If the American College of Radiology believes that cervicometry is "usually appropriate" in patients at risk (ACR, 2019), and the Canadian Society of Obstetrics and Gynaecology (SOGC, 2020) states that it "can" be used in women with previous preterm birth, the Society of Maternal-Fetal Medicine (SMFM,) and the Italian Society of Gynaecology and Obstetrics (SIGO, 2020) explicitly recommend it in patients with anamnestic risk.

According to the most recent evidence (Romero, 2018 in SOGC, 2019), as mentioned above, in a mixed population including patients with a history of prior preterm birth, Romero et al. showed that cervicometry screening and progesterone prophylaxis lead to a reduction of deliveries <34 weeks of approximately 34% (relative risk reduction - RRR), respiratory distress syndrome (53% RRR), hospitalization in neonatal intensive care unit (32% RRR), and neonatal composite mortality and morbidity (41% RRR). In a meta-analysis including 5 randomized trials (Berghella, 2011 in ACR, 2019 and SOGC, 2019), Berghella and colleagues showed that the application of cerclage in patients with singleton pregnancy, prior premature birth and short cervical length <24 weeks of gestation, reduced the risk of both birth <35 weeks (30% RRR) and neonatal mortality and morbidity (36% RRR). Similarly, a meta-analysis conducted by Jarde and colleagues (Jarde, 2019 in SOGC, 2020b), showed that progesterone prophylaxis in patients at increased risk for premature birth due to either obstetric history or short cervix could reduce both the risk of delivery <34 weeks (Odds Ratio [OR] 0.43; 95% Credible Interval [Crl] 0.21-0.78; Number Needed to Treat [NNT] 9), <37 weeks (OR 0.51; 95% Crl 0.34-0.74; NNT 7) and the risk of neonatal death (OR 0.41; 95% Crl 0.20-0.83; NNT 30) or hospitalization in neonatal intensive care unit (OR 0.39; 95% Crl 0.14-0.87; NNT 8).

No relevant data were found on the effect of cervicometry on the incidence of intraventricular haemorrhage of the newborn, however, this complication is considered comparable to the other perinatal outcomes mentioned, which are associated with prematurity (SIGO, 2020).

Question 3

Is it useful to measure cervical length in twin pregnancies at 19-21 weeks?

Recommendation 3

In twin pregnancies, it is not recommended to measure routinely the cervical length cervicometry for risk prevention of preterm delivery.

Note: The panel believes that, although twin pregnancies are at increased risk of preterm birth, there is currently no evidence that such implementation can translate into effective preventative strategies to reduce preterm delivery and that it therefore is associated with health improvement in women and children. The panel believes that the clinical data currently available on preterm delivery prevention in twin pregnancies are not sufficient to justify using resources to implement this screening universally.

Recommendations for research: the panel recommends the implementation of clinical studies on this topic.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE WAS LOW QUALITY

Literature Analysis and Evidence Interpretation

Several international Guidelines show that the risk of preterm delivery <37 weeks and <34 weeks is associated with a cervical length (CL) of <25 mm. However, SMFM does not recommend cervicometry as routine screening, although SOGC uses this value to recommend drug therapy (strong/moderate recommendation) (ISUOG, 2016; SMFM, 2016; SOGC, 2020).

As for the cut-off, in the largest multi-centre preterm delivery prediction study reported in the 2016 SMFM Guidelines, approximately 18% of twin pregnancies had shown a CL of <25 mm at 22-24 weeks compared to 9% of singleton pregnancies (Goldenberg, 1996 in SMFM, 2016); the risk of preterm delivery with a CL of <25 mm increased approximately 8-fold in twin pregnancies compared to 6-fold in singleton ones.

ISUOG states that CL measurement is the preferred screening method for preterm delivery prediction; 25 mm is the most commonly used cut-off in the second trimester (RECOMMENDATION GRADE B). In particular, in the ISUOG Guidelines Conde-Agudelo (Conde-Agudelo, 2014 and 2010 in ISUOG, 2016) emphasized that this cut-off is a moderate predictor of preterm delivery at <34 weeks, but not <37. In asymptomatic patients, identification of an even lower cervical measurement (CL ≤20 mm at 20-24 weeks) is the most accurate preterm predictor of delivery before 32 and 34 weeks (sensitivity, specificity and positive and negative likelihood ratio were 39% and 29%; 96% and 97%; 10.1 and 9.0; and 0.64 and 0.74 respectively) (ISUOG, 2016).

Various trials involving CL-reduced twin pregnancies did not collect sufficient data to demonstrate a clinical benefit to justify screening in all patients with twin pregnancies, as reported by Nicolaides in the SMFM Guidelines (Nicolaides, 2016 in SMFM, 2016).

However, a 2019 meta-analysis (Chumbo, 2019) including 16 studies and 1,211 patients demonstrated that an even lower CL value (<15 mm) can be used to implement the management of twins patients with a 3.89-week prolongation (95% confidence interval, 2.19-5.59; p=0.000; l²=0%) and reduction in childbirth at <37 weeks (risk ratio, 0.86; 95% confidence interval, 0.74-0.99; p=0.040; l²=0%), <34 weeks (risk ratio, 0.57; 95% confidence interval, 0.43-0.75; p=0.000; l²=0%) and <32 weeks (risk ratio, 0.61; 95% confidence interval, 0.41-0.90; p=0.010; l²=0%) in patients undergoing cervical cerclage compared to controls.

A meta-analysis by Jarde (2017) reported in the SOGC Guidelines on the use of medication in twin pregnancy patients with CL <25 mm did not show a significant impact on the risk of preterm delivery before 37th and 34th week or on neonatal death, but only an improvement of some secondary outcomes such as the birth of very low-weight infants (<1.500 g), or the need for hospitalization in intensive care with mechanical ventilation (Jarde, 2017 in SOGC, 2020b).

Another meta-analysis of randomized trials in asymptomatic women with CL <25 mm, also reported in the SOGC Guidelines, showed a reduced risk of birth <33 weeks with drug therapy; a significantly lower risk of neonatal death, respiratory distress syndrome, NICU hospitalization and mechanical ventilation, and neonatal morbidity/mortality, low birth weight <1.500 g (moderate evidence quality) was also observed (Romero, 2017 in SOCG, 2020). No results on neurodevelopment are reported.

Question 4

Is it useful to measure cervical length at 16-18 weeks in singleton patients with previous premature births?

Recommendation 4

In patients with singleton pregnancies at high-risk for premature delivery, measurements of the cervical length starting from 16-18 weeks are recommended.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, ONLY ONE WAS LOW QUALITY

Literature Analysis and Evidence Interpretation

The Guidelines published by the Australian Government in 2018 (Australian Gov, 2018) show that a short cervix in the second trimester can be assessed as early as 16 weeks. Women with cervical length \leq 15 mm before 20 weeks have a significantly higher-risk of preterm delivery <28 weeks (p<0.001) and <32 weeks (p=0.004) than women with a short cervix observed at 20-24 weeks. The Australian Government - Department of Health, 2019 Guidelines (Australian Government - Department of Health, 2020) show that cervicometry performed before 20 weeks can predict the risk of preterm delivery in high-risk women. However, cervical measurements >25 mm do not exclude preterm delivery in these women, who could still experience preterm delivery <37 weeks in 16-21% of cases.

The American Society of Fetal Maternal Medicine (SMFM, 2016) recommends the measurement of the cervical length for patients with previous preterm delivery (IA Recommendation Level). It also recommends to perform cervical length measurement starting from 16 to 24 weeks in such cases. In such cases, the cervix is generally monitored every 1-2 weeks. SMFM, as reported in previous Guidelines, also refers to a study including women with previous preterm delivery, in which cervicometry was performed every 2 weeks between 16 and 23 weeks, with intensification to a weekly follow-up for those with cervix between 25 and 29 mm, allowing randomization in case of cervix <25 mm to undergo cerclage vs expectant management. A significant reduction of preterm delivery <24 weeks (RR, 0.44; 95% CI 0.21-0.92) and <37 weeks (RR, 0.75; 95% CI 0.60-0.93), as well as a reduction in perinatal mortality (RR, 0.54; 95% CI 0.29-0.99), were observed in the group of women selected as high-risk and undergoing cerclage.

Finally, the 2020 SIGO Guidelines point out that repeated measurements of cervical length *versus* single measurement do not improve diagnostic accuracy in preterm delivery predictivity (II-2A) (SIGO, 2020). However, they point out that in high-risk cases undergoing close monitoring of cervical length, a strategy of 1-2 weeks interval controls between 16 and 24 weeks seems reasonable (III A) (SIGO, 2020).

Question 5

Is ultrasound measurement of cervical length useful in patients with preterm contractions?

Recommendation 5

Ultrasound measurement of the cervix is recommended in patients >24 weeks with symptoms of preterm delivery.

The panel highlights the role of this method in choosing the most appropriate clinical management and optimization of resources.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES, LOW QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

Cervicometry performed in patients at gestational age \geq 24 weeks and \leq 36+6 weeks, with symptoms of preterm labor helps to identify those at high-risk of impending premature delivery, allowing an optimal clinical management of such cases.

Available data show that 60% of patients with symptoms suggesting preterm labor and cervical length ≤15 mm deliver within 1 week (OR of 5.7). In contrast, if the cervical length is >15 mm only approximately 4% will experience preterm delivery within one week.

The main international and national guidelines examined (ACR, 2019; RANZCOG, 2017b; SOGC, 2020; NICE, 2019b; SMFM, 2016; SIGO, 2020) support the use of cervicometry to stratify preterm birth risk in symptomatic patients. A suggested cut-off of 15 mm seems to better predict preterm birth and is supported by multiple trials, predominantly randomized controlled studies or meta-analyses (Alfirevic et al., 2007; Sotiriadis et al., 2010; Berghella, 2017) (Level IC).

A cervicometry \leq 15 mm has a sensitivity and specificity of 77% and 77%, respectively, and an accuracy of 88% in predicting preterm delivery within 7 days from symptom onset. Moreover, the presence of funnelling seems an independent predictive factor of preterm delivery at <37 weeks (ACR, 2019).

The same guideline points out that there is a weak, but statistically significant correlation between cervicometry, shortening of the uterine cervical canal and time interval between onset of symptoms and preterm delivery. Additionally, in symptomatic patients, cervicometry has an inverse relationship with cervical dilatation, if ≤ 3 cm, as in case of closed cervix, confirming its high negative predictive value, also in relation to cervical dilation (ACR, 2019).

Regarding the primary outcomes considered, many of the analysed Guidelines (ACR, 2019; ILEGO, 2020; SOGC, 2020a) agree that the use of cervicometry reduces the rate of preterm delivery <37 weeks and 34 weeks of gestation, as well as the chances to deliver within the subsequent 7 days.

Regarding secondary outcomes, some Guidelines (ILEGO, 2020; NICE, 2019b; SOGC, 2020a) report that the use of cervicometry is associated with a reduction in unnecessary interventions, such as maternal hospitalization, the use of tocolysis and the use of steroids for fetal lung maturation. However, not significant results have been reported in relation to for delivery <32 and <28 weeks, birth weight <2.500 g, perinatal death, perinatal morbidity, hospitalization in NICU, IVH and RDS (Berghella et al., 2019; Berghella, 2017; SOGC, 2020a).

However, in symptomatic patients with cervical length between 16 and 29 mm, some observational studies show that the association of cervicometry with additional predictive factors, such as fetal fibronectin (fFN), phIGFBP-1 and PAMG-1, is useful to implement its predictive capacity. These results, however, were not confirmed by randomized studies.

A single randomized study (Ness, 2007 in Cochrane Berghella, 2019) shows that in the group of women with negative fFN and cervicometry \geq 30 mm, compared to the group with positive fFN and cervicometry <30 mm, there is a preterm birth rate of 13% vs 36.2% (p=0.01).

However, it has been shown that the use of fFN in cases of cervicometry <20 mm and >30 mm does not affect the predictive capacity of the latter (ACOG, 2016; SMFM, 2016). The negative predictive value of a cervicometry >30 mm is high (96-100%). On the other hand, patients with a cervical length <20 mm have high-risk of premature birth, enough to start tocolysis and steroid treatment, independently of fFN.

Therefore the conclusion seems to be that, in symptomatic patients with singleton pregnancies, the measurement of the cervix allows for an improvement in the management of the patient and to reduce inappropriate interventions, presenting, albeit with limited evidence, the possibility of a prolongation of the pregnancy compared to the control group (Berghella et al., 2019; SOGC, 2020a) (Level IIB).

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6. DOPPLER ULTRASONOGRAPHY IN OBSTETRICS

Introduction

Since its introduction in the 1980s, Doppler ultrasonography has taken on a primary role in screening, diagnosis, prognostic framing and monitoring of various diseases of both the mother and fetus, including hypertensive disorders of pregnancy, fetal growth restriction and fetal anemia. Fetal and maternal anatomical regions can now be examined with technologies that are applied to almost all ultrasound imaging systems and although Doppler ultrasonography of some anatomical regions is of particular interest for pathological cases and is therefore performed in Specialist Centres, Doppler ultrasonography is part of the basic training of Obstetricians. The rapid evolution of physiopathological knowledge and the ever-increasing application of this method means that every year a considerable number of research is conducted in this field. The recommendations presented are based on the current situation in view of the Guidelines and systematic literature reviews and the current organization of healthcare in Italy. We are aware that evidence in the field may evolve.

Recommendations

Question 1

In the general population undergoing ultrasound screening does evaluation with Doppler velocimetry of the umbilical artery improve outcomes?

Recommendation 1

Doppler ultrasonography of the umbilical artery is not recommended for screening in the general population.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

The Society of Obstetricians and Gynaecologists of Canada (SOGC) Guidelines recommend that Doppler ultrasonography of the umbilical artery should not be performed for the screening of the general population and in patients with no risk factor for fetal growth restriction.

A systematic review by the Cochrane (Alfirevic et al., 2015) comprising 5 randomized studies (14,624 women) demonstrated that the Doppler ultrasonography of the umbilical artery in pregnancies at low-risk is not associated with a reduction in the risk of mortality or perinatal morbidity.

Question 2

In the population at risk of intrauterine growth restriction and/or with prior diagnosis of intrauterine growth restriction does assessment of the umbilical artery with Doppler velocimetry improve outcomes?

Recommendation 2

Doppler ultrasonography of the umbilical artery is recommended in the high-population for the identification of fetal growth restriction and for monitoring pregnancies complicated by fetal growth restriction.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

The Guidelines of the International Federation of Gynecology and Obstetrics (FIGO, 2021) recommend that the Doppler ultrasonography of the umbilical artery should be among the parameters used for the diagnosis of fetal growth restriction (FIGO, 2021).

The Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2014) and the National Institute for Health and Care Excellence (NICE, 2019) recommend that patients with risk factors and an overall risk of more than double for fetal growth restriction (or >2.0) compared to that of the general population, including patients with abnormalities of the Doppler ultrasonography of the uterine arteries (i.e. mean pulsatility index >95th centile) between 20 and 24 weeks, should be sent for evaluation of fetal growth and Doppler velocimetry of the umbilical artery between 26 and 28 weeks (RCOG Grade of Recommendation B). The Guidelines of the National College of French Gynecologists and Obstetricians (CNOGF, 2015), of the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2012) and of the Royal College of Physicians of Ireland state that Doppler ultrasonography of the umbilical artery is recommended in all fetuses with an estimated weight of less than 10th centile in order to identify those with a fetal growth restriction.

Abnormalities of umbilical artery Doppler ultrasonography in fetuses at risk for fetal growth restriction or diagnosed with FGR are associated with a significant increase in adverse perinatal outcomes in terms of morbidity and mortality, regardless of gestational age. Being able to reduce the perinatal morbidity, the Guidelines of the RCOG, SOGC and CNOGF recommend to perform umbilical artery Doppler ultrasonography as the primary tool for monitoring the pregnancies complicated by fetal growth restriction. A Cochrane systematic review comprising 19 trials and 10,667 pregnant women (Alfirevic et al., 2017) demonstrated that the use of umbilical artery Doppler ultrasonography in pregnancies at risk for fetal growth restriction is associated to a 29% reduction in the risk of perinatal mortality (RR 0.71, 95% CI 0.52-0.98), to a 35% reduction in the risk of fetal intrauterine death (RR 0.65, 95% CI 0.41-1.04), although not statistically significant, and a reduction in the rate of caesarean sections of approximately 10% (RR 0.90, 95% CI 0.84-0.97).

The RCOG, SOGC and CNOGF Guidelines also recommend performing an umbilical artery Doppler ultrasonography in pregnancies complicated by fetal growth restriction to assess the need for early delivery. According to the SOGC Guidelines of the CNOGF, "late" abnormalities of the Doppler ultrasonography of the umbilical artery (absent end diastolic flow, AEDF, or reversed end diastolic flow, REDF) are a clinical sign in need of active management, which may include delivery in case of gestational age of more than 34 weeks. According to the RCOG Guidelines, delivery should not be deferred beyond 37 weeks in the event of abnormalities of the Doppler ultrasonography of the umbilical artery.

Question 3

In the general population does the evaluation with Doppler velocimetry of the uterine arteries in the first and second trimesters improve outcomes?

Recommendation 3a

Doppler ultrasonography of the uterine arteries in the first trimester can be used together with biochemical markers as part of a multi-parameter test for the screening of hypertensive disorders of pregnancy and fetal growth restriction in the general population.

Further studies evaluating possibilities of implementation in all regions, with particular attention to the costs and the benefits, are needed before such screening strategy is routine-ly implemented in the Italian population.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY AND A PRIMARY STUDY OF HIGH QUALITY

Recommendation 3b

Doppler ultrasonography of the uterine arteries in the second trimester is not recommended for the screening of hypertensive disorders of the pregnancy and fetal growth restriction in low-risk women.

A strong association between a pathological Doppler ultrasonography of the uterine arteries in the second trimester and pre-eclampsia, however there is no evidence on the effectiveness of drugs or strategies for the prevention of pre-eclampsia and fetal growth restriction. On this basis, the panel does not recommend the implementation of the test in the second trimester in low-risk patients.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

A systematic review (Townsend et al., 2019) summarizing the data reported in systematic reviews on the problem of pre-eclampsia prediction, reports the data of a meta-analysis relating to Doppler ultrasonography of the uterine arteries in the first trimester comprising 55,974 patients (Velauthar et al., 2019). This systematic review concluded that the finding of a pulsatility index of the uterine arteries in the first trimester >90th centile identifies: 47.8% of patients who will develop pre-eclampsia in early gestational age (criteria for early PE have not been specified, they have a false positive rate of 7.9%), 39.2% of patients who will develop early fetal growth restriction (not specified criteria for the definition of early FGR, with a false positive rate of 6.7%) and 26.4% of patients who will develop pre-eclampsia at any gestational age (6.6% false positive). The only randomized study in the literature regarding the use of uterine artery Doppler ultrasonography in the first trimester in the context of a multiparameter test including, in addition to the Doppler ultrasonography of the uterine arteries, the personal and obstetric maternal history, mean blood pressure and serum pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PGF) for screening patients at highrisk for pre-eclampsia and fetal growth restriction: it demonstrated a sensitivity greater than 75% for preterm pre-eclampsia screening in the general population, compared to 10% false positives. The same study also demonstrated that prophylaxis of high-risk patients (>1:100) by administering 150 mg/day of aspirin was associated with a reduction in the incidence of preterm pre-eclampsia by 62% (1.6% in Aspirin-treated patients vs 4.3% in placebo-treated patients, OR for Aspirin 0.38; 95% CI 0.20-0.74) (Rolnik, 2017). Based on the results of this study, screening of the general population by Doppler velocimetry of the uterine arteries has been was proposed in some places in the first trimester.

There are no studies of the impact on maternal morbidity associated with hypertensive disorders of pregnancy and uterine Doppler in the first trimester.

Doppler in the second trimester

According to the literature review published by Magee et al., Doppler ultrasonography of the uterine arteries performed between 20 and 24 weeks has a sensitivity greater than 60% for the identification of pre-eclampsia and in particular for patients at high-risk of early-onset pre-eclampsia (Magee et al. 2014; SOGC, 2012). A meta-analysis comprising 13 studies, of which 7 were conducted in low-risk patients, showed a greater than 3-fold risk of intrauterine death in patients with Doppler ultrasonography abnormalities of the uterine arteries in the second trimester (Allen et al., 2016). However, in the absence of clinical evidence demonstrating the efficacy of prevention on pre-eclampsia, intrauterine growth retardation and uterine death (Conde-Agudelo et al., 2015), Doppler ultrasonography of uterine arteries in

the second trimester is not recommended for screening low-risk patients. A Cochrane systematic review including 2 trials and 4,993 low-risk pregnant women (Stampalija et al., 2010) has shown no maternal or fetal benefits from the assessment of Doppler ultrasonography of uterine arteries in the second trimester.

A prospective study comprising 2,394 low-risk pregnant women (Myatt et al.) who underwent Doppler velocimetry of the uterine arteries in the second trimester showed that mean PI and Doppler velocimetry abnormalities of the uterine arteries are significantly more frequent in pre-eclampsia patients with severe characteristics, i.e., severe hypertension >160/110 mmHg, proteinuria >5 g/24hours, oliguria, pulmonary oedema, thrombocytopenia, HELLP syndrome and eclampsia.

Question 4

In high-risk pregnancies for hypertensive disorders of pregnancy and intrauterine growth restriction* does the assessment of Doppler velocimetry of the uterine arteries in the first trimester improve outcomes?

(*history of previous hypertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small newborn for gestational age or suspected slowing of fetal growth).

Recommendation 4

Doppler ultrasonography of the uterine arteries in the first trimester can be used together with bio-chemical markers as part of a multi-parameter test for the screening of hypertensive disorders of the pregnancy and fetal growth restriction in a population at high-risk. According to the existing guidelines, maternal and obstetric history represent the first line screening for hypertensive disorders of the pregnancy and fetal growth restriction.

The panel emphasizes, however, that the multi-parameter test has a greater sensitivity and specificity than maternal and obstetric history and may help in identifying the best preventive strategy. The panel also highlights that further cost-effectiveness studies are needed to evaluate the applicability of such screening strategy before its routine implementation.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON A HIGH QUALITY GUIDELINE AND A MODERATE QUALITY PRIMARY STUDY

Literature Analysis and Evidence Interpretation

In accordance with the National Institute for Health and Care Excellence (NICE, 2019) Guidelines, patients at high-risk of hypertensive disorders of pregnancy and fetal growth restriction are candidates for low dose Aspirin prophylaxis from the first trimester of pregnancy on an anamnestic basis and therefore Doppler ultrasonography of the uterine arteries does not provide additional useful information for a preventive program.

A secondary analysis of the only randomized study in the literature concerning the use of Doppler ultrasonography of uterine arteries in the first trimester in the context of a multi-parameter test comprising, in addition to Doppler ultrasonography of the uterine arteries, also the maternal and obstetric history of the mother, mean blood pressure and serum pregnancy-associated plasma protein type A (PAPP-A) and placental growth factor (PGF) for screening patients at high-risk for pre-eclampsia and intrauterine growth restriction (Rolnik, 2017) has however shown greater sensitivity of multi-parameter screening compared to anamnestic screening in the identification of preterm pre-eclampsia in the general population.

Question 5

In high-risk pregnancies for hypertensive disorders of pregnancy and intrauterine growth restriction* does the evaluation of Doppler velocimetry of the uterine arteries in the second trimester improve outcomes?

(*history of previous hypertensive disorders of pregnancy, autoimmune diseases such as SLE and ALPS, prior small newborn for gestational age or suspected slowing of fetal growth).

Recommendation 5

Doppler ultrasonography of the uterine arteries in the second trimester is recommended for the prediction of pre-eclampsia and fetal growth restriction in high-risk patients.

Albeit in the absence of preventive strategies, the detection of changes of the Doppler ultrasonography in high-risk patients may allow clinical surveillance aimed and improve clinical outcomes.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

The Royal College of Obstetricians and Gynaecologists Guidelines recommend that patients with three or more minor risk factors for fetal growth restriction be submitted for assessment of Doppler velocimetry of uterine arteries between 20 and 24 weeks in view of the moderate predictive value due to severe intrauterine growth restriction in patients at risk. In accordance with the Guidelines of the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2012), the assessment of Doppler velocimetry of uterine arteries may play a role in defining the aetiology of intrauterine growth restriction. Doppler velocimetry of the uterine arteries performed between 20 and 24 weeks has a sensitivity greater than 60% for the identification of pre-eclampsia. The sensitivity of ultrasound screening by Doppler velocimetry of uterine arteries increases in patients at high-risk for pre-eclampsia and for early-onset pre-eclampsia (Magee et al., 2014). A meta-analysis comprising 74 studies, including 3 randomized studies, showed that finding an abnormal pulsatility index associated with bilateral notching is the most important predictive parameter of pre-eclampsia in high-risk patients. While accuracy in identifying at-risk patients who will develop intrauterine growth restriction is lower (Cnossen et al., 2008). A second meta-analysis comprising 13 studies, including 6 studies in at-risk patients, showed a greater than 3 times higher-risk of intrauterine death in patients with Doppler velocimetry abnormalities of the uterine arteries in the second trimester (Allen et al., 2016).

Question 6

In pregnancies complicated by hypertensive disorders of pregnancy or intrauterine growth restriction does evaluation with Doppler velocimetry of the uterine arteries in the third trimester improve outcomes?

Recommendation 6

Doppler ultrasonography of the uterine arteries in the third trimester may be performed in patients with hypertensive disorders of pregnancy or fetal growth restriction. POSITIVE CONDITIONAL RECOMMENDATION

 RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES FOR INTRAUTERINE GROWTH RESTRICTION, ONLY ON PRIMARY STUDIES OF MODERATE QUALITY

FOR HYPERTENSIVE DISORDERS OF PREGNANCY

Literature Analysis and Evidence Interpretation

Pregnancies with intrauterine growth restriction

In accordance with the Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2014), Doppler velocimetry of the uterine arteries has limited accuracy in predicting adverse perinatal outcomes in pregnancies complicated by intrauterine growth restriction in the third trimester.

A meta-analysis comprising 17 observational studies and 3,461 fetuses with suspected intrauterine growth restriction evaluated the clinical role of Doppler velocimetry abnormalities of uterine arteries in predicting perinatal outcomes in fetuses with suspected gestational intrauterine growth restriction diagnosed at more than 32 weeks; these authors reported a sensitivity ranging from 34.6% to 54% for adverse perinatal outcomes compared to a specificity ranging from 74.2% to 97.2% (Martinez-Portilla et al., 2020).

Pregnancies complicated by hypertensive disorders of pregnancy

A retrospective study comprising 168 patients with pre-eclampsia demonstrated a 70% increase in the risk of adverse perinatal outcomes (OR 1.7; 95% CI 1.4-2.1, p<0.001) in patients with changes in Doppler velocimetry of uterine arteries and an increase of 60% (OR 1.6; 95% CI 1.3-1.9, p<0.001) of the risk of adverse maternal outcomes including delivery before 34 weeks due to maternal indication (Orabona et al., 2015). Regarding the usefulness of Doppler velocimetry of uterine arteries in patients with hypertensive disorders of pregnancy, a prospective study comprising of 100 patients with severe pre-eclampsia at >28 weeks of gestation, demonstrated significantly higher uterine artery PI values in symptomatic patients and in patients with complications associated with hypertensive disorders of pregnancy, including antepartum and postpartum haemorrhage, HELLP, acute pulmonary oedema and postpartum convulsions (Maged et al., 2015). Another prospective study comprising 231 pregnancies complicated by Hypertensive Disorders of Pregnancy (HDP) (152 preterm on the basis of delivery at <37 weeks and 79 at full-term) demonstrated higher mean PI values of uterine arteries in preterm HDP patients compared to patients with full-term HDP and controls (Perry et al., 2019).

Question 7

In pregnancies complicated by intrauterine growth restriction does the evaluation of Doppler velocimetry of the middle cerebral artery improve outcomes?

Recommendation 7

Doppler ultrasonography of the middle cerebral artery is recommended in pregnancies complicated by fetal growth restriction.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH OR MODERATE QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

The Guidelines of the International Federation of Gynecology and Obstetrics (FIGO, 2021) recommend Doppler ultrasonography of the middle cerebral artery in fetuses at risk for intrauterine growth restriction and for the monitoring of fetuses with fetal growth restriction (FIGO, 2021).

The Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2013) recommend that delivery should be planned no later than 37 gestational weeks in pregnancies complicated by intrauterine growth restriction presenting abnormalities of the Doppler

ultrasonography of the middle cerebral artery. In accordance with these guidelines, the finding of a middle cerebral artery pulsatility index <5th centile in small fetuses for gestational age with normal umbilical Doppler velocimetry at full-term has a moderate predictive value for acidemia at the time of delivery.

In a meta-analysis comprising 128 studies and 47,748 patients, Doppler abnormalities of the middle cerebral artery showed a sensitivity ranging from 13% to 100% and a specificity ranging from 67% to 97% for the identification of adverse perinatal outcomes in intrauterine growth-restricted fetuses (Vollgraff Heidweiller-Schreurs et al., 2018).

A meta-analysis comprising 22 studies and 4,301 patients demonstrated a sensitivity of 93% and a specificity of 76% of the cerebroplacental ratio in the identification of perinatal death, whose probability is reduced from 2% to 0,2% in the presence of a normal cerebroplacental ratio (Conde-Agudelo et al., 2018).

A systematic review of the literature comprising 9 studies and 1,198 fetuses demonstrated an association between the abnormalities of Doppler velocimetry of the middle cerebral artery and the cerebroplacental ratio in fetuses with suspected intrauterine growth restriction near full-term; it is associated with an increased risk of motor and postural abnormalities in the evaluation with the Neonatal Behavioural Assessment Scale, as well as with a lower communication score and a lower capacity to solve problems at the age of 2 in the evaluation via the Ages and Stages Questionnaire. This systematic review of the literature has also shown an association between the abnormalities in Doppler velocimetry of the middle cerebral artery and the cerebroplacental ratio in fetuses with suspected preterm intrauterine growth restriction and an increased risk of psychomotor development abnormalities at 1 year of age in the evaluation via the Bayley Scale (Meher et al., 2015).

Question 8

In pregnancies at risk for fetal anemia does the evaluation with Doppler velocimetry of the middle cerebral artery improve outcomes?

Recommendation 8

Doppler ultrasonography of the middle cerebral artery is recommended in pregnancies at risk for fetal anemia.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON A LOW QUALITY GUIDELINE

Literature Analysis and Evidence Interpretation

The Society for Maternal-Fetal Medicine Guidelines recommend the measurement of the peak systolic velocity (PSV) of the middle cerebral artery (MCA) as the primary method for screening/identifying fetal anemia in pregnancies which are only at risk of developing fetal anemia (SMFM Recommendation 1B). The data available to date demonstrate a slight correlation between MCA-PSV and the haemoglobin level in fetal blood in non-anemic or mildly anemic fetuses. However, the decrease in haemoglobin levels is associated with a progressive increase in MCA-PSV and it can therefore be used to estimate haemoglobin values with a sensitivity close to 100% for moderate or severe anemia, with a false positive rate of 12%.

In the presence of MCA-PSV >1.5 multiples of the median (MoM) in pregnancies at risk of fetal anemia, cordocentesis is indicated for the determination of fetal haemoglobin levels and possible intrauterine transfusion, with the exception of cases where the risk of premature iatrogenic delivery is lower than the risk of intrauterine transfusion (SMFM Grade of Recom-

mendation 1B). Treatment by intrauterine transfusion reduced perinatal mortality of fetuses with severe anemia to less than 10%, although there were differences related to the cause of the anemia. The Society for Maternal-Fetal Medicine Guidelines recommend that MCA-PSV be used for longitudinal monitoring in order to assess the need for a second intrauterine transfusion in the case of MCA-PSV >1.5 MoM, but not for subsequent transfusions (SMFM Recommendation Grade 2C).

Question 9

In pregnancies complicated by intrauterine growth restriction <32 weeks (severe/early) does evaluation with Doppler velocimetry of the ductus venosus improve outcomes?

Recommendation 9

Doppler ultrasonography of the ductus venosus is recommended in pregnancies complicated by fetal growth restriction <32 weeks.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A HIGH QUALI-TY PRIMARY STUDY

Literature Analysis and Evidence Interpretation

The Guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG, 2013), the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2012) and the International Federation of Gynecology and Obstetrics (FIGO, 2021) recommend the use of Doppler velocimetry of the ductus venosus in fetuses with intrauterine growth restriction at <32 weeks gestational age and Doppler velocimetry abnormalities of the umbilical artery in order to identify optimal timing of delivery. The RCOG Guidelines recommend that Doppler velocimetry of the ductus venosus be used for monitoring pregnancies complicated by intrauterine growth restriction <32 weeks, with delivery indication when late abnormalities are detected (zeroing or inversion of the "A" wave). The RCOG and CNOGF Guidelines recommend that if late Doppler velocimetry abnormalities of the ductus venosus are observed, or alternatively fetal heart rate abnormalities detected during monitoring by computerized cardiotocography (STV <3.0 msec) or conventional cardiotocography (repetitive decelerations), the recommendation is to deliver in pregnancies that are complicated by intrauterine growth restriction <32 weeks, after corticosteroid prophylaxis. The CNOGF Guidelines recommend that Doppler velocimetry of the ductus venosus be performed only by certified operators and only in cases where the delivery option is expected by the 32nd week.

In accordance with the RCOG Guidelines, Doppler velocimetry of the ductus venosus has a moderate predictive value for acidemia and adverse outcomes; its incidence increases from 12% (OR 2.12; 95% CI 0.66-6.83) in the presence of only umbilical Doppler velocimetry abnormalities to 41% (OR 5.68; 95% CI 1.67-19.32) in the presence of late changes in Doppler velocimetry of the ductus venosus.

The Guidelines of the International Federation of Gynecology and Obstetrics (FIGO, 2021) recommend that delivery by caesarean section in fetuses with Doppler velocimetry abnormalities of the ductus venosus be considered (FIGO, 2021). The most recent and extensive randomized study in the literature regarding the use of Doppler velocimetry of the ductus venosus in monitoring and timing of delivery in pregnancies complicated by intrauterine growth restriction <32 weeks reported an overall incidence of caesarean sections of 97% (Lees et al., 2013). On the basis of the results of this study, caesarean section should be considered the elective mode of delivery in the presence of alterations of the Doppler ultrasonography of the ductus venosus indicating immediate delivery.

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7. ULTRASOUND IN THE DELIVERY ROOM

Introduction

In recent years there has been an increasing number of studies on the use of ultrasound in the assessment of labour and in emergencies in the delivery room.

Although it has not yet entered into routine clinical practice, we thought it important to insert this chapter precisely to emphasize its potential role and to take stock of what the literature defines and it is our hope to encourage further clinical studies.

Ultrasound applied to the various phases of labour can in fact represent an important step forward in measuring what up to now has been only been evaluated with subjective clinical evaluations (position, station, progression) based on clinical semeiotics, that are important but perhaps not very reproducible. Far from solving problems related to childbirth in which, as we know, important clinical, psychological and welfare factors, which are still difficult "to measure" (one-to-one care, empowerment, painless delivery) intervene, ultrasound can be an important element that progressively enters our delivery rooms if clinical impact studies confirm its usefulness and reproducibility on a large scale.

Recommendations

Question 1

In women in regular active labour, is it useful to perform an ultrasound to improve the outcome of childbirth?

Recommendation 1

Routine ultrasound is not recommended to improve delivery outcomes in active labour.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

According to ISUOG Guidelines (Evidence Level 1 Grade of Recommendation A), although ultrasound was superior to clinical evaluation in the determination of fetal occiput position and the leading portion of the head in fetal head station, its greater accuracy in defining these parameters has shown no advantages in improving maternal and neonatal outcomes and in predicting the mode of delivery in low-risk, uncomplicated labour (Ghi et al., 2018). To date, there is only one randomized study in more than 1,800 patients during low-risk labour, which showed no benefits in using routine intrapartum ultrasound; it actually appears to be associated with an increased rate of medical intervention (Popowski et al., 2015). Furthermore, no benefits have been shown with regard to vaginal delivery rates or caesarean sections, or to the reduction of neonatal mortality and morbidity.

In view of the relative rarity of adverse maternal and perinatal events, prospective randomized studies with large sample size are required to demonstrate an advantage of ultrasound in affecting these.

Question 2

In women with extension/arrest of the first stage of labour, is it useful to perform an ultrasound to improve the outcome of childbirth?
Recommendation 2

It is recommended that ultrasound should not be routinely performed to improve delivery outcomes in all women with stage I labour extension/arrest.

Note: The lack of available data does not allow for a positive recommendation to be made in any case for the use of ultrasound in stage I labour extension/arrest. However, if the delivery room is equipped with an ultrasound system and healthcare workers are specifically trained in the use of ultrasound during labour, its execution can help the clinician in the management of labour and in the formulation of a prognosis for delivery.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies on the use of ultrasound in the delivery room and enhancing the specific training of doctors and midwives working in the delivery room.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

In cases with stage I arrest/extension, it has been shown that ultrasound diagnosis is more accurate than clinical diagnosis in determining the occiput position and cephalic presentation and that some ultrasound parameters were predictive of delivery outcome (Ghi et al., 2018).

The ultrasound allows for the recognition of the presence of a occiput-posterior position, which is associated with a higher probability of caesarean section (38% vs 17%) (Eggebø et al., 2014). The assessment of the degree of fetal head engagement, which can be measured with ultrasound by determining the Head Perineum Distance (HPD) and the Angle of Pregression (AoP), is in these patients associated with the delivery mode: HPD values >50 mm and AoP values <100° were associated with a higher caesarean section incidence, specifically for HPD values >50 mm the incidence of caesarean section was 82% vs 7% in cases with HPD values <40 mm; similarly, for AoP values <100° the incidence of caesarean sections was 62% vs 12% of caesarean section in cases with AoP >110° (Eggebø et al., 2014). However, it should be recognized that, although the ISUOG Guidelines recognize a 2+ Level of Evidence and a Grade of Recommendation B for the measurement of HPD and AoP in prolonged Stage I, this assumption is based only on the above data from a single multi-centre study of 150 patients (Eggebø et al., 2014).

An observational study, also reported by the ISUOG Guidelines, found that the Occiput Spine Angle (OSA) value measured in Stage I correlates with the duration of labour: values >125° are associated with a shorter duration of labour, even if parity is the most important independent factor (Ghi et al., 2016).

Ultrasound also demonstrates fetal head malpositions, deflected presentations (forehead, face) and asynclitisms that are potential causes of labour prolongation. The Level of Evidence 3 and the Grade of Recommendation C of the ISUOG Guidelines in this context derives from the publication of only case reports or a limited series of cases.

With regard to the effect of ultrasound on neonatal and maternal morbidity, given the rarity of these events, the ISUOG Guidelines and the studies available to date do not achieve scientific evidence to make recommendations.

Question 3

In women with extension/arrest of stage II labour, is an ultrasound useful in improving delivery outcomes?

Recommendation 3

It is recommended that ultrasound should not be routinely performed to improve delivery outcomes in all women with stage II labour extension/arrest.

Note: However, data are scarce and therefore do not allow for a positive recommendation to be made on the use of ultrasound to improve delivery outcomes in the case of a prolonged stage II labour. Its execution can be of assistance to the clinician, both for greater accuracy in defining fetal position and station, and in formulating a prognosis for delivery in cases where the delivery room is equipped with an ultrasound system and healthcare workers are specifically trained in the use of ultrasound during labour.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies on the use of ultrasound in the delivery room and enhancing the specific training of doctors and midwives working in the delivery room.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND SYSTEMATIC REVIEWS AND LOW QUALITY PRIMARY STUDIES

Literature Analysis and Evidence Interpretation

Observational studies have shown that in the presence of an arrest/delay in stage II labour, ultrasound, which is more accurate in the diagnosis of fetal head position and station, can help to recognize predictive parameters of delivery outcome.

It has been shown that the upward direction of the leading portion of the head in occiput-anterior position during pushing is associated with an 80% probability of vaginal delivery, while transverse or downward directions are less likely to reach vaginal delivery (41% and 20%, respectively) (Masturzo et al., 2014). A study by Kalache et al. in 2009 showed that in the case of a fetus in the OA position the amplitude of AoP is proportional to the probability of achieving vaginal delivery and that an amplitude >120° is indicative of carrying out an effective operative delivery (Kalache et al., 2009). In 2013 Gilboa et al., in a prospective study of about 60 patients in the second extended stage, showed that head progression distance, although not predictive of the delivery mode, is a valid aid in the definition of the fetal head station (Gilboa et al., 2013). Work following the publication of the ISUOG Guidelines by Dall'Asta et al. showed that in the presence of a second stage extension, HPD and the Midline Angle (MLA) are independently correlated with the outcome of delivery and with the need for medical intervention (Dall'Asta et al., 2019). In a cohort of women with stage Il extension Chan et al. showed that the measurement of AoP at rest and at the acme of contraction is associated with the feasibility of an uncomplicated operative delivery in 80% of cases (Chan et al., 2019).

Again, ultrasound can be helpful in these cases as it allows for the observation of the presence of fetal head malpositions (occiput-posterior), deflected presentations (forehead, face) and asynclitisms at the base of stage II dystocia. The Level of Evidence 3 and Grade of Recommendation C of the ISUOG Guidelines is derived from case reports or a limited series of cases. A recent meta-analysis analysed the ability of intrapartum ultrasound to detect persistent occiput-posterior fetal positions, defining a sensitivity and specificity of the method when performed after 4 cm of dilation of 92% and 85%, respectively (Tao et al., 2019).

Observational studies have found that in selected healthcare contexts, ultrasound demonstration to the mother of the progression of the head during the push may increase the effectiveness of the expressed effort (visual coaching) (Bellussi et al., 2018; Gilboa et al., 2018).

As for neonatal and maternal morbidity, given the rarity of these events, current studies do not allow recommendations to be made.

Question 4

In women in stage II of labour, where there are indications for an urgent operative delivery, is it useful to perform an ultrasound prior to the application of the obstetric vacuum extractor to improve maternal and perinatal outcome?

Recommendation 4

In women in stage II of labour where indication is given for an operative delivery, the panel suggests performing an ultrasound check when the operator is unsure of the position of the fetal occiput after clinical evaluation and there are no emergency conditions.

Recommendations for research: the panel emphasizes the importance of implementing clinical studies and enhancing the training of doctors and midwives working in the delivery room for a broader use of ultrasound in the delivery room.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON MODERATE QUALITY GUIDELINES AND MODER-ATE QUALITY PRIMARY STUDIES

Literature Analysis and Evidence Interpretation

Ultrasound evaluation allows for a more accurate diagnosis of the occiput position before an operative vaginal delivery (ISUOG Level of Evidence 1 Grade Recommendation A) (Ghi et al., 2018) and is advised prior to operative vaginal delivery when the operator, after clinical evaluation, is unsure of the fetal head position (RCOG, 2020, Evidence Level A) (Murphy, Strachan, Bahl, 2020).

A randomized controlled study showed that the use of the obstetric vacuum extractor is more accurate and used at a more optimal time (flexion point) when the operator also uses ultrasound rather than only clinical methods (Wong GY, Mok, Wong SF, 2007).

Some observational studies have highlighted a possible role of ultrasound in predicting the success of operative delivery, by analysing both qualitative and quantitative parameters. The upward direction of the fetal head in the case of anterior occiput was predictive of a successful outcome of the operative delivery (ISUOG Evidence Level 3 Grade Recommendation C) (Henrich et al., 2006). A retrospective study on a consecutive series of 196 patients undergoing operative delivery showed that the "occiput sign" for fetuses in OA and the "forehead sign" in fetuses in OP correlate with the success of operative delivery (Bellussi et al., 2019).

An observational study of 41 cases of operative delivery with an occiput-anterior fetus showed that AoP values >120° correlate with a probability of success and ease of execution of operative delivery in 90% of cases (ISUOG Level of Evidence 2+ Grade Recommendation B) (Kalache et al., 2009). An observational study including 235 patients demonstrated that operative delivery failure was associated with a lower mean AoP value compared to a successful assisted delivery (136.6° *vs* 145.9°) (Bultez et al., 2016), while in a study of more than 600 patients HPD values of >40 mm were associated with a difficult instrumental extraction (Kasbaoui et al., 2017).

Recently, some studies have proposed a dynamic evaluation of the ultrasound parameters (HPD and AoP), measured at rest and at the pushing acme, as a further aid in defining the feasibility and success of operative delivery (Kahrs et al., 2019).

In a single prospective multi-centre study (Kahrs et al., 2019), the duration of operative vaginal delivery was also compared to ultrasound parameters, resulting in lower duration in cases with HPD <25 mm.

In a randomized, multi-centre Italian study R.I.S.P.O.S.T.A., intrapartum ultrasound prior to vacuum extraction, although more accurate in defining the position of fetal occiput, did not however, show any benefits in terms of predicting failure of the procedure and impact on maternal-perinatal outcomes. It should be noted, however, that the study was interrupted early and the sample size was underpowered for evaluating the outcome.

A second, more recent, randomized study (Barros et al., 2021) showed no evidence of the usefulness of pre-instrumental ultrasound in terms of maternal-neonatal outcomes, but the sample was undersized for the evaluation of these outcomes.

There is no evidence from the data available to date that the use of ultrasound prior to operative delivery has an impact on maternal-neonatal morbidity.

Question 5

In women with haemorrhage after vaginal delivery, is it useful to perform a transabdominal ultrasound to improve outcomes?

Recommendation 5

Routine ultrasound evaluation to improve outcomes is not recommended in women with bleeding after vaginal delivery.

STRONG NEGATIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND MODERATE QUALITY PRIMARY STUDIES

Literature Analysis and Evidence Interpretation

According to the RCOG Guidelines, pelvic ultrasound is able to identify the presence of material that is deemed placental (RCOG Level of Evidence 2+ Grade Recommendation C) but has a very variable degree of sensitivity and specificity that make the diagnosis unreliable (No, 2017). Although the use of colour Doppler can be proposed and is particularly useful in the presence of arteriovenous malformations, according to the RCOG indications it does not achieve a level of evidence as to give a recommendation (Kahrs et al., 2017).

If necessary and if the operator has the competence, it is possible to carry out a curettage by means of ultrasound guidance (RCOG Evidence Level 3) (Kahrs et al., 2017). There is no evidence that ultrasound can predict the need for intrauterine tamponade. There are case reports on the use of ultrasound in guiding the positioning of the Bakri balloon (Cho et al., 2008).

A prospective study has shown that the assessment of uterus size (distance from the bottom of the isthmus) and the presence of material inside which has a sonographic thickness of >2 cm correlate with a loss of haemoglobin >3 g/dl (Hori et al., 2020).

There is no evidence that ultrasound improves maternal outcomes.

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8. ULTRASOUND IN GYNAECOLOGY

Introduction

Pelvic ultrasound has become an integral part of gynaecological evaluation, allowing for an undeniable significant increase in diagnostic accuracy.

It is performed with a combined transvaginal and transabdominal approach in combination with Doppler assessment.

It is an easily accessible examination, carried out directly by the gynaecologist during the check up, it is neither invasive nor painful, and it is not expensive.

Unlike other imaging techniques, ultrasound is an interactive and dynamic examination, based on communication between the physician and the patient. It provides information of fundamental importance for the management approach. In fact, it is able to discriminate between benign adnexal masses and malignant masses with high accuracy.

It allows examiners to evaluate the entire pelvis, identifying adnexal, endometrial, myometrial and cervical pathologies and uterine malformations.

Recommendations

Question 1

In women with pelvic pain does performing a transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 1

Transvaginal ultrasound is recommended in all cases of pelvic pain as it allows for a differential diagnosis and adequate management.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH OR MODERATE QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Pelvic pain is a frequent symptom, which can occur in acute, subacute and chronic forms. It can affect woman of all ages. Acute pain is more common in premenopausal periods (ACR, 2020). There may be several different causes, which can be divided into (ACR, 2015; ACOG, 2020):

- gynaecological causes (benign or malignant ovarian masses, endometriosis, adenomyosis, pelvic inflammatory disease, ovarian torsion, uterine fibroids, endometritis, adhesive disease) or obstetric causes (ectopic pregnancy, miscarriage, placental abruption);
- non-gynaecological causes (appendicitis, inflammatory bowel disease, intestinal infections, diverticulitis, urinary tract stones, pyelonephritis, pelvic thrombophlebitis).

The imaging technique of first choice should be established on the basis of diagnostic suspicion, after collecting the detailed and comprehensive history of the patient, performing a careful clinical evaluation and requesting laboratory tests in a targeted manner (ACR, 2015).

According to NICE (2017) in case of pelvic pain, examiners should consider transvaginal (and transabdominal) ultrasound:

- in case of severe, persistent or recurrent pelvic signs and/or symptoms suspected of endometriosis;
- in case of suspected endometriosis, even if the pelvic and abdominal examinations are normal;
- to identify endometriomas and deep endometriosis that involves the intestine, bladder or ureter.

The possibility of endometriosis should not be excluded if abdominal or pelvic examination, ultrasound or MRI are normal. If clinical suspicion and symptoms persist, consider referring the patient to a Specialist Centre for further evaluation and investigation (NICE, 2017).

ESHRE also believes that transvaginal ultrasound is useful for diagnosing or excluding ovarian endometriosis (A) (ESHRE, 2013).

The American College of Radiology (ACR) believes that pelvic ultrasound (transvaginal and transabdominal) is the preferred imaging method for initial assessment of pelvic pain when obstetric or gynaecological aetiology is suspected due to: its widespread availability, the absence of exposure to ionizing radiation, and its diagnostic versatility (ACR, 2015; ACR, 2018; ACR, 2020).

Doppler assessment is an integral part of the pelvic ultrasound (ACR, 2020), helping to improve a differential diagnosis (ovarian torsion, PID, study of adnexal masses, uterine fibroids).

According to the SOGC (SOGC, 2018) pelvic ultrasound is also a useful imaging technique to approach patients with pelvic pain.

According to the American College of Obstetricians and Gynecologists (ACOG), patients with uterine or adnexa tenderness or suspected pelvic masses should undergo transvaginal ultrasound. Even in cases of suspected chronic pelvic inflammatory disease, carrying out a transvaginal ultrasound (ACOG, 2020) is suggested, especially in cases of difficult diagnosis (RCOG, 2003). Ultrasound may identify the presence of dilated and inflamed salpinges and tubo-ovarian abscesses/complexes (RCOG, 2003) when associated with the use of Doppler.

According to the French guidelines (CNGOF/SPILF, 2020) pelvic ultrasound does not seem to contribute to the diagnosis of PID if not complicated, because its sensitivity and specificity are both not very high. However, the recommendation is to look for signs of complicated PID (collections of inhomogeneous hypoechoic fluid) or to use ultrasound for the differential diagnosis (Grade C). Waiting to carry out the ultrasound should not delay the initiation of antibiotic treatment (CNGOF/SPILF, 2020).

The RCOG also considers transvaginal ultrasound to be an appropriate method of investigation in the identification of adnexal masses in women with chronic pelvic pain (B) and in the diagnosis of adenomyosis (B) (RCOG, 2012).

According to the CNGOF/HAS Guidelines (2018) the first-line diagnostic investigations in case of suspected endometriosis are a gynaecological evaluation (if possible) and pelvic ultrasound (Consensus of experts). If an indeterminate ovarian mass is observed at ultrasound (with a non-endometrioma appearance), ultrasound should be repeated with an expert examiner (Grade A) or pelvic magnetic resonance imaging (Grade B) is recommended. Patients with an endometrioma often also present with deep endometriosis lesions, therefore a detailed ultrasound assessment of the entire pelvis is recommended for the investigation of these possible lesions (Grade C). Specifically, in patients with chronic pelvic pain, the recommendation is to search for the following via ultrasound: lesions of deep endometriosis in cases of dyschezia during menstruation, cyclical urinary symptoms or severe deep dys-

pareunia, or in cases of infertility (Grade B). In the case of deep endometriosis, second-level pelvic ultrasound performed by an ultrasound examiner and/or pelvic magnetic resonance imaging interpreted by an experienced radiologist may be offered to confirm the diagnosis (Grade B), in particular prior to surgery for the removal of deep pelvic endometriosis, in order to determine if any urinary tract or bowel surgical procedures are also needed (Grade C).

Pelvic ultrasound for deep endometriosis should be performed by an ultrasound examiner with extensive experience in endometriosis patients evaluation (Grade B) (CNGOF/ HAS, 2018).

Pelvic ultrasound and pelvic magnetic resonance imaging have similar performance levels for the diagnosis of endometrioma in terms of diagnostic accuracy (Grade B) (CN-GOF/HAS, 2018).

Transvaginal pelvic ultrasound performed by an examiner who is experienced in endometriosis is more sensitive than pelvic magnetic resonance imaging for the diagnosis of rectum and rectosigmoid endometriosis. The diagnostic accuracy of pelvic ultrasound in the diagnosis of anterior deep endometriosis (bladder lesions) shows a very variable sensitivity ranging from 15% to 100% associated with excellent specificity between 98% and 100% (Grade C). Normal ultrasound findings do not exclude the presence of deep endometriosis of the anterior compartment. The diagnostic accuracy of transvaginal ultrasound is higher when the examiner is informed of the existence of deep endometriosis. Transvaginal ultrasound is more sensitive than clinical examination for the diagnosis of endometriomas, endometriosis lesions of uterine ligaments and of the lesions of rectosigmoid (Grade B). The combination of the gynaecological examination associated with transvaginal ultrasound may increase the diagnostic sensitivity of ultrasound, particularly for the diagnosis of pouch of Douglas obliteration (Grade B) (CNGOF/HAS, 2018).

For the diagnosis of deep endometriosis, pelvic magnetic resonance imaging is more sensitive but less specific than pelvic ultrasound. A negative pelvic magnetic resonance image allows deep endometriosis to be excluded with the same accuracy as laparoscopic diagnosis, however, ultrasound does not. A positive transvaginal ultrasound allows operators to ascertain the presence of deep endometriosis nodules with a specificity that can be superimposed to a laparoscopic diagnosis, in contrast to pelvic magnetic resonance which is often characterized by a series of false positives (Grade B) (CNGOF/HAS, 2018).

There is no scientific evidence to allow us to respond to outcome 1 and outcome 2. It is not possible to determine whether pelvic ultrasound can reduce the number of hospital admissions in women with pelvic pain or whether it can reduce the number of days of hospitalization. It is possible, however, to assume that pelvic ultrasound performed by an experienced examiner as an initial diagnostic examination, is able to distinguish between the causes of pain requiring conservative medical treatment and those requiring urgent surgical treatment (ACR, 2015). This may reduce the number of inappropriate admissions and may reduce the number of days of hospitalization, providing essential diagnostic elements for adequate follow-up during conservative management (e.g. haemoperitoneum from a bleeding corpus luteum in haemodynamically stable patients). Moreover, ultrasound can potentially reduce the number of surgical interventions, identifying cases that could benefit from a conservative management.

In the assessment of patients with pelvic pain of gynaecological origin, pelvic ultrasound can help in differential diagnosis, distinguishing between causes requiring medical treatment (functional ovarian cysts, PID/*Outcome* 4) and causes requiring an urgent surgical management (ovarian torsion/*Outcome* 3) (ACR, 2015).

Question 2

In women with abnormal uterine bleeding, does transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 2

A pelvic ultrasound is recommended in women with abnormal uterine bleeding, both in fertile and postmenopausal age, because: it allows for a differential diagnosis, it identifies patients at high-risk for endometrial cancer and contributes to appropriate management. STRONG POSITIVE RECOMMENDATION

➡ RECOMMENDATION BASED ON HIGH OR MODERATE QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

Abnormal uterine bleeding (AUB) is an abnormal blood loss from the uterus with regard to regularity, volume, frequency and duration.

It may be acute or chronic, affecting women of childbearing age (heavy menstrual bleeding HMB/intermenstrual bleeding IMB) or women in menopause. The causes can be differentiated into:

- organic (PALM/COEIN classification: polyps, adenomyosis, leiomyomas, malignant uterine disease and hyperplasia);
- non-organic (coagulopathies, ovulatory, endometrial, iatrogenic, not yet classified dysfunctions).

The organic causes can be diagnosed with *imaging* techniques; in premenopause the most frequent causes are: polyps, adenomyosis, uterine fibromas. Although abnormal uterine bleeding may be due to benign organic causes (polyps, endometrial hyperplasia) during menopause, endometrial carcinoma is the most serious cause and represents about 1-11% of all possible aetiologies. Therefore, the main focus of the workup in postmenopause patients with AUB is on the exclusion of endometrial cancer or precancerous lesions (ACR, 2020).

NICE believes that pelvic ultrasound or hysteroscopy are the most effective diagnostic strategies in the evaluation of patients with atypical blood losses. Pelvic ultrasound is the most widely used technique as it is an easily accessible and available examination, considered less invasive than hysteroscopy. On the other hand, hysteroscopy can allow for the simultaneous treatment of intrauterine diseases (submucosal fibroids, uterine polyps) and can facilitate the insertion of LNG-IUS. The gynaecological history and examination may guide the gynaecologist in choosing the first-line imaging technique in women with abnormal uterine bleeding (NICE, 2018).

NICE specifies that sonohysterography should not be used as a first-choice examination in the diagnosis of HMB/"heavy menstrual bleeding" (NICE, 2018). The American College of Radiology believes that sonohysterography plays a role in the diagnosis of abnormal uterine bleeding in cases where findings from the transvaginal ultrasound need further diagnostic definition (e.g. finding of focal endometrial lesions in transvaginal ultrasound). In postmenopausal women with abnormal uterine bleeding and endometrial thickening sonohysterography can help in the differential diagnosis between focal and diffuse pathology. Saline solution is considered the contrast medium of choice, despite the use by some authors of certain gels (ACR, 2020).

NICE also suggests offering transvaginal ultrasound (preferring it to transabdominal ultrasound or magnetic resonance imaging) to women with abnormal uterine bleeding who have significant amenorrhoea or an increased uterine volume and painful uterus on clinical examination, that may suggest adenomyosis (NICE, 2018). Even according to the American College of Radiology (ACR, 2020) in patients with abnormal uterine bleeding, transvaginal and transabdominal pelvic ultrasound in combination with Doppler is the most appropriate initial imaging technique of choice (ACR, 2020).

The Royal College of Obstetricians and Gynaecologists (RCOG) believe that transvaginal ultrasound may play a role in the diagnosis of endometrial hyperplasia in pre- and post-menopause (RCOG, 2016). In premenopausal women, endometrial thickness and morphology vary depending on the phase of the menstrual cycle. Numerous studies have shown that the thickness of the premenopausal endometrium is not an indicator of endometrial disease and even in cases of endometrial thickness less than 5 mm, polyps or other endometrial diseases may be present. There are no validated cut-offs for the upper limit of endometrial thickness considered normal in premenopause (ACR, 2020). The most appropriate phase of the menstrual cycle to perform an optimal ultrasound evaluation of the endometrium is the early follicular phase, once the menstruation has ended.

Both in post- and premenopause, irregular echogenicity and irregular endometrial ecostructure have been correlated with a significant risk of intrauterine disease (ACR, 2020).

For the American College of Radiology (ACR) in postmenopausal women with abnormal uterine bleeding, transvaginal ultrasound is also considered the first-line investigation for the diagnosis of endometrial carcinoma (ACR, 2020).

An endometrial thickness of 4 mm in postmenopause expresses a negative predictive value for endometrial carcinoma of almost 100% (ACR, 2020).

Although transvaginal ultrasound is sensitive in assessing endometrial thickness, it is not reliable in determining the aetiology of endometrial thickening. Therefore, in particular in postmenopausal women, a thickened endometrium (>/= 5 mm) generally determines an indication to perform an endometrial biopsy (ACR, 2020).

However, it is specified that there is no unanimously accepted endometrial cut-off, and that it is always advisable to proceed with a careful qualitative evaluation of the endometrium.

The RCOG points out that cut-offs of 3 mm or 4 mm have been proposed, below which the probability of diagnosis of endometrial carcinoma is less than 1% (RCOG 2016, Evidence Level 2++). However, a higher cut-off value has been suggested for women (both symptomatic and asymptomatic) taking hormone replacement therapy or tamoxifen (RCOG, 2016; Evidence Level 2++).

In menopausal women with abnormal uterine bleeding during hormone replacement therapy, the French National College of Gynaecologists and Obstetricians (CNGOF) and the Study Group on Menopause and Hormonal Ageing (GEMVi) suggest performing ultrasound imaging after they have stopped taking progestin tablets (if undergoing cyclical HRT) or indiscriminately in users of combined HRT. In the case of a single AUB episode and if the endometrial thickness at ultrasound is less than or equal to 4 mm, no further investigation needs to be carried out. In case of recurrent episodes of AUB or if the endometrial thickness is greater than 4 mm, further investigation (hysteroscopy and endometrial biopsy) is recommended (CNGOF/GEMVi, 2021).

FOGSI (the Federation of Obstetric and Gynecological Societies of India) also suggests ultrasound imaging in women with AUB to assess the uterus adnexa and the endometrial thickness (Grade A, Level 1); Doppler helps in case of suspected arteriovenous malformations, suspected malignancy and to differentiate between uterine fibroids and adenomyomas (Grade B, Level 3). If intracavitary lesions are suspected and hysteroscopy is not available, sonohysterography (Grade A, Level 1) is recommended (FOGSI, 2016).

FOGSI (2016) recommends hysteroscopy for intracavitary lesions (Grade A, Level 1) and endometrial biopsy in case of abnormal uterine bleeding:

- in women >40 years (Grade A, Level 2);
- in women <40 years at high-risk of endometrial cancer (irregular bleeding, obesity, hypertension, PCOS, diabetes, endometrial thickness >12 mm, family history for ovarian/breast/endometrial/colon cancer, intake of tamoxifen, HNPCC, AUB not responsive to medical treatment (Grade A, Level 2).

The ACR also agrees in suggesting an endometrial biopsy in women at high-risk for endometrial cancer (obesity, chronic anovulation, family history, age, late menopause) regardless of ultrasound findings (ACR, 2020).

Finally, also in cases where the endometrium is not exhaustively and conclusively evaluable during ultrasound (due to adenomyosis, fibromatosis, uterine version, habitus of the patient), an endometrial biopsy should be considered on the basis of risk factors for endometrial carcinoma (ACR, 2020).

There is no scientific evidence to respond to outcome 1 (reduction in hospital admissions) and outcome 3 (identification of patients eligible for medical therapy). It is not possible to determine whether pelvic ultrasound can reduce the number of hospital admissions in women with abnormal uterine bleeding, nor can it be determined whether ultrasound can identify patients who are candidates for medical treatment. However, it is realistic to assume that pelvic ultrasound performed by an experienced examiner, used as an initial diagnostic assessment in women with abnormal uterine bleeding, can help distinguish between the various organic causes, it can help direct management (medical or surgical treatment) and reduce the number of inappropriate admissions.

Question 2 cannot be answered in a comprehensive and conclusive way, as there are no unanimously accepted and shared endometrial cut-offs to establish the referral of a patient with AUB (of childbearing age and postmenopausal) to hysteroscopy examination and/or invasive procedures. According to ACR in postmenopausal women, a thickened endometrium (>/= 5 mm) generally determines an indication for endometrial biopsy (ACR, 2020). An endometrial thickness of 4 mm in postmenopause expresses a negative predictive value for endometrial carcinoma of almost 100% (ACR, 2020).

Question 3

In women with an adnexal mass, does performing a transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 3

The panel recommends the use of transvaginal and possibly transabdominal ultrasound as the first choice imaging method in women with an adnexal mass.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

All the guidelines in the literature define ultrasound as the first choice imaging method in the study of adnexal masses.

The RCOG Guidelines (2016) specify that pelvic ultrasound with a transvaginal approach is the most effective imaging method in the assessment of ovarian cysts in postmenopausal women. The transabdominal approach should be treated as a complement to the transvaginal assessment, particularly in the case of large masses, which are beyond the range assessed by intracavity examination.

Ultrasound should be performed by experienced examiners using high frequency endocavitary probes. Colour Doppler evaluation and vascular indexes are not required for initial routine assessment, the same goes for 3D assessment.

Transvaginal ultrasound has the task of identifying 'simple' cysts, worthy of conservative management, from 'complex' cysts, characterized by the presence of one or more of the following characteristics: complete septa, solid components, papillae.

For morphological evaluation, RCOG suggests following the classification elaborated by the International Ovarian Tumor Analysis group (Timmerman, 2000).

The subjective assessment of the risk of malignancy ('subjective assessment' and 'pattern recognition') is the most effective parameter for discriminating benign adnexal formations from malignant ones, in order to reduce the number of unnecessary surgeries.

The recommendations of the SOGC (2020 and 2018) and the GOC/SOGC (2020) confirm the role of the subjective evaluation on behalf of the operator, who should classify the masses into: benign, probably malignant or indeterminate. An alternative to subjective evaluation is the application of mathematical models for assessing the risk of malignancy, such as the Simple Rules (Timmerman, 2018) or ADNEX (Van Calster, 2014), both developed by the IOTA group.

The following should be reported during the ultrasound evaluation: lesion size, laterality (mono/bilateral) and origin (ovarian or extra-ovarian). In case of 'complex' masses, it is advisable to indicate the presence of septa, solid components and/or papillae, the presence of ascites, peritoneal carcinosis and increased vascularization of the neoformation.

Benign adnexal formations can be re-evaluated sonographically at 8-12 weeks after diagnosis and thereafter the frequency of check ups can be annual for 5 years.

Adnexal formations classified as indeterminate can be managed in several ways: monitored in the short term (8-12 weeks), sent to on oncological referral centre, or referred for level II Imaging (MRI).

The SOGC recommendations, as well as the RCOG ones, propose using the mathematical models defined by the IOTA group (in particular Simple Rules and ADNEX) to assess the risk of malignancy as an alternative to the pattern of recognition.

The NICE guidelines (2011) underline the importance of ultrasound and CA125 assays in patients with symptoms that are suggestive of ovarian cancer.

The French guidelines (FRANCOGYN, CNGOF, SFOG and GINECO-ARCAGY, 2019; CN-GOF, 2021) differentiate the ultrasound method for assessing the risk of malignancy based on examiner experience: in case of an expert examiner, it is appropriate to evaluate the lesion according to pattern recognition, while less experienced ultrasound examiners are encouraged to apply IOTA mathematical models.

Question 4

In asymptomatic women on hormone replacement therapy, does performing a transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 4

In asymptomatic women on hormone replacement therapy, the panel suggests that routine transvaginal ultrasound should not be performed.

Note: However, the panel believes that, although there is no evidence in the literature of the usefulness of ultrasound during hormone replacement therapy, such an examination may be recommended as a baseline assessment prior to the initiation of hormone replacement therapy and suggests that a periodic assessment may lead to a better customization of dosages and treatment plans.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

While there are no suggestions in the Guidelines for asymptomatic women on Hormone Replacement Therapy (HRT), in case of abnormal uterine bleeding in a menopausal woman on HRT, pelvic ultrasound is recommended at the end of progestin administration in sequential HRT or at any time in case of combined therapy (expert advice).

The sensitivity of the measurement of endometrial thickness via ultrasound for the detection of endometrial cancer in women with AUB on HRT is 100%, specificity is 60%, the positive predictive value is of 25% and the negative predictive value is of 100% when assuming a thickness of 4 mm as the upper limit of the norm. Additional complementary diagnostic procedures (hysteroscopy + histology) (Grade A) (CNGOF and GEMVi, 2021) are recommended in HRT patients with recurrent AUB.

The RCOG Guidelines points out that cut-offs of 3 mm or 4 mm have been proposed, below which the probability of diagnosis of endometrial carcinoma is less than 1% (RCOG, 2016; Recommendation Level 2++). However, a higher cut-off value has been suggested for women (both symptomatic and asymptomatic) taking hormone replacement therapy or tamoxifen (RCOG, 2016; Recommendation Level 2++).

Monitoring of endometrial thickness should not be proposed during treatment for vulvovaginal atrophy (NICE, 2020).

Question 5

In the general asymptomatic population does performing a transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 5

Routine transvaginal ultrasound is not indicated in the general asymptomatic population. **Note:** While highlighting that there are no elements in the literature in favour of routine ultrasound examinations, the panel notes that the use of gynaecological ultrasound is very widespread as a complementary assessment to a gynaecological examination.

NEGATIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES

Literature Analysis and Evidence Interpretation

According to the American College of Radiology (ACR Appropriateness criteria Ovarian Cancer Screening, 2020), there is no evidence from the literature that supports transvaginal ultrasound for ovarian cancer screening in women without premenopausal or post-menopausal risk factors. The failure of ovarian cancer screening programs in the general population is also highlighted in the British Gynaecological Cancer Society (2017), AFRQ (2018), SIGN (2018) and Cancer Australia (2019) Guidelines.

All of the above Guidelines refer to the impossibility of early detection of ovarian cancer and the absence of benefit on cancer-specific mortality in patients included in screening programs involving annual transvaginal ultrasound associated with or without CA125 testing.

With regard to early diagnosis of endometrial cancer, screening in the general asymptomatic population is not recommended by the major Scientific Organizations (Cancer Australia, 2019; BCGS, 2017), in particular due to the risk of false positives which may lead to further unnecessary diagnostic investigations and increase anxiety in patients.

However, in a 2014 Cochrane Systematic Review (Crosbie, Morrison, 2014), in view of the increase in incidence of endometrial cancer due to widespread risk factors such as obesity, risk stratification was suggested in patients to be referred to personalized monitoring care pathways.

Question 6

In the population that is at higher-risk of developing cancer due to hereditary factors, does performing a transvaginal ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 6

In the asymptomatic hereditary cancer risk population (BRCA1 and 2; mutations of genes involved in DNA mismatch repair [MMR] with diagnosis of Lynch syndrome II) the panel recommends performing prophylactic surgery. However, ultrasound monitoring may be considered in women aged 30-35 onwards only if the patient does not accept surgery or wishes to postpone the surgical procedure. The literature does not define the exact time interval, the panel suggests an ultrasound every 6 months associated with CA125 testing.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

In the 2019 Cancer Australia Position Statement, it is noted that in women at high or potentially high-risk for ovarian cancer there is no evidence that any test (gynaecological examination, CA125 test or other markers, ultrasound) or combination of tests result in reduced ovarian cancer mortality.

The same conclusion can be found in the Scottish Intercollegiate Guidelines Network (2018) and RCOG recommendations (2015).

In the RCOG document in particular, the recommendation is not to offer the possibility of conservative surveillance in place of prophylactic surgery.

Randomized trials similar to those for the general asymptomatic population have not been conducted in this subset of patients; numerous studies are reported in the ACR Guidelines (2017), but all are on a relatively small and heterogeneous series (often they consider a mix of pre- and postmenopausal patients).

The largest study conducted in a high-risk ovarian cancer population is the UK Familial Ovarian Cancer *Screening Study* (Rosenthal et al., 2013), which evaluated the serial use of ultrasound and the marker CA125 assay in 4,348 women with an estimated lifetime risk of developing ovarian cancer of >10%. In phase I of the trial, the annual ultrasound assessment associated with the CA125 assay helped to improve the optimal cytoreduction rate, although there was a poor sensitivity for early tumour diagnosis.

In phase II of the trial (Rosenthal et al., 2017) the screening schedule was intensified with check ups every 4 months: the final results of phase II show a significant shift toward early staging of the tumour at diagnosis, although the impact on mortality is unknown.

The National Cancer Comprehensive Cancer Network (NCCN, 2021) Guidelines report that a screening protocol with CA125 testing and ultrasound in women at high-risk for ovarian cancer could potentially allow for early diagnosis of the tumour, although the impact on survival remains unknown. Prophylactic surgery remains the standard of care for carriers of mutations in BRCA 1/2 genes; the CA125 test combined with an ultrasound is suggested by NCCN as an option for the clinician in women aged 30-35 and over who refuse or postpone risk reduction surgery.

For patients at high-risk for endometrial cancer, in women with a known or suspected mutation in one of the genes responsible for DNA mismatch repair, endometrial sampling should be offered annually from the age of 30-35 years. Transvaginal ultrasound does not play a role in screening for endometrial cancer in premenopausal high-risk women, although it may play a role in the evaluation of adnexa in this subgroup of patients (Auranen, Joutsiniemi, 2011).

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9. POINT OF CARE ULTRASOUND

Introduction

Point of care ultrasound (POCUS) is an ultrasound examination used as an aid to the obstetric and gynecological examination, performed with the aim to answer specific clinical questions. In the Italian version of these Guidelines, POCUS has been named "Office ultrasound", a designation recalling the main field of application of this ultrasound evaluation in Italy, which is the private or public clinic *(office)*, during the assessment of an obstetric or gynecological evaluation.

Point of care ultrasound can be performed during obstetric or gynecological examination in clinics, in emergency rooms (ER) or in hospital wards, by doctors and midwives, after an appropriate training. Most of the efficacy studies conducted on this topic refer to its use by emergency and general practitioners, during the evaluation of a woman with a possible obstetric or gynecological problem. The POCUS must be clearly distinguished from the "standard" ultrasound examination: in the former, the clinician will use the ultrasound as support to obtain only limited information, in order to complete the obstetric and gynecological examination; in the latter, a full examination will be performed, which must include all the assessments required by the protocols provided in these Guidelines. The POCUS can support both the obstetric and gynecological assessment in the ER and the activities in the obstetric and gynecological wards, with the result of limiting the pressure on clinics dedicated to standard ultrasound. If an abnormal finding is encountered during the POCUS, a standard ultrasound examination should be prescribed. Following the POCUS examination, the woman will not receive any report or images, as the information obtained during the exam is only intended to support real-time clinical work.

The SIEOG has developed a POCUS protocol, published in the Annex to these Guidelines.

Recommendations

Question 1

In emergency/urgent obstetric and gynecological cases, can POCUS improve the outcomes that are important to women?

Recommendation 1

A point of care ultrasound is recommended in emergency/urgent cases in order to facilitate the identification of some medical conditions and to reduce the length of stay in hospital.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON LOW QUALITY PRIMARY STUDIES AND SYSTEM-ATIC REVIEWS

Literature Analysis and Evidence Interpretation

There are no studies on the specific use of POCUS in the obstetric and gynecological ER, but the evidence refers to its use by emergency doctors in the general ER. With regard to these settings, two meta-analyses reported on the usefulness of POCUS in the diagnosis of ectopic pregnancy (Sorensen, Hunskaar, 2019). According to one meta-analysis, which includes 10 observational studies, the use of POCUS may facilitate the diagnosis of ectopic pregnancy in emergency/urgent settings. It has been estimated that the visualization of an intrauterine pregnancy with POCUS can rule out an ectopic pregnancy with a sensitivity of 97% (95% CI 92%-99%) and a specificity of 71% (95% CI 60%-80%) (Stein et al., 2010).

A meta-analysis of 5 observational studies and one RCT demonstrated that, in case of symptomatic patients in the first weeks of pregnancy, the use of POCUS can reduce the length of stay in the ER (mean reduction of 73.8 min; 95% CI 49.1-98.6 min) (Beals et al., 2019).

A retrospective observational study concluded that the use of ultrasound as a complement to the clinical examination in emergency/urgent settings may facilitate the detection of non-critical patients requiring hospitalization for emergency surgery or initiation of pharmacological treatment (Golea et al., 2016).

There are no data on the impact on maternal mortality and ICU admission.

Question 2

When the gynecological examination does not allow a satisfactory clinical evaluation, can a complementary ultrasound lead to an improvement in the outcomes that are important to women?

Recommendation 2

When the gynaecological examination does not allow a satisfactory clinical assessment, the use of a complementary ultrasound to improve the outcomes that are important to women is not supported by evidence. However, the panel of experts believes that a complementary ultrasound by trained gynecologists may reduce the need for further instrumental examinations and should therefore be considered.

POSITIVE CONDITIONAL RECOMMENDATION

▶ RECOMMENDATION BASED ON SYSTEMATIC REVIEWS OF LOW QUALITY

Literature Analysis and Evidence Interpretation

The complementary use of ultrasound during the gynecological examination is widely practiced. A survey conducted in Australia concludes that most of the gynecologists performing an ultrasound examination during the gynecologic assessment, do not refer the patient for additional specialized ultrasounds if they do not find any alterations (Van der Wal, Robson, Choong, 2013).

There are no data on the usefulness of complementary ultrasound in cases where the clinical examination is not satisfactory in an outpatient setting.

Question 3

In post-term pregnancy, does performing an ultrasound to assess the single deepest amniotic fluid pool improve perinatal outcome?

Recommendation 3

The panel recommends ultrasound assessment of the single deepest amniotic fluid pool as part of the clinical monitoring of post-term pregnancies.

STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF LOW QUALITY

Literature Analysis and Evidence Interpretation

According to the NICE Guidelines (NICE, 2019) and the Australian Government Department of Health Guidelines (Australian Government Department of Health, 2021), evaluation of the single deepest amniotic fluid pool in post-term pregnancy should be offered at least twice a week in patients who refuse induction after 42 weeks, while SOGC (SOGC, 2017) (Recommendation I-A) recommends an amniotic fluid evaluation starting at 41+0 weeks. There is no antenatal monitoring recommended for pregnancies up to 41 weeks (evidence quality: very low) (KCE, 2015).

Oligohydramnios, although associated with an increased risk of intrauterine death, meconium-stained fluid, intrauterine growth restriction, cardiotocographic abnormalities and caesarean section, has an only moderate diagnostic value in predicting unfavorable outcomes (Vayssiere et al., 2013).

According to a meta-analysis that included 657 cases of isolated oligohydramnios (defined as AFI <5 cm) and 3,216 controls between 37 and 42 weeks' gestation, isolated oligohydramnios was associated with a higher-risk of obstetric interventions (OR 2.46; 95% CI 1.03-2.58). However, no differences were observed with other outcomes, such as the incidence of SGA fetuses (OR 1.4; 95% CI 0.38-5.22), or admissions to neonatal intensive care (OR 1.33; 95% CI 0.50-3.36) (Rossi, Prefumo, 2013).

Question 4

Is the ultrasound assessment of fetal presentation in addition to the obstetrical examination, at patient admission or in advanced third trimester, associated with an improvement in outcomes that are important to the women?

Recommendation 4

Ultrasound examination is recommended to assess fetal presentation in doubtful cases or when breech presentation is suspected at the obstetric examination carried out at the admission or in advanced third trimester.

POSITIVE CONDITIONAL RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND A SYSTEMATIC REVIEW OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

According to the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Australian Government Department of Health Guidelines on management of breech presentation at full-term, in case of doubt or suspicion of a breech presentation, an ultrasound should be carried out to confirm fetal presentation (RANZCOG, 2016; Australian Government Department of Health, 2021). According to a prospective cohort study that included 3,879 nulliparous women, the introduction of a universal ultrasound screening at 36 weeks would reduce the rate of emergency caesarean sections by 0.7 percentage points. Of the 179 cases of breech presentation found in this cohort at ultrasound examination, only 44.1% of cases were suspected on the basis of the clinical examination (Wastlund et al., 2019). There is no evidence of the impact of ultrasound assessment of fetal presentation on the number of external cephalic versions.

Question 5

Does ultrasound evaluation of fetal heart beat improve maternal-fetal outcome in doubtful cardiotocography cases?

Recommendation 5

The panel opinion is that in all cases of difficult identification of the fetal heart beat by the use of cardiotocography, the ultrasound evaluation can help in identifying the correct positioning of the cardiotocographic sensor on the maternal abdomen, and allows for a rapid and accurate evaluation of the fetal heart rate. This recommendation is based on the opinion of the panel as there is no scientific evidence available on this issue.

POSITIVE CONDITIONAL RECOMMENDATION

QUALITY OF SCIENTIFIC EVIDENCE: THERE IS NO SCIENTIFIC EVIDENCE

Literature Analysis and Evidence Interpretation

There is no scientific evidence on ultrasound evaluation of fetal heart beat when the identification is doubtful by the use of cardiotocography, however, based on clinical experience, it is reasonable to perform an ultrasound evaluation when the identification of the fetal heart beat in not straightforward or when there is doubt about overlapping with the maternal heartbeat, in order to allow a rapid and accurate evaluation of the fetal heart rate.

Question 6

In patients evaluated in the ER for antenatal bleeding in the third trimester does an ultrasound assessment of placental localization improve maternal and fetal outcomes?

Recommendation 6

In women with antenatal bleeding in the third trimester an ultrasound assessment of placental localization can be performed as a POCUS in the when an adequately trained obstetrical medical staff is not available for a diagnostic ultrasound. This recommendation is based on the panel's opinion that this ultrasound cannot be classified as a POCUS.

POSITIVE CONDITIONAL RECOMMENDATION

QUALITY OF SCIENTIFIC EVIDENCE: THERE IS NO SCIENTIFIC EVIDENCE

Literature Analysis and Evidence Interpretation

For ultrasound evaluation of placental localization, please refer to the chapter on ultrasound in the third trimester and the related PICO. The panel considers placental localization to be a complex ultrasound assessment requiring an expertise beyond the scope of a POCUS. Moreover, there is no evidence that the introduction of such an assessment during a POCUS performed in the ER on patients with antenatal bleeding in the third trimester could lead to an improvement in the maternal and fetal outcomes considered.

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10. REFERRAL SCAN

Introduction

The term referral scan refers to a particularly thorough ultrasound performed by experienced physicians, using high-level ultrasound equipment to investigate fetal ultrasound suspition identified at the screening examination, or for specific maternal conditions associated with an high-risk of developing fetal malformations.

Referral scans such as fetal echocardiography or fetal neurosonography are carried out to exclude or confirm congenital fetal abnormalities of specific anatomical districts. Like all diagnostic tests, it cannot be performed in the entire pregnant population, but only in case of specific maternal or fetal indications. In fact, as highlighted in a high-quality Guideline (Sussman et al., 2021), there is no relevant literature supporting fetal echocardiography in the low-risk female population. The care process necessary for the definition of fetal malformation, the search for any other associated structural anomalies, the prognostic definition of the disease, the implementation of other invasive diagnostic methods (CVS, amniocentesis) or non-invasive (fetal echocardiography, fetal neurosonography, MRI) all require a multidisciplinary approach that should encompass, in addition to the presence of obstetricians with experience in fetal medicine, the contribution of pediatricians, as well as consultant in genetics and clinical psychology.

Only in few Italian regions, via regional standards, referral centers for prenatal diagnosis or of maternal-fetal medicine have been formally identified according to criteria regarding the know how and the experience of operators, structural, setting and technological characteristics of the ultrasound centre.

Therefore it is necessary to formalize the duty of this role on a regional basis throughout the Country and achieve formal recognition of this tests that, in view of the effort given in terms of time, technological equipment, multidisciplinarity and the need for particularly experienced operators cannot be compared to routine screening ultrasound, also for its value within the National Healthcare Service.

Recommendations

Question 1

In a pregnant patient at risk* for fetal malformations, is it useful to perform a referral scan in order to study fetal anatomy in a detailed manner?

*At least one maternal risk factor:

- Diabetes
- Obesity
- ART
- Family history of malformations
- Maternal infections (TORCH)
- Consumption of/Exposure to teratogens
- Risk of fetal anemia (Parvovirus B19 infection or high titre positive indirect Coombs test)

At least one fetal risk factor:

- Abnormal ultrasound aspects at screening
- Increased NT

Recommendation 1

In all women with at least one significant maternal or fetal risk factor for congenital fetal malformations, a referral scan is recommended for the detailed evaluation of the fetal anatomy. STRONG POSITIVE RECOMMENDATION

RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND SYSTEMATIC REVIEWS OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

Maternal factors

Diabetes during pregnancy

The WHO Guidelines (2016) report that women with hyperglycaemia detected during pregnancy are at increased risk of adverse outcomes. Both type 1 and type 2 diabetes in pregnancy carry a significantly higher maternal and fetal risk than gestational diabetes (GDM). Fetal and maternal outcomes are directly related to the degree of maternal glycaemic control. The WHO Guidelines (2016) indicate that the management of diabetes mellitus in pregnancy, especially when identified in the first trimester, is different from that of gestational diabetes.

Major malformations are the main cause of perinatal mortality in pregnancies complicated by pre-existing diabetes. With regard to malformations in fetuses of mothers with pre-existing diabetes, the 2018 ACOG Guidelines report an incidence of between 6 and 12%. The most reported malformations were: complex cardiac defects, central nervous system abnormalities (especially anencephaly and spina bifida), skeletal abnormalities (e.g. sacral agenesis). The SIGN Guidelines, published in 2017, recommend that pregnant women with pre-existing diabetes should have detailed ultrasound at 20-22 weeks gestational age. The Italian Society of Diabetology in 2018 reported that the fetal monitoring will depend on the severity of maternal hyperglycaemia combined with the coexistence of other possible risk factors; in fact, it is reported that a referral scan is recommended if diabetes is diagnosed before the 14th week of gestational age.

The conclusion of the work group is to recommend the execution of the referral scan in case of pre-existing diabetes or manifest diabetes diagnosed by the first trimester of pregnancy.

Obesity

The incidence of obesity in pregnancy has increased significantly in all countries, albeit in different ways. In Italy the incidence of this condition in women within reproductive age is about 10% of pregnant women. With respect to clinical management, the Queensland Clinical Guidelines (2020) reported that there was a modest amount of high-quality scientific evidence useful for defining the management of obesity in pregnancy; furthermore, it was reported that the Body Mass Index (BMI) is a much more effective parameter than weight measurement alone in determining maternal and neonatal outcomes. Therefore, it is recommended that maternal BMI should be calculated as early as the first clinical check up using prior weight or weight recorded in early pregnancy, and that BMI be documented on the pregnancy clinical diary and reported on the ultrasound examination request. Obesity in pregnancy is a risk factor that can generate maternal and fetal problems. Fetal risks include fetal macrosomia, an increased risk of intrauterine death and congenital abnormalities. In relation to the latter of these, the Canadian Guidelines (SOGC, 2019) reported an increased incidence of neural tube defects (OR 1.87; 95% CI 1.62-2.15), cardiac abnormalities (OR 1.30; 95% CI 1.12-1.51), and limb reduction abnormalities (OR 1.434; IC 1.03-1.73) in obese mothers; The same Guidelines also reported that this may be partially related to the reduction in probability of detecting malformations in the presence of maternal obesity (OR 0.77; 95% CI 0.60-0.46).

In the high quality guidelines taken into consideration for the preparation of these recommendations, no particular consideration is given to obese pregnant women with a BMI of <40. The Queensland Clinical Guidelines (2020) recommend a referral scan for parturients with a BMI of >40. Early referral to a Specialist Centre is recommended, where the ideal time and method of performing the examination, which may also include transvaginal ultrasound assessment, will be evaluated.

With regard to the ultrasound study of fetal anatomy for prenatal detection of structural malformations, several Guidelines (Queensland Clinical Guidelines, 2020; SOGC, 2019; NICE, 2019) emphasize that maternal obesity is in itself a limiting factor in the study of fetal anatomy and that the woman must be informed of this. The above Guidelines also state that ultrasound examination for the evaluation of fetal anatomy in the second trimester in obese pregnant women may take longer and that repeated attempts and special care may be required to complete the ultrasound examination, including the use of transvaginal ultrasound. In summary, it is reported that the probability of completing an adequate assessment of fetal anatomy in a single attempt is reduced with an increase in BMI, from 97.5% in women with normal BMI to 74% in women with BMI of >30 kg/m² and to 41% when BMI is >40. The likelihood of poor visualization of the heart (37% vs 19%) and spine (43% vs 29%) is increased in obese women compared to normal weight women. According to the SOGC Guidelines (2019) other fetal structures that are particularly difficult to visualize in obese women include the face, genitals and extremities.

The conclusion of the work group is to recommend early referral of obese parturients with pre-pregnancy BMI >40 kg/m² to a Specialist Centre for ultrasound examinations.

Assisted Reproductive Technology (ART)

The incidence of congenital malformations in fetuses derived by assisted fertilization techniques appears to be significantly higher for singleton pregnancies obtained via FIVET/ ICSI than those spontaneously conceived, whereas no significant differences appear between twin pregnancies obtained from IVF/ICSI compared to twins obtained from spontaneous pregnancies. From a recent meta-analysis (Zheng et al., 2018) the relative risk of congenital malformation in IVF/ICSI pregnancies compared to those spontaneously conceived is RR 1.4 (95% CI 1.30-1.52) for singleton pregnancies and RR 1.18% (95% CI 0.98-1.42) for twin pregnancies. No significant differences were found between subgroups divided according to FIVET or ICSI techniques. However, although the risk of congenital malformation in the singleton FIVET/ICSI pregnancy is higher, it does not appear high enough to justify routine referral of these pregnancies to Specialist Centres for the study of fetal anatomy.

Positive family history

A high-quality Guideline (Sussman et al., 2021) highlights that a detailed assessment of fetal anatomy is recommended in case of a family history of fetal congenital anomalies. In the literature, there are only older studies on the risk of recurrence of congenital abnormalities in women with a previously affected fetus. Therefore, the work group's suggestion is to consider

the presence of a congenital abnormality in a previous pregnancy as a positive family history. However, in view of the possible recurrence of certain structural abnormalities on the basis of genetic mutations of a hereditary nature, consult by a geneticist to a referral scan is recommended in cases where such recurrence has not been excluded by specific genetic tests.

Infections during pregnancy

Ultrasound plays an important role in the diagnosis and management of congenital infections. In some cases, the result of a screening examination of suggestive/suspected ultrasound abnormalities leads to carrying out maternal serological tests for a diagnosis of infection; in other cases the diagnosis of maternal infection leads to the performance of targeted ultrasound scans with the aim of diagnosing possible fetal involvement.

When a diagnosis of congenital infection is made, ultrasound examination may help to define the fetal prognosis and the management of the pregnancy. However, the woman must be informed that normal referral scan results do not exclude late onset or postnatal abnormalities with particular reference to neurosensory outcomes which may also appear in paediatric age (ISUOG, 2020).

Cytomegalovirus (CMV)

A referral scan is recommended in case of a known maternal and/or fetal infection when CMV is documented. In case of maternal infection, ultrasound may detect signs of fetal infection. In the case of documented fetal infection via PCR on amniotic fluid, the referral scan, together with laboratory tests, and possibly fetal magnetic resonance imaging, can help to define prognosis, also in relation to the new possibilities of prevention and treatment of fetal disease (Official Journal no. 6 09/01/2021, AIFA resolution 16/12/2020 no. 142618/2020 - 20°07138). However, it should be stressed that ultrasound abnormalities may appear several months after infection (ISUOG, 2020).

Toxoplasmosis

A referral scan is recommended in case of a documented maternal and/or fetal infection with Toxoplasma gondii. In case of maternal infection, ultrasound may detect signs of fetal infection. In the case of documented fetal infection via PCR on amniotic fluid, a referral scan, together with laboratory tests, and possibly fetal magnetic resonance imaging, may help to define prognosis (ISUOG, 2020).

Parvovirus B19

Parvovirus B19 may cause anemia, fetal hydrops and intrauterine death within 3 months of infection. In case of documented maternal infection with Parvovirus B19, it is recommended to perform serial referral scans every 2 weeks starting from approximately 4 weeks after infection up to 12 weeks after infection. The aim of the ultrasound evaluation is to precociously recognize a state of anemia or fetal hydrops potentially treatable by intrauterine transfusion. Therefore the recommendation is to investigate the presence of ascites, cardiomegaly, hydrops and peak velocity values in the middle cerebral artery at each check up as they could be indicative of fetal anemia (ISUOG, 2020).

Rubella

Rubella infection is now rare thanks to the ongoing vaccination program. Fetal rubella infection contracted early in pregnancy may lead to congenital defects and late onset manifestations during the first years of life.

Ultrasound diagnosis of congenital rubella infection is extremely difficult given the nature

of the possible malformations (SOGC, 2018), however, referral scan and ultrasound follow-up are recommended (ISUOG, 2020; SCOG, 2018).

Chickenpox

A referral scan and appropriate follow-up are recommended in case of primary maternal infection documented with varicella zoster virus (VZV) if diagnosed before the 20th week. There appears to be no risk of fetal varicella syndrome if the infection is contracted between 20 and 36 weeks. Fetal infection may be demonstrated with amniocentesis (PCR search for VZV-DNA). In any case, the positivity of the amniocentesis does not necessarily imply fetal disease, nor can its negativity exclude the absence of disease altogether. Ultrasound signs may be seen approximately 5 weeks after maternal infection (ISUOG, 2020; SOGC, 2018).

Human immunodeficiency virus (HIV)

Women with HIV have an increased risk of adverse pregnancy outcomes, including preterm delivery, compared to the general population. Therefore, a 19-21-week referral scan, supplemented by ultrasound measurement of cervical length (SIMIT, 2017), is recommended in these pregnancies.

Drugs and radiation

Although we cannot exclude the possibility that many substances or drugs may interfere with organogenesis, only in a few cases significant associations have been reported between their consumption and the risk of congenital anomalies.

With the regard to **medications for epilepsy**, recent meta-analyses (Weston et al., 2016) have shown a significant increase in the risk of congenital anomalies, compared to women without epilepsy, when treated with carbamazepine (OR 2.01; 95% CI 1.2-3.36), levetiracetam (OR 2.16; 95% CI 0.76-6.17), oxcarbazepine (OR 1.94; 95% CI 0.53-7.15), phenobarbital (OR 2.84; 95% CI 1.57-5.13), phenytoin (OR 2.38; 95% CI 1.12-5.03), topiramate (OR 3.69; 95% CI 1.36-10.07) and valproate (OR 5.69; 95% CI 3.33-9.73). The work group's suggestion is to perform a referral scan only in the case of these drugs or in the case of polytherapy.

Among selective serotonin reuptake inhibitors (SSRIs) recent meta-analyses (Gao et al., 2018) consistently suggest an increased risk of congenital malformations for paroxetine and fluoxetine only, but not for other SSRIs.

Antithyroid drugs result in a modest increase in the risk of congenital malformations (Morales, 2021), and the work group's recommendation is to perform a referral scan only in the case of combination therapy with propylthiouracil + methimazole/carbimazole.

Furthermore, since the teratogenicity/fetotoxicity of drugs may vary with dosage, trimester of use, and knowledge of the more recently introduced drugs in clinical practice, the work group's recommendation is to perform a referral scan in all patients where the indications for the examination comes from **multidisciplinary specialist advice**.

With regard to exposure to **ionizing radiation**, the possible indication to perform a referral scan may be formulated only after multidisciplinary evaluation, based on an evaluation by a specialist in medical physics on the dose absorbed by the unborn child, as provided for in Art. 166 of the Legislative Decree of 21st July 2020 no. 101 (implementation of Directive 2013/59/Euratom, which specifies basic safety standards for protection against the dangers arising from exposure to ionizing radiation, and annuls Directives 89/618/Euratom, 90/641/ Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom and the reordering of the relevant legislation pursuant to Article 20(1)(a), of Law no. 117 of 4th October 2019).

Risk of fetal anemia

In pregnancies at risk of fetal anemia (for Parvovirus B19 infection, indirect positive Coombs high titre test, fetus with or at risk of genetic diseases associated with fetal anemia), it is recommended to perform serial referral scans, with gestational age and interval varying based on the indication. In order to recognize an early condition of anemia or fetal hydrops potentially treatable by intrauterine transfusion, the recommendation is to investigate at each check up the presence of: ascites, cardiomegaly, hydrops, and peak velocity values in the middle cerebral artery which could be indicative of fetal anemia (Martin-ez-Portilla et al., 2019).

Fetal factors

Abnormal ultrasound findings at screening scan

The ultrasound examination carried out as a screening on the general population and in particular at 19-21 weeks of gestational age is aimed at checking fetal anatomy and searching for any significant deviations from normal conditions. Therefore this test is not designed for the precise diagnosis of a malformation, much less the prognostic definition of what is suspected.

The referral scan performed in case of diagnostic suspicion is more reliable than the screening examination as it is performed at Specialist Centres. In fact, high quality Guidelines (RANZCOG, 2018; NICE, 2019; ACOG, 2014; Queensland Guidelines, 2020) report that, in case of a suspected fetal malformations, it is recommended that the pregnant woman to be referred to a Specialist Center for diagnostic confirmation, especially in view of the different detection rates between screening and referral scans. The ACOG (2014) pointed out that if one or more fetal anatomical structures are not adequately visualized at the screening ultrasound examination, a dedicated check up should be programmed, and only after this attempt, in case of persistent suspicious findings, it is essential to schedule a detailed ultrasound examination at a Specialist Centre. In addition, as reported in the section regarding second trimester screening, conditions such as mild ventriculomegaly, hyperechogenic bowel, renal pyelectasis and short femor may emerge during this examination, which may be useful for selecting women at risk for fetal structural or developmental abnormalities, other than aneuploidies. Therefore detecting these specific conditions is also a indication for a referral scan.

Thus in all modern health organizations, a screening test where the presence of a fetal malformation is suspected, must be followed by in-depth examinations such as so-called referral scans, fetal echocardiography or fetal neurosonography.

High quality Guidelines (RANZCOG, 2018; NICE, 2019; ACOG, 2014; Queensland Guidelines, 2020; Australian Government Department of Health, 2020) report that if congenital pathologies emerge in the referral scan, future parents must be informed in detail about the characteristics of the anomaly, its aetiology, any relevant associated pathologies, possible further investigations needed, labour/delivery method and future life prospects.

It is also recommended that the couple be able to interact with a multidisciplinary team via which they can address all diagnostic, prognostic and counselling issues.

The conclusion of the work group is to recommend the referral of the parturient to a

Specialist Centre in case of suspect ultrasound findings for malformation or in case of a repeated impossibility of adequately visualizing one or more anatomical structures, in any trimester of pregnancy.

Increased nuchal translucency

The finding of increased nuchal translucency at the first trimester ultrasound leads not only to an increased risk of fetal aneuploidy, but also to congenital malformations. This risk gains as the nuchal translucency increases. High quality Guidelines (Audibert et al., 2017; Australian Government Department of Health, 2019; Sussman et al., 2021) therefore recommend that referral scans be performed in fetuses with a nuchal translucency $\geq 99^{th}$ centile (3.5 mm).

Early fetal hypo-development

As recommended by high quality Guidelines (SOGC, 2013; SMFM, 2020; RCOG, 2014), in cases where early fetal growth restriction (<32 weeks gestational age) is suspected due to the presence of an estimated fetal weight or a fetal abdominal circumference measurement <10th centile for gestational age, it is recommended to refer the patient to a specialist center for maternal fetal Doppler velocimetry assessment and a detailed study of fetal anatomy.

A summary of the indications for a referral scan is given in Table 1.

Family indications	 Previous pregnancy affected by a congenital malformation Inherited genetic diseases associated with malformations (when not excluded from prenatal genetic tests)
Maternal indications	 Prior BMI >40 kg/m² Pregestational diabetes (types 1 and 2) or manifest diabetes diagnosed by the first trimester of pregnancy Maternal rubella infections, Toxoplasma, CMV, Parvovirus B19, varicella, HIV Taking medicines during pregnancy (carbamazepine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, polytherapies with anticonvulsants, paroxetine, fluoxetine, propylthiouracil + methimazoloicarbimazole) Exposure to ionizing radiation (after medical physics specialist assessment of the dose absorbed by the unborn child) Conditions at risk for fetal anemia (Parvovirus B19 infection, indirect positive Coombs test, fetus with or at risk of genetic diseases associated with fetal anemia)
Fetal indications	 Suspected congenital malformation at screening ultrasound examination NT ≥ 3.5 mm (99th centile) Early fetal hypo-development

Table 1Indications for referral scan

There is no clear scientific evidence from the literature that prenatal findings of fetal malformations have a direct influence on perinatal mortality and morbidity. However, a recent meta-analysis (Glinianaia et al., 2020) showed a marked reduction, from the 1990s to today, in perinatal mortality related to congenital anomalies. The authors attribute this improvement to the increase in detection rate of fetal malformations, with a consequent increase in pregnancy interruptions in the presence of severe conditions associated with high perinatal mortality. As a result, carrying out a referral scan, and increasing the detection rate of major malformations, may indirectly lead to a reduction in perinatal mortality itself. Moreover, for some disease groups, such as congenital heart diseases, their prenatal detection would appear to have an impact on the reduction of perinatal mortality (Holland, 2015).

Although there is no strong evidence, the work group believes that prenatal recognition of certain fetal structural abnormalities, such as those susceptible to intrauterine treatment (transfusions, infections) or specific delivery strategies (EXIT), are positively affected by referral to Specialist Centres where the timeliness of neonatal care and the quality of perinatal care can reduce perinatal morbidity and mortality.

A systematic review (Rossi, 2017) carried out on 19 studies (3,534 fetuses) with the aim of evaluating the diagnostic accuracy of the referral scan by comparing the data derived from the ultrasound evaluation and those from the post mortem examination in case of pregnancy termination or intrauterine death, showed that ultrasound diagnosis corresponded to autopsy findings in 68% of cases and that in 22.5% of cases autopsy examination revealed other malformations that had not been shown in the ultrasound examination. However, the diagnostic accuracy of the examination varied depending on the type of anomaly considered. The greatest concordance between referral scan and autopsy was observed for central nervous system disorders (79.2%), followed by urinary (76.6%), skeletal (76.6%), cardiac (75.5%), thoracic (69.7%), gastrointestinal (62.6%), and those of the limbs (23.3%). The review reports a reduced rate of false negatives (2.8%) and 65.8% of misdiagnoses related to limb abnormalities.

Among the factors limiting the sensitivity of the scan in this systematic review there is the natural history of congenital anomalies. This concept refers to evolutionary pathologies, i.e. those which are more evident later, in the third trimester of pregnancy (for example intestinal obstructive diseases) or only in postnatal age (for example, oesophageal atresia with tracheo-oesophageal fistula).

Additionally, the presence of referral scan limiting factors reduces the sensitivity of the examination. A high-quality Guideline (Simpson et al., 2020) reported that among the factors influencing the sensitivity of the examination we can find: maternal obesity, the presence of abdominal scars, an unfavourable fetal position and the performance of the examination in twin pregnancies.

The purpose of the referral scan is to diagnose or rule out the presence of fetal malformation in patients at high-risk for these abnormalities. As recommended by high quality Guidelines (NICE, 2019), in cases where a congenital fetal abnormality is detected, the pregnant woman must be informed in detail on regard. As a systematic review of the literature (Marokakis, 2016) shows, most couples who have received a postnatal diagnosis of a fetal disease report that they would have preferred to have known of the presence of an abnormality in the prenatal period. However, learning about the presence of fetal malformation generates anxiety and stress in the couple. This systematic review of the literature (Marokakis, 2016) has also shown that after multidisciplinary prenatal counselling parents report a reduction in pregnancy-related anxiety. Uncertainty about prognosis causes the most anxiety in parents. Specifically, the RANZCOG Guidelines (2018) recommend that:

- the couple receives detailed information on: the pathological condition found, its probable aetiology, information on relevant associated diseases and investigations which may lead to further genetic testing (through invasive prenatal diagnosis) or imaging;
- the couple should receive information on the implications of the diagnosed fetal disease on pregnancy, labour and delivery and on the outlook of the unborn child both during the neonatal phase and later in life;
- the couple should be given the opportunity to access multidisciplinary counselling in order to deal with all the possible diagnostic, prognostic and pre- and postnatal management problems.

There is no strong evidence on the efficacy of prenatal counselling on psychological outcomes such as on the general psychological well-being of parents and the amount of knowledge the couple has about the health conditions of the fetus.

A systematic review (Rossi, 2017) shows that the referral scan has a high specificity with a low percentage of false positives (3.2%).

In fact, some anomalous findings highlighted in the referral scan may be transient and resolve with the course of pregnancy, such as mild ventriculomegaly.

The risk of false positives is greater for minor abnormalities and for those that occur with non-specific ultrasound signs in the prenatal period such as oesophageal atresia with fistula in which polyhydramnios and the finding of poor gastric filling do not allow for a certain diagnosis of this pathological condition in prenatal age. In circumstances such as these, for any case confirmed in the postnatal period there will be a significant percentage of false positive cases. Such an occurrence definitely has a big negative impact on the parturient, causing unmotivated anxiety.

Question 2

In pregnant patients at risk* for fetal heart disease, is fetal echocardiography useful? *At least one maternal risk factor:

- Heart disease in a first-degree relative
- Hereditary diseases associated with heart disease
- Insulin-dependent diabetes
- Phenylketonuria
- Autoimmune diseases (Ro/SSA or La/SSB)
- ART (TPT)
- Maternal infections (TORCH)
- Consumption of/Exposure to teratogens

At least one fetal risk factor:

- Major extracardiac malformations
- Suspected fetal heart disease at screening
- Fetal arrhythmia
- Increased NT
- Velocimetry defect of the ductus venosus (RF) or tricuspid regurgitation detected in the first trimester
- Early fetal hypo-development
- Fetal hydrops
- Monochorionic twin pregnancy

Recommendation 2

In all women with at least one significant maternal or fetal risk factor for congenital fetal heart disease, fetal echocardiography is recommended to improve pregnancy outcomes.

- STRONG POSITIVE RECOMMENDATION
- RECOMMENDATION BASED ON HIGH QUALITY GUIDELINES AND ONLY ONE OF MODERATE QUALITY, AND SYSTEMATIC REVIEWS AND PRIMARY STUDIES OF MODERATE QUALITY

Literature Analysis and Evidence Interpretation

Family risk factors

In the literature, only older primary studies on CHD risk recurrence are available. These studies show that the risk of recurrence varies according to the type of lesion and the degree of kinship, and appears to be significant only if a first degree relative of the fetus has CHD (mother, father and siblings). However, in view of the strong emotional impact that a family history of CHD has on pregnant women, the work group's opinion is to perform fetal echo-cardiography in these cases (of first-degree kinship).

As evidenced by a high quality Guideline (Sussman et al., 2021) the presence of inherited genetic diseases associated with CHD are an indication for carrying out fetal echocardiography. In fact, most of these gene mutations are detectable in the prenatal period by means of current molecular genetic techniques. Fetal echocardiography is recommended in pregnancies where such recurrence has not been excluded by genetic testing.

Maternal risk factors

An "Umbrella" review (Zhang et al., 2021; a review of systematic review or meta-analyses) carried out on maternal risk factors, showed that the strongest factors are those that related severe obesity (BMI >40 kg/m²) and the risk of CHD (p<10⁻⁶, low study heterogeneity and a large sample size with more than 1,000 cases). However, given that obesity is an indication for a referral scan, the work group's opinion is that fetal echocardiography is not necessary in this subset of pregnant women.

Regarding the risk of CHD in pregnant women with diabetes, a recent meta-analysis (Chen et al., 2019) compared the prevalence of CHD in women without diabetes and women with all types of diabetes and found that women with diabetes, regardless of type (Type 1 and type 2), have a higher CHD prevalence in each subset of CHD. However, a strong association, such as to justify fetal echocardiography, was detected only for pregestational diabetes (Odds Ratio [OR] 3.18; 95% CI 2.77-3.65). On the other hand, the association between gestational diabetes and the risk of CHD is less strong (OR 1.98; 95% CI 1.66-2.36) and therefore does not justify fetal echocardiography.

The risk of CHD is increased in pregnant women with phenylketonuria. However, the high quality European Guidelines on phenylketonuria (van Wegberg et al., 2017) have shown that this risk is significantly increased only in parturients with a baseline phenylalanine value of >900 microM (15 mg/dL) and with a phenylalanine value of >600 microM (10 mg/dL) within 8 weeks of gestational age. Therefore, fetal echocardiography is not indicated for women with well-controlled phenylketonuria, whose phenylalanine levels, in the preconception period or in the first trimester, are <10 mg/dl, whereas it is indicated if the levels are >10 mg/dl.

A systematic review of the literature (Andreoli et al., 2017) confirmed a datum known for some time, that is, that women's positivity to IgG antinuclear autoantibodies (anti-Ro/SSA

or anti-La/SSB), regardless of clinical symptoms for connective tissue disease, is associated with an increased risk of complete atrioventricular block (complete AV block), myocardial and endocardial fibroelastosis. Complete AV block associated with anti-Ro/SSA and/or an-ti-La/SSB has a recurrence risk of 16% in women who have had affected fetuses in previous pregnancies. For this reason, fetal echocardiography is recommended in women with a history of congenital complete AV block from 16 weeks onwards, at intervals of 1-2 weeks, up until the 26th week. In view of the low-risk (0.7-2%) of complete AV block in women who have not had this fetal complication in previous pregnancies, it is unclear whether intensive monitoring in the positive female population for these self-antibodies is cost-effective. Therefore, examination is recommended in all cases of suspicion of complete AV block, myocarditis and endocardial fibroelastosis. Echocardiographic surveillance is at least recommended in cases of women who are positive for anti-Ro/SSA and/or anti-La/SSB with a history of complete AV block in previous pregnancies.

Among the infections occurred in pregnancy, as evidenced in a recent meta-analysis (Ye et al., 2019) only rubella (OR 3.49; 95% CI 2.39-5.11) and cytomegalovirus infections (OR 3.95; 95% CI 1.87-8.36) have a clear association with an increased risk of CHD. For other maternal infections, however, there was no statistically significant association with fetal CHD. However, in view of the small size of the studies examined in this meta-analysis for CMV and the high degree of inhomogeneity thereof, the work group's opinion is to recommend fetal echocardiography only for rubella infection.

Pregnancies arising from assisted reproductive technologies (ART) and in particular those using in vitro fertilization (IVF) seem associated with a higher-risk of CHD than the general population. However, an "umbrella" review (Zhang et al., 2021) on maternal risk factors has shown that scientific evidence is suggestive only with regard to the association between the risk of heart disease and ICSI. A recent meta-analysis (Giorgione et al., 2018) shows that the risk of CHD is higher in ICSI pregnancies than those obtained with spontaneous conception (OR 1.45). However, analysis of the qualitative distribution of the type of CHD showed that the increased risk of CHD was statistically significant only for smaller CHDs such as VSD. Therefore, in view of the exponential growth in the use of this conception method in Italy and the still unclear association between major CHD and ICSI, the work group's opinion is that ICSI is not to be considered an indication for carrying out fetal echocardiography.

Although the concrete possibility that many substances or drugs may interfere with cardiac organogenesis, a significant associations between their consumption and the risk of CHD is reported only for a few. As evidenced in a recent "umbrella" review (Zhang et al., 2021), a strong association between CHD and drug consumption is reported only for the lithium (statistical significance P<10⁻⁶ and a large sample size with more than 1,000 cases). Also in this review there was no correlation between the consumption of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and CHD except for paroxetine and fluoxetine for which weak evidence confirmed an association. Therefore the indication to perform the test dose exists only for these two SSRIs taken during pregnancy. Based on a recent meta-analysis (Buawangpong, 2020) on the teratogenicity of ACE inhibitors taken in the first trimester of pregnancy, there is an increased risk of CHD (OR 2.96; 95% CI 2.57-3.39, p<0.0001; RR 2.87). Thus, taking these medicines is an indication for fetal echocardiography. In addition, a recent systematic review of the literature (Ohlsson, 2020) showed that NSAID consumption in the third trimester of pregnancy is associated with an increased

risk of premature closure of the ductus arteriosus. Therefore, given the high-risk of adverse fetal outcomes related to the closure of the ductus arteriosus in utero, the recommendation is to perform fetal echocardiography in order to exclude a restriction in this area. The teratogenicity potential of retinoic acid has been widely demonstrated in animal studies and its consumption is not indicated during pregnancy. In the case of inadvertent pregnancy, even in the absence of strong evidence in the literature on the increased risk of CHD in these patients, the work group's recommendation is to always perform fetal echocardiography in these patients. A meta-analysis (Grigoradis et al., 2013) showed no correlation between taking antidepressants in pregnancy and the risk of CHD, therefore their consumption is not an indication for fetal echocardiography. However, as a recent meta-analysis (Veroniki et al., 2017) showed that the risk of CHD associated with taking anticonvulsants depends on the type of drug taken. In fact, while for new-generation anticonvulsants such as levetiracetam and lamotrigine monotherapy, no increased risk was demonstrated compared to controls, for gabapentin monotherapy (Or 5.98; 95% Crl 1.37-19.73) or in polytherapies such as carbamazepine plus phenytoin (OR 6.58; 95% Crl 2.25-18.97), phenobarbital plus valproic acid (OR 8.01; 95% Crl 1.17-35.40), phenytoin plus valproic acid (OR 8.88; 95% Crl 2.62-30.65), and carbamazepine plus clonazepam (OR 10.08; 95% Crl 1.40-51.22), these were associated with a statistically significant risk of CHD compared to controls. Therefore, the work group's opinion is to perform echocardiography only in the case of gabapentin monotherapy or in the case of polytherapies.

Furthermore, the work group's recommendation is to perform fetal echocardiography in all patients where the examination indication comes from multidisciplinary specialist advice.

Fetal risk factors

The detection of chromosomal aberrations in the fetus is an important risk factor for CHD. The highest association is between aneuploidies and CHD. The prevalence of CHD also increased in fetuses with pathological copy number variation (CNV) that can be seen at CGH array. Among pathological CNVs, 22q11 microdeletion is the one that has the greatest association with CHD. As evidenced by a meta-analysis and systematic literature review (Rozas et al., 2019) CHDs are present in 50-60% of the affected individuals regardless of the size of the deleted zone. Fetal echocardiography is indicated in fetuses with aneuploidies and 22q11 microdeletion. In other cases, the work group's suggestion is to perform echocardiography in fetuses with genetic abnormalities, as instructed by the geneticist who performs the prenatal counselling.

As reported by a high-quality Guideline (Sussman et al., 2021), CHD suspicion on screening ultrasound examinations, the detection of major fetal extracardiac abnormalities, fetal hydrops, and the presence of fetal arrhythmias are an indication for echocardiography. However, the work group specifies that within fetal arrhythmias we should only consider persistent rhythm abnormalities and not episodic forms of bradycardia, tachycardia, or extrasystole.

A high-quality Guideline (Simpson et al., 2020) recommends performing fetal echocardiography only in fetuses with a NT \geq 99th centile (3.5 mm) at the screening of first trimester aneuploidies. In fact, using this NT cut-off approximately 1% of patients who perform the first trimester screening for aneuploidies will be referred to perform echocardiography, therefore, given the low proportion of patients reported and the high prevalence of CHD in this subgroup of patients, fetal echocardiography is recommended only in the presence of a NT \geq 99th centile (3.5 mm). These guidelines also report that tricuspid regurgitation during the first-trimester screening examination is associated with a 10-fold increase in CHD risk. Whereas for reverse flow of the ductus venosus the risk of CHD increases 3-fold only when it is present in fetuses with increased NT. Therefore fetal echocardiography is recommended in fetuses with tricuspid regurgitation at the first trimester examination even if isolated and reverse flow of the ductus venosus when associated with an increased NT (>95th centile).

Moreover, these Guidelines (Simpson et al., 2020) report that strong evidence exists in literature only on increased risk of CHD in monochorionic twin pregnancies and that this risk increases considerably in complicated pregnancies with twin-to-twin transfusion syndrome (TTTS). Therefore, fetal echocardiography is recommended only in monochorionic twin pregnancies.

There is no strong evidence to correlate early fetal growth restriction with the risk of CHD. Furthermore, the early detection of an SGA fetus is an indication to refer the patient for referral scan, the work group's opinion is that fetal echocardiography is not required in this subset of pregnant women.

A summary of the indications for fetal echocardiography is given in Table 2.

Family indications	 Familiarity for CHD (first degree kinship) Inherited genetic diseases associated with CHD (when not excluded from prenatal genetic tests)
Maternal indications	 Pregestational diabetes (types 1 and 2) Phenylketonuria (women with phenylalanine values >10 mg/dl or in the first trimester) Positive anti-Ro/SSA or anti-La/SSB autoantibodies in case of suspicion of complete AV block, myocarditis and endocardial fibroelastosis. Echocardiographic monitoring from 16 to 26 weeks in women with a history of congenital complete AV block Maternal rubella infection in the first trimester of pregnancy Taking medicines during pregnancy (lithium, paroxetine, fluoxetine, ACE inhibitors, retinoic acid, gabapentin monotherapy or polytherapy with anticonvulsants, taken in the first trimester of pregnancy)
Fetal indications	 Fetuses with aneuploidies or 22q11 microdeletion (or on indication of geneticist) Suspected heart disease at screening ultrasound examination Fetal extracardiac malformation Fetal hydrops Persistent fetal arrhythmias (not including episodic forms of bradycardia, tachycardia, or extrasystole) NT ≥3.5 mm (≥99th centile) Tricuspid regurgitation in the first trimester Reverse flow of ductus venosus in the first trimester only if associated with increased NT Monochorionic twin pregnancies

 Table 2

 Indications for fetal echocardiography

The work group's recommendation is to perform fetal echocardiography in all patients where the examination indication comes from multidisciplinary specialist advice.

There is strong evidence in the literature to support the fact that prenatal diagnosis improves the survival of birth-critical CHD children. In fact, as evidenced in a 2015 meta-analysis (Holland, 2015) the prenatal diagnosis of this subgroup of CHD improves the preoperative survival of affected infants. Furthermore, infants with a prenatal diagnosis of critical CHD were significantly less likely to die prior to scheduled surgery than children with postnatal diagnosis of the same cardiac defect, the same standard risk factors, and parent orientation to surgical treatment (pooled odds ratio 0.26; 95% CI 0.08-0.84). Moreover, the results of this meta-analysis also suggest that prenatal diagnosis of these CHDs may improve, not only preoperative survival, but also overall survival.

Another 2016 meta-analysis (Li et al., 2016) showed a statistically significant reduction in preoperative mortality in children with CHD who had received prenatal diagnosis compared to those in whom heart disease was diagnosed after birth (3.51% *vs* 8.3%) (*odds ratio* 0.41; 95% CI 0.18-0.94, p=0.04). The reduction in postoperative mortality between the two groups was equally significant (14.07% *vs* 17.32%) (*odds ratio* 0.66; 95% CI 0.46-0.94, p=0.02). In this case, as well, the heart disease with the greatest impact from prenatal diagnosis on pre and postoperative mortality rates (95% CI 0.06-0.80; 95% CI 0.01-0.82, respectively) was a critical heart disease at birth, id est, the transposition of the great arteries.

There is no strong evidence to support the impact of prenatal diagnosis of CHD on reducing morbidity in affected children. However, the 2016 Li meta-analysis shows that the low data available and the different morbidity analysed in studies did not allow the results to be grouped together. However, what emerges from these studies is that prenatal diagnosis allows for earlier haemodynamic stabilization of infants, which should indirectly reduce postnatal morbidity.

Another 2017 meta-analysis (Thakur et al., 2017) conducted in children with hypoplastic left heart syndrome, demonstrated that infants with prenatally diagnosed CHD reach the surgery with a better hemodynamics when compared with those with postnatal diagnosis. (mean difference 0.07; 95% CI 0.05-0.1, p<0.01) and required less inotropic support (OR 0.16; 95% CI 0.04-0.7, p=0.01). The authors of this meta-analysis also hypothesize that the best haemodynamic profile of infants receiving a prenatal diagnosis may be related to better long-term neurocognitive outcomes.

However the correlation between prenatal diagnosis of CHD and postnatal morbidity represents an important hint for future research.

A 2015 meta-analysis (Zhang et al., 2015) of the diagnostic value of fetal echocardiography reports that the sensitivity of fetal echocardiography in the diagnosis of CHD in the population of women with at least one maternal or fetal risk factor per CHDs is 85%.

Factors that limit the sensitivity of the examination when performed in the second trimester of pregnancy include developmental heart disorders, i.e. those that appear exclusively during the third trimester of pregnancy (e.g. cardiomyopathies or cardiac tumours) and those that become more apparent later (e.g. valve stenosis or aortic coarctation). This is one of the main reasons why, as reported in Zhang's 2015 meta-analysis, the sensitivity of fetal echocardiography increases from the second to the third trimester of pregnancy.

The diagnostic accuracy of fetal echocardiography, as reported in Zhang's 2015 meta-analysis, is high, in fact the ROC curves were >0.9924 for all the data analysed. This is also apparent from another recent meta-analysis (Maimsh, 2019) that reports 86% overall diagnostic accuracy for fetal echocardiography. However, the diagnostic accuracy of the examination varies depending on the type of CHD considered, certainly high for hypoplastic left heart syndrome (91.5%), hypoplastic right heart syndrome (88.2%), univentricular heart (90.8%), atrial-ventricular septal defects (93.4%) and truncated cone abnormalities (87.2%); intermediate for aortic arch anomalies (75%), anomalies of venous return (69%), isomerism (75%) and in general biventricular CHD (71%).

Additionally, the presence of referral scan limiting factors reduces the sensitivity of the examination. A high-quality Guideline (Simpson et al., 2020) reported that among the factors
influencing the sensitivity of the examination we can find: maternal obesity, the presence of abdominal scars, an unfavourable fetal position and the performance of the examination in twin pregnancies.

The Guidelines of the American College of Radiology (Simpson et al., 2020) also point out that, although the ideal gestational age for performing fetal echocardiography remains at 18-22 weeks of pregnancy, there is sufficient evidence to support the possibility of performing early fetal echocardiography. Early fetal echocardiography can be performed from 11 weeks of gestation, but a complete study of fetal heart anatomy is feasible in 90% of cases within 13-14 weeks. In 11-14 weeks, the diagnostic accuracy of early fetal echocardiography varies depending on the type of CHD, greater for CHDs such as the hypoplastic left heart and the atrioventricular canal (about half of the cases identified) and less for truncated cone CHD (less than 1/4 of the cases). Due to examination limitations, these Guidelines recommend that standard fetal echocardiography be always repeated at 18-22 weeks. A recent meta-analysis (Yu, 2020) reported an overall sensitivity of 75% and a very high specificity of the examination (99%). A high-quality Guideline (Sussman et al., 2021) highlights that in obese women anticipating the evaluation of fetal anatomy (including the heart) to the first trimester has the undoubted advantage of exceeding the limit of the examination with a transvaginal approach. Therefore, a transvaginal assessment in the first trimester in combination with a transabdominal assessment in the second trimester can improve the detection rate of fetal abnormalities.

The purpose of fetal echocardiography is to diagnose or rule out the presence of a CHDs in patients at high-risk for these abnormalities. In cases where the presence of a CHD is detected, the pregnant woman, as recommended by high guality Guidelines, must be informed in detail in order to protect her right to an informed pregnancy, and so she can choose between continuing or interrupting the pregnancy (NICE, 2019). As a systematic review of the literature (Marokakis, 2016) shows, most couples who have received a postnatal diagnosis of a fetal disease report that they would have preferred to have known of the presence of an abnormality in the prenatal period. Nonetheless, learning about the presence of a CHD generates anxiety and stress in the couple. This systematic review of the literature (Marokakis, 2016) has also shown that after multidisciplinary prenatal counselling parents report a reduction in pregnancy-related anxiety. Uncertainty about prognosis causes the most anxiety in parents. This is why, in order to develop an adequate prognosis on the basis of which the couple can arrive at a conscious choice on the continuation of pregnancy, it is recommended, regardless of the result of the screening tests previously performed, to offer genetic counselling and an invasive diagnostic test for a fetal karyotype and CGH array if the standard karyotype is normal or inconclusive. There is no strong evidence on the efficacy of prenatal counselling on psychological outcomes such as on the general psychological well-being of parents and the amount of knowledge the couple has about the health conditions of the fetus.

A 2015 meta-analysis (Zhang et al., 2015) on the diagnostic value of fetal echocardiography reports that the specificity of fetal echocardiography is very high (99%). The high specificity of the examination makes false positive cases very infrequent, i.e. the diagnosis of CHD in the presence of normal cardiac anatomy is not common. The risk of false positives is greater for minor CHDs (atrial and ventricular septal defects) and for CHDs that manifest with non-specific ultrasound signs in the prenatal period such as isthmic coarctation of the aortic arch. For each case correctly identified, there will be a significant percentage of false positive cases. Certainly this occurrence has a major negative impact on the parturient, causing unmotivated anxiety and sometimes unnecessary invasive diagnostic examinations. However, this is a CHD where prenatal suspicion significantly reduces mortality and morbidity associated with this abnormality. This is an example of how, for some of these conditions, prenatal suspicion or diagnosis is so important that the weight of a certain percentage of false positives is acceptable.

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