ORIGINAL ARTICLE

The natural history of monoamniotic twin pregnancies: a case series and systematic review of the literature

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ABSTRACT

Objective To describe the natural history of monoamniotic twin pregnancies in contemporary practice.

Method Cohort study of monochorionic monoamniotic twin pregnancies with two live fetuses diagnosed at less than 16 weeks and prospectively followed up between 2004 and 2013. A systematic review of the literature using Medline, Embase and Scopus to determine the perinatal mortality rate after 24 weeks of gestation in monoamniotic twins was also performed.

Results Twenty pregnancies were analyzed. Four were terminated (in three cases as a result of fetal abnormalities). Another six miscarried spontaneously. Among ten pregnancies reaching viability, there was double intrauterine death in one, and both fetuses were alive at delivery in the other nine. There were no neonatal deaths. Overall survival for fetuses alive at the initial scan was 18/40 (45%; 95% CI 29 to 62%). At meta-analysis of 13 studies (including the current series), the perinatal mortality rate after 24 weeks was 4.5% (95% CI 3.3 to 5.8%).

Conclusions Despite early diagnosis and intensive monitoring, of those fetuses alive before 16 weeks less than half survive until the neonatal period. Most losses are attributable to fetal abnormalities and spontaneous miscarriage and are therefore unlikely to be reduced by further improvements in fetal assessment and monitoring. © 2014 John Wiley & Sons, Ltd.

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INTRODUCTION

Monoamniotic twin pregnancies are a rare event, reported to occur approximately in 1% of monochorionic twin pregnancies.[1] Monoamniotic pregnancies have been associated with a higher mortality and morbidity rate than monochorionic diamniotic twin pregnancies, given the increased risk of preterm delivery, fetal structural anomalies, stillbirth and complications at delivery. Recent publications report a mortality rate in monoamniotic twins of 10–15%,[2] with a significant improvement from the 30–40% rate reported in older literature.[3–5]

Despite the increasing availability of literature on monoamniotic pregnancies in the two last decades, most reports are based on small series and retrospectively analyze cases sent to referral centers just near the time of childbirth or as a result of the development of complications in the second or third trimester.

The first aim of this study was to describe the natural history of monoamniotic twin pregnancies diagnosed at our institution in early pregnancy and managed throughout the course of gestation in a dedicated twin pregnancy clinic. The second aim was to systematically review the literature on perinatal survival in monoamniotic twins.

METHODS

Case series

We searched our electronic database to identify monochorionic monoamniotic twin pregnancies with two live fetuses who were prospectively followed up at our institution between April 2004 and February 2013, with a first scan performed before 16^{+0} weeks of gestation. Cases referred for known fetal abnormalities were not included in the search. Pregnancies examined for the first time at a later gestation, higher order pregnancies with a monoamniotic component and cases lost to follow up were excluded from the analysis. As this was a retrospective audit of clinical data presented in anonymized form, no ethical committee approval was necessary according to national regulations.

Monoamnionicity was diagnosed in monochorionic twin pregnancies before 16^{+0} weeks, and ideally at 11–14 weeks, based on a combination of the following ultrasound signs: lack of dividing membrane; presence of a single yolk sac; and presence of cord entanglement confirmed by visualization of the 'galloping horse sign' at pulse wave Doppler examination.[6,7]

As with other monochorionic pregnancies, follow-up included ultrasound examinations at 16 weeks and 2-weekly thereafter, unless there was evidence of complications, in which case the frequency of examinations was increased as necessary.[8] The deepest pocket of amniotic fluid, bladder appearance, umbilical artery pulsatility index and middle cerebral artery peak systolic velocity (starting from 2008) were assessed at each examination. Fetal biometry was obtained at least every 4 weeks for the assessment of growth. At 19–21 weeks, a detailed anomaly scan and fetal echocardiography were performed. On the same occasion, transvaginal cervical length measurement was performed[9] and repeated weekly if cervical length was less than 30 mm. Twin-to-twin transfusion syndrome (TTTS) was defined by the association of polyhydramnios (deepest vertical pool of amniotic fluid of at least 8 or 10 cm before and after 20 weeks respectively) and non-visualization of the bladder in one of the twins. Selective intrauterine growth restriction (sIUGR) was defined as an estimated fetal weight below the 10th percentile in one twin together with abnormal umbilical artery Doppler.[10]

We proposed hospitalization with twice daily cardiotocography and twice weekly ultrasound evaluation from 28 weeks until delivery and planned elective cesarean section at 32 weeks, after steroid administration. Until 2008 included, from 20 weeks of gestation, we also offered maternal sulindac oral treatment to reduce amniotic fluid volume as previously described.[11] Beginning in 2009, we no longer offered sulindac treatment.

Outcome data were obtained from obstetric and neonatal hospital notes. We considered pregnancy outcome in terms of gestational age at delivery, fetal loss <24 weeks, perinatal mortality. Monoamnioticity was confirmed postnatally in all cases by pathological examination of the placenta. In neonates, acute respiratory distress syndrome was diagnosed in case of respiratory distress, together with typical radiological abnormalities and need for oxygen therapy with a $FiO_2 \geq 0.40$ for over 24 h. Necrotizing enterocolitis was diagnosed based on radiological, surgical or autopsy findings. Intraventricular hemorrhage was diagnosed and classified according to Papile's criteria.[12] Periventricular leukomalacia was diagnosed as described by de Vries et al.[13]

Systematic review

The systematic review of the literature was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analyses.[14,15] MEDLINE (from 1966), EMBASE (from 1974) and Scopus (since inception) were searched electronically on the 14th of May 2014 and 14th of August 2014 using combinations of the relevant medical subject heading (MeSH) terms, key words and word variants for 'Monochorionic*', 'Monoamniotic*', 'Twin*', 'Outcome*'. Reference lists of relevant articles and reviews were hand searched for additional reports.

All abstracts were reviewed independently by two authors (GP, FP). Agreement about potentially relevant articles was reached by consensus, and full text copies were obtained. Both authors independently extracted data regarding study characteristics, outcome and quality using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria.[14] Inconsistencies were discussed by the reviewers and consensus reached. Authors were contacted for those articles in which information was not reported, but the methodology was such that this would have been recorded initially.

Studies were assessed according to the following criteria: population, outcome and study design. Perinatal mortality was defined as fetal/neonatal demise between 24 weeks of gestation and 28 days after birth. In order to avoid bias, fetuses with known structural or chromosomal abnormality, TTTS and twin reversed arterial perfusion (TRAP) sequence cases were excluded from the analysis. Studies were excluded from the analysis in case of (1) population smaller than five cases; (2) unavailable gestational age at stillbirth; and (3) non-English language publication. Between-study heterogeneity was explored graphically within the forest plot and statistically assessed using the I^2 statistic, which represents the percentage of between-study variation that is because of heterogeneity rather than chance.[16] A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥50% indicate a substantial level of heterogeneity.[17] We planned to use a fixed effects model if substantial statistical heterogeneity was not present. Random effects models were used if heterogeneity was significant ($I^2 > 50\%$). Publication bias was explored using funnel plots and was assessed statistically using both Begg and Mazumdar's rank correlation test and Egger test.[18] Cumulative meta-analysis was performed if publication bias was observed. Statistical analyses were performed using Stata 11 (release 11.2. College Station, Texas, USA) and GrapPhad Prism (GraphPad Software, San Diego, California, USA) statistical software.

RESULTS

Case series

From our database, we identified 30 monochorionic monoamniotic twin pregnancies. Of these, ten were excluded from further analysis: seven because the first ultrasound scan was performed after 16 weeks; two because the monoamniotic component was part of a triplet pregnancy; and one as a result of loss to follow-up.

Baseline characteristics of the pregnancies are shown in Table 1. In four pregnancies, the mother requested termination of pregnancy: in three cases, as a result of fetal abnormalities (cystic hygroma in one twin; acrania in one twin, diaphragmatic hernia in the other twin; body stalk anomaly in both twins, this latter case has been described in detail elsewhere[19]) and in one case for social reasons. In six other cases, the pregnancy miscarried spontaneously before

Table 1 Baseline characteristics of the study population ($n = 20$)

Maternal age, median (range)	32 (20–43) years
Primiparous, *n* (%)	12 (60%)
Spontaneous conception, *n* (%)	20 (100%)
Gestational age at first assessment, median (range)	12^{+4} (8^{+4}–15^{+6}) weeks
Sulindac treatment, *n* (%)	6 (30%)

24 weeks of gestation. There were ten pregnancies that reached viability: In one, there was a double intrauterine fetal death diagnosed at 28^{+3} weeks on hospital admission after a previous normal scan 2 weeks before (both fetuses were normally grown, with a 2% birth weight discordance; cord entanglement was present but with no evidence of cord vascular accidents); in nine, both fetuses were alive at delivery, at a median gestational age of 32 weeks (range 31^{+0}–32^{+5}). All deliveries took place by elective cesarean section, except for one case of emergency cesarean section at 31 weeks as a result of non-reassuring cardiotocography. The median birth weight was 1600 g (range 1230 to 2000 g), with a median birth weight discordance of 8% (range 1 to 15%). No cases of pre-eclampsia or diabetes were observed. A chart summarizing case flow is shown in Figure 1. We observed no cases of TTTS or sIUGR. Neonatal complications are shown in Table 2: Although most newborns were admitted to the neonatal intensive care unit, severe respiratory morbidity was present in one third of cases only, there were no neonatal deaths, and major complications were infrequent. The overall perinatal survival for fetuses alive at the initial scan was therefore 18/40 (45%; 95% confidence interval 29 to 62%).

Systematic review

The electronic search yielded a total of 62 possible citations; of these, 40 were excluded by review of the title or abstract as they did not meet the selection criteria. Full manuscripts were retrieved for 22; 8 manuscripts were excluded because they did not meet the inclusion criteria. Thus, a total of 14 studies in addition to our series were eligible for meta-analysis [11,20–32] (Figure 2). Characteristics of the eligible studies are shown in Table 3. Quality assessment is shown in Supplementary Figure 1. Fixed effects model showed significant heterogeneity ($I^2 > 50\%$) between eligible studies. The funnel plot for perinatal mortality rate was observed to be asymmetric indicating a lack of small studies with low event rate (Supplementary Figure 2). Egger test, but not Begg and Mazumdar's rank correlation test, showed significant publication bias ($p = 0.02$ and $p = 0.07$, respectively). Cumulative meta-analysis showed that older studies with higher perinatal mortality rate were likely to bias the analysis unbalancing the results to higher rates (Supplementary Figure 3). However, no differences between these two studies[21,22] and the others were observed in terms of time of study period, inclusion criteria and study design. When these studies were excluded, fixed effects model failed to show significant heterogeneity ($I^2 = 44.5\%$), the funnel plot for perinatal mortality rate was observed to be symmetric (Figure 3) and both Begg and Mazumdar's rank correlation test and Egger test failed to show significant publication bias ($p = 0.36$ and $p = 0.17$, respectively).

The pooled proportion of perinatal mortality rate in monochorionic monoamniotic twin pregnancies after 24 weeks of gestation (involving 13 studies and 1110 fetuses) was 4.5% (95% CI 3.3 to 5.8%; Figure 4). (Supplementary Figure 4 shows the pooled proportion of perinatal mortality rate considering also the two studies excluded after cumulative meta-analysis).[21,22]

Table 2 **Major neonatal complications**

Admission to neonatal intensive care unit	16/18
Length of hospital stay, median (range)	40 (18–60) days
Neonatal death	0/18
Respiratory distress syndrome with mechanical ventilation	6/18
Days on ventilator, median (range)	1 (0.5 to 5) days
Intraventricular hemorrhage	0/18
Periventricular leukomalacia	1/18
Sepsis	0/18
Necrotizing enterocolitis	1/18

DISCUSSION

We report that in a contemporary series of 20 monochorionic monoamniotic twin pregnancies followed up at a single

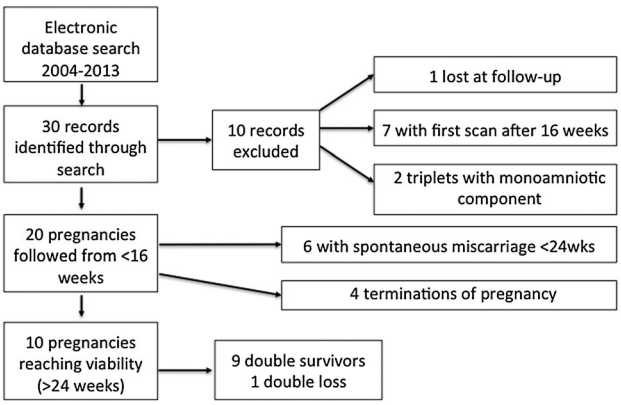

Figure 1 **Flowchart of the study population**

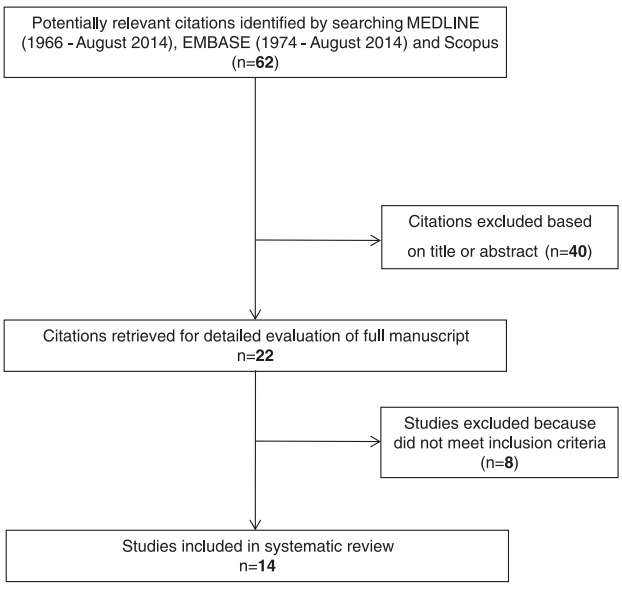

Figure 2 **Flowchart of the studies included in the meta-analysis**

Table 3 **Characteristics of the studies included in the meta-analysis**

Author, year	Study period	Study population	Study design	Country	Antenatal management from second trimester	IUFD	LB	NND	Strobe Score
Allen, 2001	1993–2000	25	Multicentric, retrospective	Canada	Unclear	1	41	0	12/18
Sau, 2003	1994–2000	7	Single centre, retrospective	UK	US every 2 weeks, CS at 32 weeks	1	7	1	12/18
Demaria, 2004	1993–2001	19	Single centre, retrospective	France	US every 2 weeks, CS at 36 weeks	5	25	3	14/18
Heyborne, 2005	1993–2003	96	Multicentric, retrospective	USA	Unclear	13	163	2	14/18
Cordero, 2006	1990–2005	36	Single centre, retrospective	USA	According to subgroup, CS at 32–34 weeks	0	60	1	14/18
De Falco, 2006	1991–2001	26	Multicentric, retrospective	USA	According to subgroup	3	40	0	14/18
Pasquini, 2006	1994–2005	43[a]	Single centre, retrospective	UK	US every 4 weeks, CS at 34 weeks	0	40	0	13/18
Hack, 2009	2000–2007	103	Multicentric, retrospective	Netherlands	Admission at 30–32, CS at 32–34 weeks	5	164	5	13/18
Baxi, 2010	2001–2009	25	Single centre, retrospective	USA	Admission at 26–28, CS at 34 weeks	0	41	1	12/18
Dias, 2010	2001–2008	32	Single centre, retrospective	UK	US every 4 weeks, CS at 34 weeks	0	32	0	16/18
Morikawa, 2012	2002–2009	101	Multicentric, retrospective	Japan	Unclear	12	163	2	14/18
Murata, 2013	2001–2011	38	Single centre, retrospective	Japan	Admission at 24–26, CS at 34 weeks	1	53	3	14/18
Suzuki, 2013	Unclear	18	Single centre, retrospective	Japan	Unclear	4	23	0	11/18
Van Mieghem, 2014	2003–2012	117	Multicentric, restrospective	Belgium, Canada, Netherlands, Switzerland	According to individual centre's protocol	8	223	8	14/18
Prefumo, 2014	2004–2013	10	Single centre, retrospective	Italy	Admission at 28 weeks, CS at 32 weeks	2	18	0	Not assessed

MCMA, monochorionic monoamniotic; IUFD, intrauterine fetal death; LB, live birth; NNM, neonatal death; CS, cesarean section.
[a]One triplet case excluded.

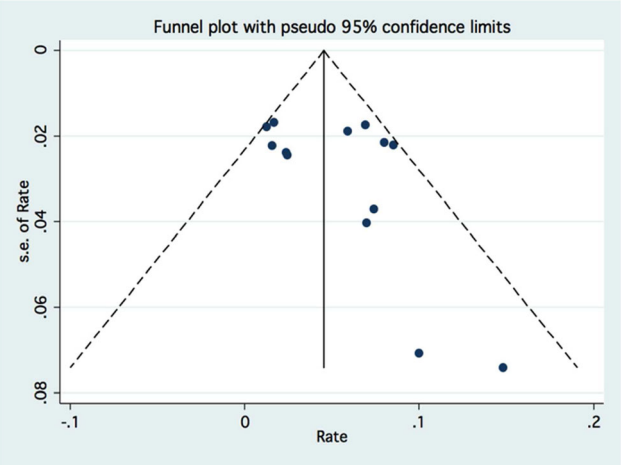

Figure 3 Funnel plot showing the perinatal mortality rate for monochorionic monoamniotic twin pregnancies after 24 weeks of gestation (biased studies excluded). s.e., standard error

institution from before 16 weeks of gestation, the overall neonatal survival was 18/40 (45%). The greatest proportion of adverse outcomes took place before 24 weeks (almost half of the pregnancies miscarried or were terminated because of fetal abnormalities). Among the ten pregnancies that reached viability, 18/20 fetuses (90%) survived the neonatal period. A meta-analysis of the literature, including our series, showed that the estimated perinatal mortality rate after 24 weeks, after the exclusion of fetuses with known structural or chromosomal abnormality, TTTS and TRAP sequence, was 4.1% (95% CI 1.9 to 6.4%).

Although monoamnionicity is known to be associated with a high rate of complications, in the literature, different rates of mortality are reported, ranging from no mortality at all to 70%.[20,26,33–38] This may be attributed to the fact that some studies included women followed from the first trimester,

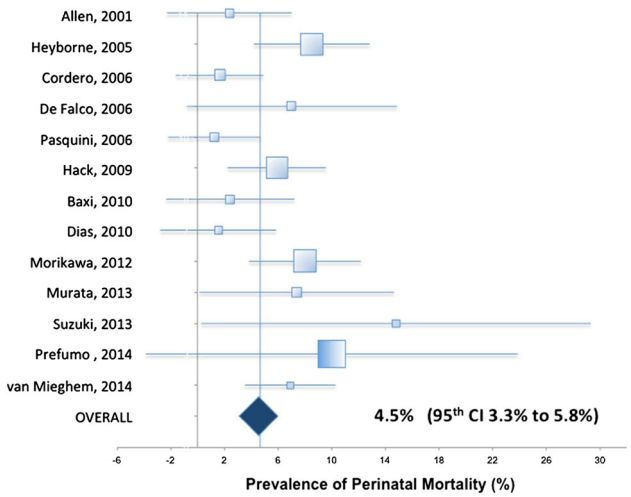

Figure 4 Pooled proportion (forest plot, fixed effects model) of perinatal mortality rate in monochorionic monoamniotic twin pregnancies after 24 weeks of gestation (biased studies excluded)

reporting therefore also fetal demises. Other studies, instead, described women mainly after mid-pregnancy, when they were referred to a tertiary center. Like ours, the majority of published studies are based on relatively small series. The most recent studies reported survival rates approaching 90%,[2] with an improved perinatal survival compared with the previous decades attributed to an earlier diagnosis of monoamnioticity and closer obstetric surveillance.[11,26,28] In pregnancies that reached viability, the prospective risk of intrauterine fetal death has been estimated as about 14% and declines with gestational age.[29]

As observed in our series, the presence of fetal abnormalities has significant influence on outcome: we registered an overall incidence of 15%, with an adverse outcome of 100% in terms of mortality rate as a result of spontaneous miscarriage or pregnancy termination. A review of series including pregnancies from 1991 until 2009 reported an overall prevalence of major congenital anomalies of 11% (37/334 fetuses).[27] Congenital anomalies are therefore one of the main causes of perinatal mortality in monoamniotic pregnancies, and they typically regard heart or head structures, usually just in one twin.[39,40] TRAP sequence also affects monoamniotic twins, and conjoined twinning is a severe complication peculiar to monoamnionicity.[40]

Given the differences in design and outcome definitions of the different studies available, we decided to perform a systematic review of the literature concentrating on the most reproducible and commonly reported outcome, that is, perinatal mortality after viability (24 weeks). We did not attempt to include in the review outcomes such as termination of pregnancy for fetal abnormality or intrauterine death before viability, which are more likely to be affected by local health care organization and referral patterns. Excluding fetuses with known structural or chromosomal abnormality, TTTS and TRAP sequence, the estimated perinatal mortality rate was only 4.1%.

Traditionally, vascular accidents related to cord entanglement have been proposed as the major cause of adverse outcome and perinatal mortality in monoamniotic twins. However, Dias et al. reported that if systematically evaluated at ultrasound examination, umbilical cord entanglement is present in the large majority of monoamniotic twins, if not in all.[28] They suggested that cord entanglement per se is therefore unlikely to be the cause of increased perinatal mortality, proposing that the latter may be associated primarily with conjoined twinning, TRAP sequence, discordant anomalies and spontaneous miscarriage. A systematic review of 114 monoamniotic twin sets also concluded that cord entanglement does not contribute to prenatal morbidity and mortality.[2]

It is our policy to delivery monoamniotic twins by planned cesarean section at 32 weeks after administration of corticosteroids, following ultrasound assessment every 2 weeks, and more frequent ultrasound scans and daily cardiotocography after 28 weeks. Although a management with intensive fetal monitoring and elective cesarean delivery starting from 32 weeks is advocated by some guidelines, there is no consensus on the modalities of monitoring, and the timing of elective delivery is a matter of debate.[41,42] The evidence described above

about the prognostic significance of cord entanglement challenges the need for early delivery at 32 weeks.

The strengths of the current study are inclusion of a well-defined cohort of monoamniotic pregnancies managed with predefined protocols; exclusion of pregnancies examined for the first time at $\geq 16^{+0}$ weeks or referred because of pregnancy complications. We believe that this makes our cohort well representative of the natural history of monoamniotic twin pregnancies in contemporary clinical practice. The main limitation of our study is the small population, which is however comparable with most published single centre series.

CONCLUSION

We demonstrated that despite early ultrasound diagnosis and intensive monitoring of monoamniotic twin pregnancies, of those fetuses viable before 16 weeks, only slightly more than 40% survive until the neonatal period. Most of these losses are attributable to fetal abnormalities and spontaneous miscarriage and are therefore unlikely to be reduced by further improvements in fetal assessment and monitoring. If viability is attained, the chance of neonatal survival is more than 95%.

ACKNOWLEDGEMENTS

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Recent series report a mortality rate in monoamniotic twins of 10–15%, with a significant improvement from the 30–40% rate reported in older literature.
- Most series retrospectively analyze cases sent to referral centers just near the time of childbirth or as a result of the development of complications in the second or third trimester.

WHAT DOES THIS STUDY ADD?

- This series is representative of the natural history of monoamniotic twin pregnancies in contemporary clinical practice.
- Despite early ultrasound diagnosis and intensive monitoring of monoamniotic twin pregnancies, of those fetuses viable <16 weeks less than half survive until the neonatal period.
- Most losses are attributable to fetal abnormalities and spontaneous miscarriage and are therefore unlikely to be reduced by further improvements in fetal assessment and monitoring.
- After exclusion of fetal abnormalities, the perinatal mortality rate >24 weeks estimated from meta-analysis is 4.5%.

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SUPPORTING INFORMATION

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