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Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis

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KEYWORDS: amniocentesis; chorionic villus sampling; CVS; fetal loss; invasive diagnostic procedure; miscarriage; pregnancy loss; prenatal diagnosis; procedure-related loss

ABSTRACT

Objectives *To estimate procedure-related risks of miscarriage following amniocentesis and chorionic villus sampling (CVS) based on a systematic review of the literature and a meta-analysis.*

Methods *A search of MEDLINE, EMBASE, CINHAL and The Cochrane Library (2000–2014) was performed to review relevant citations reporting procedure-related complications of amniocentesis and CVS. Only studies reporting data on more than 1000 procedures were included in this review to minimize the effect of bias from smaller studies. Heterogeneity between studies was estimated using Cochran's Q, the* I^2 *statistic and Egger bias. Meta-analysis of proportions was used to derive weighted pooled estimates for the risk of miscarriage before 24 weeks' gestation. Incidence–rate difference meta-analysis was used to estimate pooled procedure-related risks.*

Results *The weighted pooled risks of miscarriage following invasive procedures were estimated from analysis of controlled studies including 324 losses in 42 716 women who underwent amniocentesis and 207 losses in 8899 women who underwent CVS. The risk of miscarriage prior to 24 weeks in women who underwent amniocentesis and CVS was 0.81% (95% CI, 0.58–1.08%) and 2.18% (95% CI, 1.61–2.82%), respectively. The background rates of miscarriage in women from the control group that did not undergo any procedures were 0.67% (95% CI, 0.46–0.91%) for amniocentesis and 1.79% (95% CI, 0.61–3.58%) for CVS. The weighted pooled procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% (95% CI, −0.04 to 0.26%) and 0.22% (95% CI, −0.71 to 1.16%), respectively.*

Conclusion *The procedure-related risks of miscarriage following amniocentesis and CVS are much lower than are currently quoted.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Amniocentesis and chorionic villus sampling (CVS) are commonly performed invasive procedures for prenatal diagnosis. It is vital that pregnant women are given accurate information about procedure-related risks of miscarriage to enable them to make informed choices about invasive prenatal testing. The UK National Health Service Fetal Anomaly Screening Programme states in its information leaflet for parents that the overall risk of miscarriage after an amniocentesis is about 1% and that after CVS it is about 1–2%[1]. There is inconsistency in the recommendations from various national bodies regarding the procedure-related risks of miscarriage, with the guidelines and information leaflets from the Royal College of Obstetricians and Gynaecologists (RCOG) stating that the additional risk of miscarriage from an amniocentesis is about 1% and that the additional risk from CVS may be slightly higher than that of amniocentesis, and could be in the region of 1–2%[2,3]. The American College of Obstetricians & Gynecologists mentions that the procedure-related loss rate after mid-trimester amniocentesis is less than 1 in 300–500 and that the loss rate for CVS may be the same as that for amniocentesis[4]. The committee opinion from the Society

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of Obstetricians and Gynaecologists of Canada states that the risk of pregnancy loss following amniocentesis is unique to an individual and is based on multiple variables, but may range from as low as 0.19% up to 1.53% based on results from various studies[5].

The differences in the procedure-related risks given in the published literature have been highlighted in recent reviews that suggest that there is a wide variation in studies reporting pregnancy losses and complication rates after both amniocentesis and CVS[6,7]. These disparities relate not only to the study design, with only five out of 29 studies in the amniocentesis group and none out of 16 in the CVS group reporting results from controlled studies, but there is also considerable ambiguity with regard to the definition of pregnancy loss, some studies reporting loss within a few days of the procedure, others reporting loss prior to 24 weeks' or 28 weeks' gestation and still others reporting a total pregnancy loss rate[6]. The inclusion of studies with a wide variation in sample size, with some reporting results from a little more than 100 procedures to other large studies reporting results from more than 30 000 procedures, adds further to heterogeneity between studies[8,9]. These disparities between results from various studies – some of which were conducted decades ago when equipment, expertise and techniques were very different from those of today – do not provide an accurate estimate of the current procedure-related risks following these invasive procedures.

Although amniocentesis and CVS are carried out for a variety of reasons, the main indication remains diagnosis of fetal aneuploidies, primarily trisomy 21. Screening for fetal aneuploidies has evolved considerably in the last few decades from being based primarily on maternal age in the 1970s to widespread implementation of routine first-trimester combined screening based on the assessment of fetal nuchal translucency thickness and maternal serum biochemistry[10,11]. These developments have two main implications: first, the procedure of choice for invasive testing is likely to be first-trimester CVS rather than second-trimester amniocentesis and second, advances in screening have not only improved detection rates but also lowered the false-positive rates, thereby reducing the number of women being offered invasive testing. This will also be affected by recent developments in cell-free DNA (cfDNA) testing, which is very likely to lower the false-positive rate even further, and therefore significantly reduce the number of invasive procedures carried out[12,13]. It is essential that these improvements are integrated into clinical practice, but it is equally important that women are provided with accurate estimates of procedure-related risks of pregnancy loss so that when they are faced with a screen-positive result for fetal aneuploidy, they make choices based on accurate and up-to-date information rather than exaggerated estimates of risk based on historical data.

The objectives of this study were first, to estimate the risk of miscarriage before 24 weeks' gestation in women undergoing amniocentesis and CVS, second, to estimate the background risk of miscarriage in women not undergoing any invasive testing in appropriately controlled studies and finally, to determine accurately the procedure-related risk of miscarriage following these invasive procedures.

METHODS

Data sources and search strategy

An electronic search of MEDLINE, EMBASE, CINHAL and The Cochrane Library, including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) was carried out on 31 January 2014 utilizing combinations of the relevant Medical Subject Heading (MeSH) terms, keywords, and word variants for 'amniocentesis', 'chorionic villus sampling (CVS)', 'miscarriage', 'pregnancy loss' and 'procedure-related risk' (Table S1). The search and selection criteria were restricted to studies reported in English. The citations retrieved following this search strategy were examined for relevance to this study based on the type of invasive prenatal procedure, study design, sample size of the study, study period and gestational age at assessing pregnancy outcome.

Selection criteria of studies

We only included those studies reporting results on amniocentesis and CVS and excluded all other studies examining procedure-related complications following other prenatal diagnostic procedures. The studies included in this systematic review were limited to those published after the year 2000 to allow for relative uniformity of equipment, consumables and techniques utilized in performing the procedures, thus minimizing the potential for bias due to these issues. We included all studies that reported results from a minimum of 1000 invasive procedures in order to mitigate the effects of random errors and biases from smaller studies that could potentially lead to overestimation of effects in the meta-analysis[14]. We chose 24 weeks' gestation as the primary outcome measure for assessing the risk of miscarriage, as this is the currently accepted gestational threshold for viability[15]. The citations were examined by two independent reviewers to produce a list of relevant studies to be included in the systematic review. The reference lists of relevant articles and reviews were hand searched for additional reports, and any inconsistencies were discussed to reach a consensus.

Data extraction and synthesis

The data regarding type of procedure, study design, gestational age at sampling, definition of pregnancy loss and miscarriage rates in the study and control groups were extracted from each study included in this review and documented in contingency tables. If there was a zero in any cell of the table, 'Haldane correction', which adds

0.5 to each count in the table to allow for estimation of variance and pooled effects, was used.

Quality assessment

The methodological quality of studies included in the review was evaluated using the Newcastle–Ottawa Scale (NOS), which assesses the quality of non-randomized studies such as case–control and cohort studies with specific regard to three perspectives: selection of study groups, comparability of groups and ascertainment of outcome of interest[16].

The quality of this systematic review and meta-analysis was validated with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The PRISMA statement includes a checklist and a flow-diagram to allow uniform and transparent reporting of the systematic review and meta-analysis[17].

Meta-analysis and estimation of pooled statistics

Meta-analysis of extracted data was carried out in the following steps: summary statistics for miscarriage rate with 95% CIs were derived for each study and these individual study statistics were then combined to obtain a pooled summary estimate, which was calculated as a weighted average of the individual study estimates. The weighted pooled miscarriage rate was estimated for the invasive-procedure group as well as for the control group to derive a background risk of miscarriage from the latter. The pooled summary statistics were estimated using both fixed- and random-effects models. The fixed-effects model weights each study by the inverse of its variance and only considers variability in results within studies and not between studies. The random-effects model allows for between-study variability in results by weighting studies using a combination of their own variance and the between-study variance. Random-effects models are generally preferred, as they provide a conservative estimate of pooled statistics with wider CIs[18]. The procedure-related risk of miscarriage for each study that reported data from both the invasive-procedure group and the control group was estimated using incidence–rate difference (IRD) meta-analysis. The summary statistics of procedure-related miscarriage rate in each study were combined to calculate a weighted pooled estimate of procedure-related risk of miscarriage for amniocentesis and CVS with IRD meta-analysis using a random-effects model. Forest plots of summary statistics for each study and final pooled estimates were constructed using data from the random-effects models.

Assessment of heterogeneity, inconsistency and bias

Heterogeneity between studies was estimated using Cochran's heterogeneity statistic Q, which was calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method[19]. Inconsistency between study results was assessed using the I^2 statistic, which was calculated as $I^2 = (100 \times (Q - df)/Q)\%$, in which df is the degrees of freedom. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance and is particularly useful, as it does not depend on the number of studies in the meta-analysis[20]. It varies between 0 and 100%. Values of the I^2 statistic of 0–40% might be unimportant, 30–60% might be moderate, 50–90% may be substantial and 75–100% considerable[21]. The publication bias in studies included in the analysis was assessed graphically using funnel plots and by using Egger's bias, which assesses the asymmetry of the plot[22].

The statistical software package StatsDirect version 2.7.9 (StatsDirect Ltd, Cheshire, UK) was used for data analysis.

RESULTS

Data search results

The electronic search of the databases yielded 1506 potential citations; of these, 1381 were excluded after reviewing the title or the abstract, as they did not meet the eligibility criteria. A total of 125 manuscripts were retrieved in full text for detailed assessment. Of these, 104 studies did not meet the inclusion criteria, leaving 21 studies for final inclusion in the systematic review and meta-analysis (Figure 1). These 21 studies (from 19 citations) included 14 studies on amniocentesis[9,23–35] and seven studies on CVS[9,30,36–40] (Tables 1 and 2).

Characteristics of studies included in the systematic review

In the amniocentesis group there were 14 studies, comprising six observational retrospective cohort studies without a control group[9,24,27,31,32,35], four observational retrospective cohort studies with a control group from an unselected population during the same study period[23,25,29,30], including one study based on a national-registry database[30], and four case–control studies[26,28,33,34]. There were differences with regard to reporting the gestational age at which amniocentesis was carried out: of the 14 studies, five (35.7%) studies[24,25,27,34,35] did not provide a mean or median gestational age and two (14.3%) studies[9,25] did not provide the range or SD of gestational age at which the procedure was carried out (Table 1).

In the CVS group, there were seven studies, comprising three observational retrospective cohort studies without a control group[9,36,37], one observational retrospective cohort study with a control group matched for gestational age[39], another similar cohort study with unmatched controls[38], one control group that was derived from a 11-year national-registry database[30] and another study that was a prospective observational study for adverse pregnancy outcomes in which the controls were

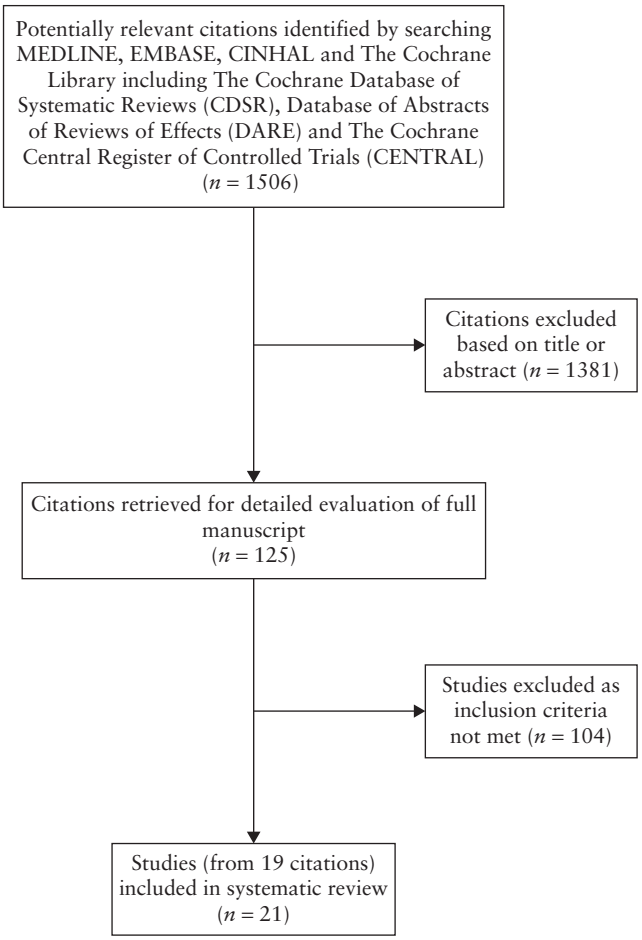

Figure 1 Flowchart showing selection of studies included in the systematic review.

unselected women who had routine screening during the same period[40]. In four out of seven studies[9,30,39,40] CVS was performed in the first trimester, but there were three studies in which the procedure was carried out in the second or third trimester[36–38]. In three out of four studies with a control group[38–40] there was a defined starting point, all women in the control group being documented as having a viable fetus confirmed on ultrasound scan. This was, however, not the case with the national-registry based study[30], for which it was not possible to confirm that in all pregnancies that did not have an invasive procedure, there was a viable fetus at the gestational age at which the invasive procedure was carried out (Table 2).

Assessment of quality and heterogeneity of studies

The methodological quality of studies included in this systematic review was assessed using the NOS. The rating of the included studies according to the NOS based on selection, comparability and outcome is shown in Table S2.

There was considerable heterogeneity in studies in both the amniocentesis and CVS groups, as demonstrated by the values of Cochran's Q statistic, the I^2 statistic and Egger bias (Tables 1–4). Funnel plots showing the publication bias in studies reporting on amniocentesis and CVS are shown in Figure 2.

Amniocentesis group

All reported studies

In a total of 14 studies that reported miscarriage prior to 24 weeks' gestation, there were 1107 losses in 124 001

Table 1 Meta-analysis to derive aggregate summary statistics from studies reporting the rate of miscarriage before 24 weeks' gestation in women who underwent amniocentesis and those who did not undergo any invasive procedure

		Amniocentesis group		*Control group*	
Reference	*GA (weeks)**	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*
Muller, 2002[23]	18 (15–24)	3472	31 (0.89 (0.61–1.27))	47 004	197 (0.42 (0.36–0.48))
Centini, 2003[24]	? (15–19)†	3294	10 (0.30 (0.15–0.56))	—	—
Eddleman, 2006[25]	?‡	3096	31 (1.00 (0.68–1.42))	31 907	300 (0.94 (0.84–1.05))
Caughey, 2006[9]	17 (?)‡	30 893	256 (0.83 (0.73–0.94))	—	—
Kong, 2006[26]	18 (15–22)	3468	39 (1.12 (0.80–1.53))	1125	13 (1.16 (0.62–1.97))
Mazza, 2007[27]	? (15–18)†	4917	33 (0.67 (0.46–0.94))	—	—
Towner, 2007[28]	18 (15–20)	15 005	69 (0.46 (0.36–0.58))	17 045	90 (0.53 (0.42–0.65))
Odibo, 2008[29]	17 (15–22)	11 695	113 (0.97 (0.80–1.16))	39 594	335 (0.85 (0.76–0.94))
Tabor, 2009[30]	16 (?14–20)	32 852	457 (1.39 (1.27–1.52))	633 308	5692 (0.90 (0.88–0.92))
Zhang, 2010[31]	18 (16–22)	2346	3 (0.13 (0.03–0.37))	—	—
Kalogiannidis, 2011[32]	18 (16–22)	5948	15 (0.25 (0.14–0.42))	—	—
Pitukkijronnakorn, 2011[33]	17 (16–22)	2990	11 (0.37 (0.18–0.66))	1495	3 (0.20 (0.04–0.59))
Corrado, 2012[34]	? (15–19)†	2990	30 (1.00 (0.68–1.43))	487	4 (0.82 (0.22–2.09))
Dhaifalah, 2012[35]	? (16–20)†	1035	9 (0.87 (0.40–1.64))	—	—
Pooled analysis (random effects)		124 001	1107 (0.70 (0.50–0.92))	771 965	6634 (0.70 (0.53–0.90))
Cochran's Q (*P*)			228.24 (< 0.0001)		200.81 (< 0.0001)
I^2 statistic (% (95% CI))			94.3 (92.5–95.5)		96.5 (95.3–97.3)
Bias (*P*)			−3.5537 (0.1112)		−2.6328 (0.2539)

Only first author is listed for each study. *Reported mean or median (range) gestational age (GA) at which amniocentesis was carried out. †Study did not provide a mean or median GA. ‡Study did not provide a range or SD of GA.

Table 2 Meta-analysis to derive aggregate summary statistics from studies reporting on the rate of miscarriage before 24 weeks' gestation in women who had chorionic villus sampling (CVS) and those who did not undergo any invasive procedure

		CVS group		*Control group*	
Reference	*GA (weeks)**	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*
Brambati, 2002[36]	? (11–20)†	2706	20 (0.74 (0.45–1.14))	—	—
Papp, 2002[37]	? (10–32)†	1044	62 (5.94 (4.58–7.55))	—	—
Lau, 2005[38]	12 (10–21)	1355	25 (1.85 (1.20–2.71))	1125	13 (1.16 (0.62–1.97))
Caughey, 2006[9]	10 (9–13)	9886	308 (3.12 (2.78–3.48))	—	—
Odibo, 2008[39]	11 (10–14)	5148	138 (2.68 (2.26–3.16))	4803	161 (3.35 (2.86–3.90))
Tabor, 2009[30]	10 (9–14)	31 355	589 (1.88 (1.73–2.03))	633 308	25 063 (3.96 (3.91–4.01))
Akolekar, 2011[40]	12 (11–14)	2396	44 (1.84 (1.34–2.46))	31 460	360 (1.14 (1.03–1.27))
Pooled analysis (random effects)		53 890	1186 (2.36 (1.68–3.16))	670 696	25 597 (2.26 (0.81–4.41))
Cochran's Q (*P*)			136.84 (< 0.0001)		1073.23 (< 0.0001)
I^2 statistic (% (95% CI))			95.6 (93.6–96.8)		99.7 (99.7–99.8)
Bias (*P*)			2.8129 (0.4902)		−11.1446 (0.3542)

Only the first author is listed for each study. *Reported mean or median (range) gestational age (GA) at which CVS was carried out. †Study did not provide a mean or median GA.

Table 3 Incidence–rate difference meta-analysis to derive aggregate summary statistics for estimated procedure-related loss before 24 weeks' gestation in women undergoing amniocentesis

	Amniocentesis group		*Control group*			
Reference	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Procedure-related loss (% (95% CI))*	P
Muller, 2002[23]	3472	31 (0.89 (0.61–1.27))	47 004	197 (0.42 (0.36–0.48))	0.47 (0.24 to 0.71)	0.0003
Eddleman, 2006[25]	3096	31 (1.00 (0.68–1.42))	31 907	300 (0.94 (0.84–1.05))	0.06 (−0.30 to 0.42)	0.6976
Kong, 2006[26]	3468	39 (1.12 (0.80–1.53))	1125	13 (1.16 (0.62–1.97))	−0.03 (−0.75 to 0.68)	0.8727
Towner, 2007[28]	15 005	69 (0.46 (0.36–0.58))	17 045	90 (0.53 (0.42–0.65))	−0.07 (−0.22 to 0.09)	0.4258
Odibo, 2008[29]	11 695	113 (0.97 (0.80–1.16))	39 594	335 (0.85 (0.76–0.94))	0.12 (−0.07 to 0.31)	0.2348
Pitukkijronnakorn, 2011[33]	2990	11 (0.37 (0.18–0.66))	1495	3 (0.20 (0.04–0.59))	0.17 (−0.18 to 0.51)	0.4099
Corrado, 2012[34]	2990	30 (1.00 (0.68–1.43))	487	4 (0.82 (0.22–2.09))	0.18 (−0.77 to 1.13)	0.4720
Pooled analysis (random effects)	42 716	324 (0.81 (0.58–1.08))	138 657	942 (0.67 (0.46–0.91))	0.11 (−0.04 to 0.26)	0.1435
Cochran's Q (*P*)		46.43 (< 0.0001)		117.15 (< 0.0001)	9.97 (0.1259)	
I^2 statistic (% (95% CI))		87.1 (74.5–92.0)		94.9 (92.3–96.3)	39.8 (0.0–73.4)	
Bias (*P*)		2.9443 (0.3653)		0.2387 (0.9441)	0.6228 (0.6661)	

Only the first author is listed for each study.

women undergoing amniocentesis, with a miscarriage rate of 0.70% (95% CI, 0.50–0.92%). The background rate of miscarriage prior to 24 weeks was calculated from 6634 losses in 771 965 women in the control groups, corresponding to a pooled estimate of 0.70% (95% CI, 0.53–0.90%) (Table 1).

Controlled studies

The procedure-related risk of miscarriage was estimated from seven studies that reported results from 42 716 women who had an amniocentesis, of whom 324 miscarried, and 138 657 women who did not have an invasive procedure, of whom 942 had a miscarriage. There was no significant difference in the rate of miscarriage between the amniocentesis group (0.81% (95% CI, 0.58–1.08%)) and the control group (0.67% (95% CI, 0.46–0.91%)) ($P = 0.1435$). The pooled procedure-related risk of miscarriage before 24 weeks was estimated to be 0.11% (95% CI, −0.04 to 0.26%) (Table 3, Figure 3).

Chorionic villus sampling group

All reported studies

In a total of 53 890 women who underwent CVS, there were 1186 losses prior to 24 weeks, corresponding to a pooled loss rate of 2.36% (95% CI, 1.68–3.16%). The background rate of miscarriage was calculated using data from controlled studies in 670 696 women who did not undergo an invasive procedure, including 25 597 losses, corresponding to a loss rate of 2.26% (95% CI, 0.81–4.41%) (Table 2).

Table 4 Incidence–rate difference meta-analysis to derive aggregate summary statistics for estimated procedure-related loss before 24 weeks' gestation in women undergoing chorionic villus sampling (CVS)

	CVS group		*Control group*			
Reference	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Total* (n)	*Miscarriage rate* (n *(% (95% CI)))*	*Procedure-related loss (% (95% CI))*	P
Lau, 2005[38]	1355	25 (1.85 (1.20–2.71))	1125	13 (1.16 (0.62–1.97))	0.69 (−0.29 to 1.67)	0.2276
Odibo, 2008[39]	5148	138 (2.68 (2.26–3.16))	4803	161 (3.35 (2.86–3.90))	−0.67 (−1.35 to 0.01)	0.0653
Akolekar, 2011[40]	2396	44 (1.84 (1.34–2.46))	31 460	360 (1.14 (1.03–1.27))	0.69 (0.24 to 1.15)	0.0042
Pooled analysis (random effects)	8899	207 (2.18 (1.61–2.82))	37 388	534 (1.79 (0.61–3.58))	0.22 (−0.71 to 1.16)	0.6385
Cochran's Q (*P*)		6.69 (0.0352)		99.47 (< 0.0001)	10.21 (0.0061)	
I^2 statistic (% (95% CI)		70.1 (0.0–89.1)		98.0 (96.9–98.6)	80.4 (0.0–91.9)	
Bias (*P*)		−5.08 (0.2873)		7.06 (0.6332)	—	

Only the first author is listed for each study.

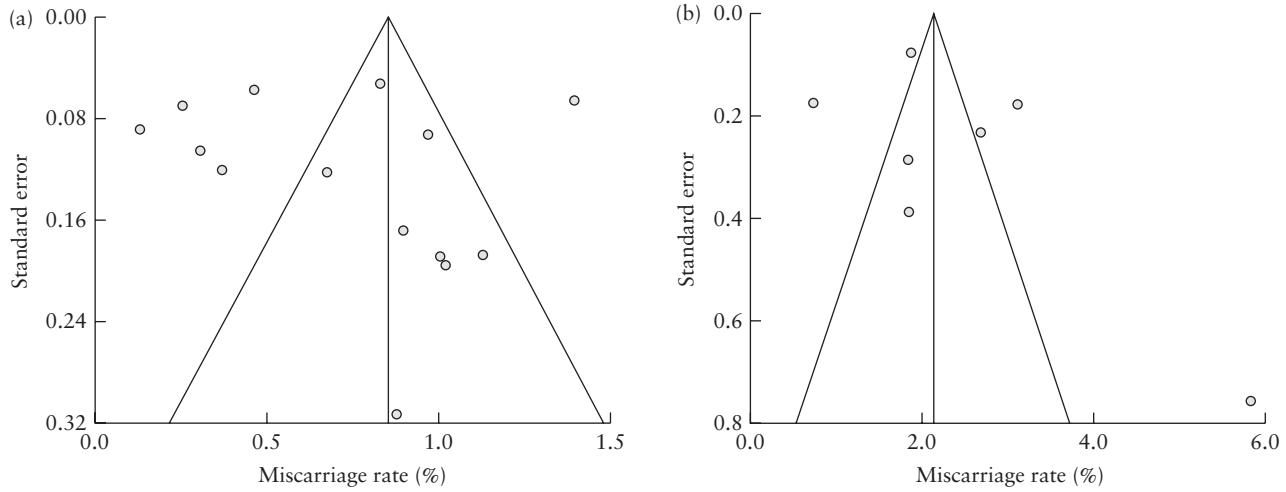

Figure 2 Funnel plots showing bias in published studies in women who underwent amniocentesis (a) or chorionic villus sampling (b).

Controlled studies

The weighted pooled procedure-related risk of miscarriage was estimated from analysis of controlled studies using the IRD meta-analysis of three studies that reported results from 8899 women who had CVS, of whom 207 miscarried, and 37 388 who did not have an invasive procedure, of whom 534 had a miscarriage. There was no significant difference in the rate of miscarriage between the CVS and control groups ($P = 0.6385$), and the pooled procedure-related risk of miscarriage before 24 weeks following CVS was estimated to be 0.22% (95% CI, −0.71 to 1.16%) (Table 4, Figure 4).

DISCUSSION

Principal findings of the study

The findings of this study demonstrate that the risk of miscarriage before 24 weeks' gestation in women who have an amniocentesis or CVS is not significantly different from that of those who do not undergo any invasive procedure. The estimate of a loss attributable to the invasive procedure is 0.1% for amniocentesis and 0.2% for CVS.

Limitations of the study

The limitations of our study are those related to the pooling of data in meta-analyses, such as biases introduced owing to differences in study design, inclusion of studies carried out over a period of time, publication bias, heterogeneity between studies and methods used for the analysis of data. To minimize these biases we did a systematic review based on the following criteria: first, we included studies published after the year 2000 to allow for a relative uniformity of equipment and consumables. Second, we included only studies that provided data on more than 1000 procedures, to minimize overestimation of effect size owing to inclusion of smaller studies[14,41]. Third, we estimated weighted pooled statistics using both fixed- and random-effects models, but chose the latter as they take into account variation within and between studies to yield wider estimates of confidence intervals

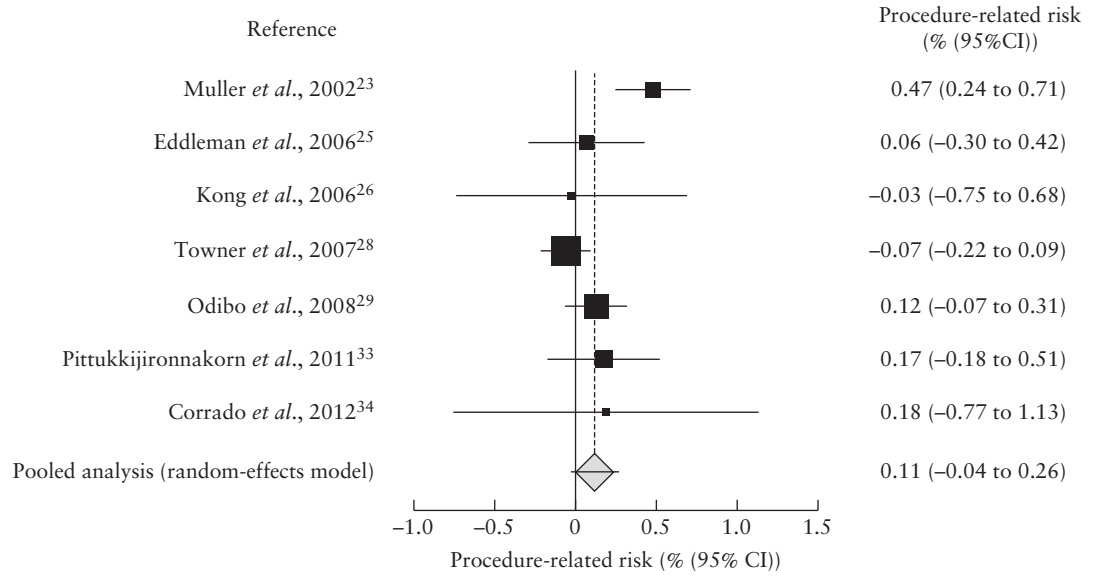

Figure 3 Forest plot showing estimated procedure-related risk of miscarriage before 24 weeks' gestation with 95% CIs derived from each of the controlled studies and weighted pooled summary estimate using a random-effects model and incidence–rate difference meta-analysis in women who underwent amniocentesis.

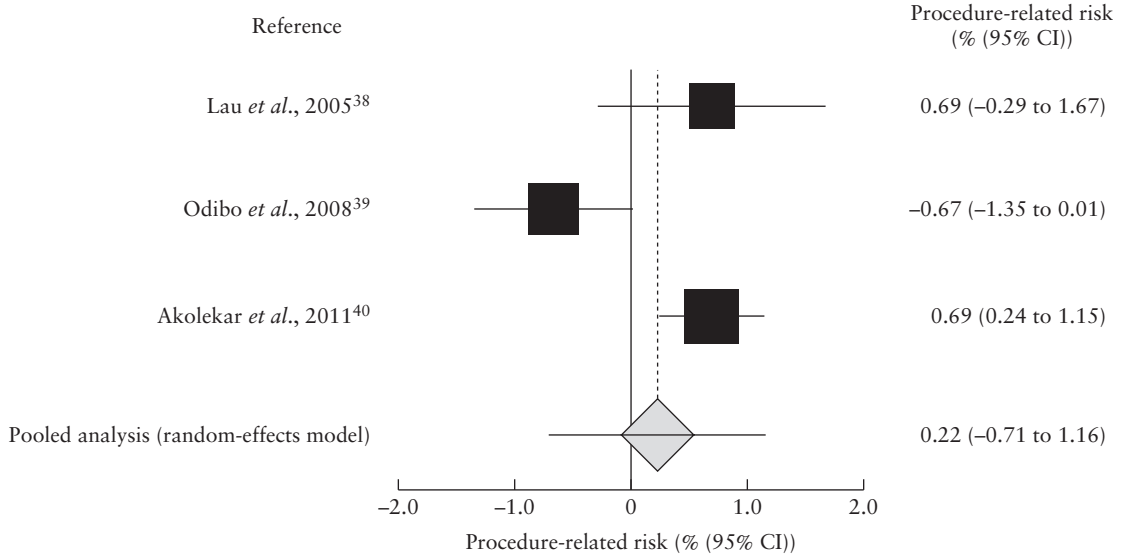

Figure 4 Forest plot showing estimated procedure-related risk of miscarriage before 24 weeks' gestation with 95% CIs derived from each of the controlled studies and weighted pooled summary estimate using a random-effects model and incidence–rate difference meta-analysis in women who underwent chorionic villus sampling.

that are more clinically generalizable[18,42]. Last, in spite of strict selection criteria, there is still the potential for heterogeneity between studies and therefore in estimation of the procedure-related risk, we only chose studies that had control groups at a similar gestational age, with a live fetus demonstrated by ultrasound scan. In spite of the above measures to address the causes of clinical heterogeneity between studies, there are factors such as the use of free-hand *vs* needle-guided technique and transabdominal *vs* transvaginal technique for CVS that remain potential limitations that cannot be accounted for in the study.

Another potential limitation of this study in deriving estimates of procedure-related loss is the inability to adjust for maternal and pregnancy characteristics in the invasive and control groups. There is evidence that pregnancy characteristics such as high fetal nuchal translucency, reversed a-wave in the ductus venosus and decreased maternal serum pregnancy-associated plasma protein-A (PAPP-A), which increase the risk of chromosomal abnormalities and therefore the uptake of CVS, are also associated with an increased risk of miscarriage[43–46]. Therefore, failure to adjust for these factors is likely to lead to overestimation of procedure-related risks[40].

Studies on amniocentesis

The preferred study design to estimate the true procedure-related risk of miscarriage following invasive

procedures is a randomized controlled study. There was one such study carried out regarding amniocentesis in the 1980s, in which the authors reported that the procedure-related risk of miscarriage after 16 weeks' gestation was 1.0%[47]. Although the results of this landmark study formed the basis for the recommendations from various national bodies, these figures should now be reviewed in the context of current practice, as many of the factors have changed since this study was conducted. It is unlikely that such a randomized controlled study will be carried out again and therefore it is necessary to combine data from large well-controlled studies conducted in recent years in order to get an estimate of procedure-related risk in current practice.

There are two studies that have systematically reviewed the literature relating to loss rates following amniocentesis[6,48]. In the first such study, the author reported that the procedure-related risk of pregnancy loss before 28 weeks was 0.6%, but they did not report any assessment for heterogeneity between studies[48]. The other review reported that the risk of miscarriage before 24 weeks was 0.9%, but the authors included smaller studies in the analysis, thus rendering the findings less generalizable[6]. There are two relatively recent studies reporting that the procedure-related risk of miscarriage following amniocentesis is much lower than is currently quoted[25,29]. The results from this meta-analysis are consistent with those of these studies, which also give a miscarriage rate of about 0.1% following amniocentesis.

Studies on chorionic villus sampling

There are no randomized controlled studies examining the risks of pregnancy loss in women who undergo CVS compared with those who do not have any invasive testing. These risks are derived from studies comparing amniocentesis with CVS, which report that the risk of total pregnancy loss following transabdominal CVS is comparable to that associated with amniocentesis[49–51]. Although these studies report similar risks of total pregnancy loss, they do not give an estimate of loss rate before 24 weeks' gestation.

There is evidence from recent studies that the risk of miscarriage in women undergoing CVS may be lower than those that are currently stated. In a retrospective cohort study of 5148 women who had CVS compared with 4803 women who did not, the authors reported that there was no significant difference in the estimated fetal loss rate between the two groups (−0.67% (95% CI, −1.35 to 0.01%))[39]. In another study, of 33 856 women including 2396 who underwent CVS, there was no significant difference in the risk of miscarriage after adjusting for maternal and pregnancy characteristics in women who had CVS compared with those who did not[40]. The authors stated that although the procedure-related risk of miscarriage associated with CVS could be derived by comparing pregnancy outcomes in women undergoing the procedure with outcomes in those who did not have an invasive test, such comparisons are likely to overestimate the risks in the CVS group because the same components of screening leading to increased risk for chromosomal defects and therefore the uptake of CVS, such as high fetal nuchal translucency, reversed a-wave in the fetal ductus venosus and decreased serum pregnancy PAPP-A, are also associated with an increased risk of miscarriage[40].

Implications for current practice

The results of this study show that the risk of miscarriage following amniocentesis and CVS is lower than currently stated. These figures can be useful as benchmarks for counseling women who wish to undertake an invasive test for prenatal diagnosis. The results from our meta-analysis are derived from large studies reporting results from more than 1000 invasive procedures, which were mostly carried out by skilled operators in specialist centers. Therefore, it is possible that miscarriage rates in smaller units carrying out fewer procedures and those undertaken by non-specialists may be higher. The RCOG guidance states that experienced operators may have a lower rate of procedure-related loss and that operators who perform these procedures occasionally may have an increased rate[2]. There is considerable evidence from many studies that report that the risk of pregnancy loss following invasive procedures is related to the skill and experience of the operator[30,52,53]. It is appropriate that women contemplating invasive procedures are provided with an accurate risk of procedure-related loss when carried out in specialist centers by appropriately trained specialists rather than loss rates associated with operators carrying out these procedures occasionally. This brings to the fore the question of where these invasive procedures should be undertaken and supports the arguments in favor of centralization to allow operators to maintain competence and expertise by carrying out a minimum number of such procedures.

The evolution in screening for fetal aneuploidies over the last few decades, as well as the advances in cfDNA testing, are likely to affect significantly the practice of invasive prenatal testing. First, the move to first-trimester combined screening for fetal aneuploidies over the last decade suggests that invasive testing will shift to the first trimester, with CVS being the preferred diagnostic test. Second, improvements in detection rates for fetal aneuploidies have also been accompanied by a drop in the false-positive rate[11]. As opposed to in the 1970s, when amniocentesis was offered to women over 35 years of age (who constituted 5% of the population), the current recommendation from the UK National Screening Committee states that the desirable screen-positive rate for those accepting combined screening should be less than 2%[54]. This, essentially, implies that the number of women who are offered invasive testing because of a high-risk screening result has more than halved with effective screening strategies. Third, the number of invasive prenatal tests undertaken for major fetal aneuploidies is likely to be reduced further in the near future owing to the wider availability of cfDNA testing. Therefore, in current practice, centers offering prenatal diagnostic tests

are more likely to offer CVS than amniocentesis, and are likely to carry out far fewer procedures than they did in previous years. These factors have important implications not only for training and acquiring competence but also for maintaining skills and expertise.

Future studies and actions

The estimates of procedure-related loss following amniocentesis and CVS in this study are derived using pooled data from the meta-analysis of individual studies, which have a certain degree of inherent heterogeneity in spite of adjustments made in this meta-analysis to correct for this. A drawback relating to this meta-analysis is the inability to adjust for maternal and pregnancy characteristics between the two groups. The only study design apart from a randomized controlled trial – which is unlikely to be carried out – that may be able to overcome the above limitations is an individual participant data (IPD) meta-analysis[55]. This would entail obtaining raw individual data relating to maternal and pregnancy characteristics as well as pregnancy complications and outcomes in the invasive and control groups from authors of previous studies, which are then examined in a two-step approach in an IPD meta-analysis[56].

A useful method of ensuring safe practice according to accepted standards is to audit performance. In relation to invasive diagnostic procedures, complications such as miscarriages should be audited in various centers to maintain a high standard of care according to accepted benchmarks. Although there are recommendations suggesting that individual centers and operators should counsel women about their own miscarriage rates in addition to the national figures[2], there is no definitive evidence that such a practice is regularly being followed. The UK National Screening Committee supports the Down's Syndrome Screening Quality Assurance Support Service, which is a confidential support service for those centers offering combined screening for trisomy 21. This service ensures that individual units offering screening have parameters within an acceptable normal range and in those cases in which deviations are detected, appropriate actions are recommended[57]. As much as ensuring quality of screening is important, it is equally necessary that miscarriage rates from individual centers are reported to a common database and audited not just locally but nationally to detect trends and practices that depart from acceptable figures. The assessment of operator competence against benchmark figures can be carried out using cumulative sum (CUSUM) analysis, which can not only assess continued operator competence but can also be used as a training tool for operators wishing to achieve competence[58–60]. The data from this meta-analysis could be used as benchmark rates to compare operator performance in individual specialist centers.

Conclusion

The results of this study demonstrate that there is no significant difference in the risk of miscarriage before 24 weeks' gestation in women who undergo amniocentesis or CVS and in those who do not have any invasive testing. The procedure-related risks of miscarriage in specialist centers performing a large number of procedures are considerably lower than the figures that are currently given. The combined data from all recent studies suggest that the added procedure-related risks of miscarriage following amniocentesis and CVS are in the region of 0.1% and 0.2%, respectively. It may be that these risks are unrelated to the invasive procedure, but instead may reflect the pregnancy characteristics of the women undergoing invasive testing.

It is essential that pregnant women should be provided with accurate estimates of procedure-related risks associated with invasive testing to allow them to make appropriate choices rather than provide them with exaggerated risks based on historical data, which may unnecessarily deter women from testing. There is a need to review and update information provided to women to allow them to make choices based on accurate estimation of these procedure-related risks.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Combinations of Medical Subject Heading (MeSH) terms, keywords, and word variants used for electronic search of MEDLINE, EMBASE, CINHAL and The Cochrane library

Table S2 Quality assessment of studies according to the Newcastle–Ottawa scale (NOS) for case–control and cohort studies in the amniocentesis and chorionic villus sampling study groups