Risk of miscarriage following amniocentesis and chorionic villus sampling – a systematic review of the literature

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Key words: Amniocentesis, Chorionic villus sampling, CVS, Miscarriage, Pregnancy loss, Fetal loss, Procedure-related loss, Invasive diagnostic procedure, Prenatal diagnosis

Short title: Procedure-related risk of miscarriage

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Conflict of interest: None

ABSTRACT

Objectives: To estimate the risk of miscarriage after amniocentesis or chorionic villus sampling (CVS) based on a systematic review of the literature.

Methods: A search of MEDLINE, EMBASE, and The Cochrane Library (2000-2017) was carried out to identify studies reporting complications following CVS or amniocentesis. The inclusion criteria for the systematic review were studies reporting results from large controlled studies (n≥1,000 invasive procedures) and those reporting data for pregnancy loss prior to 24 weeks' gestation. Data for cases that had invasive procedure and controls were inputted in contingency tables and risk of miscarriage was estimated for each study. Summary statistics were calculated after taking into account the weighting for each study included in the systematic review. Procedure-related risk of miscarriage was estimated as a weighted risk difference from the summary statistics for cases and controls.

Results: The electronic search from the databases yielded 2,465 potential citations of which 2,431 were excluded, leaving 34 studies for full-text review. The final review included 10 studies for amniocentesis and 6 studies for CVS, which were used to estimate risk of miscarriage in pregnancies that had an invasive procedure and the control pregnancies that did not. The procedure-related risk of miscarriage following amniocentesis was 0.35% (95% confidence interval [CI]: 0.07 to 0.63) and that following CVS was 0.35% (95%C CI: -0.31 to 1.00).

Conclusion: The procedure-related risks of miscarriage following amniocentesis and CVS are lower than currently quoted to women.

Introduction

Amniocentesis and chorionic villus sampling (CVS) are procedures used commonly for prenatal diagnosis. It is essential that women are given accurate information regarding risk of miscarriage from invasive procedures carried out by Fetal Medicine experts in experienced centres who routinely perform them. There is however inconsistency in the information from professional bodies which state that the risk following amniocentesis is about 1% whereas that following CVS is about 1-2%.[1-5] This contrasts with evidence from recent studies which report a significantly lower rate of procedure-related risks following amniocentesis and CVS.[6,7] A meta-analysis of large controlled studies reporting results from 324 losses in 42,176 women who underwent amniocentesis and 207 losses in 8,899 women who underwent CVS stated that the procedure-related risks is about 0.1% and 0.2%, respectively.[6] Another large nationwide population-based study of 147,987 women with a singleton pregnancy including 5,072 who underwent CVS and 1,809 who underwent amniocentesis, reported that the procedure-related risk of miscarriage at 21 days following CVS was -0.21% and that at 28 days following amniocentesis was 0.56%.[7] It is important to standardise information provided to women especially in light of recent changes in clinical practice with the introduction of cell-free DNA (cfDNA) testing so that when women are faced with a high-risk result, they make choices about risks and benefits based on up-to-date evidence rather than basing decisions on historical figures.

The objective of this study was to estimate the procedure-related risks of miscarriage following amniocentesis and CVS from a systematic review of literature.

Methods

Data sources and search strategy

An electronic search of MEDLINE, EMBASE, and The Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR) was carried out on 30th September 2017 utilising combinations of the relevant Medical Subject Heading (MeSH) terms, key words, and word variants for “Amniocentesis”, ”Chorionic Villus Sampling (CVS)”, “miscarriage”, “pregnancy loss” and “procedure-related risk”. The search and selection criteria were restricted to studies reported in English language. 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 of studies for systematic review

The selection of studies for the systematic review was based on identifying studies that provided results from large controlled studies. Firstly, we only included those studies reporting results on amniocentesis and CVS and excluded studies examining procedure-related complications following other prenatal diagnostic procedures. Secondly, we included those studies that provided data regarding risks of pregnancy loss not only from those that had an invasive procedure but also control pregnancies to allow for estimation of procedure-related risks. Thirdly, only those studies that reported results from at least 1,000 procedures were included to minimize biases from introduction of smaller case-studies. Lastly, we excluded those studies reporting data regarding preterm birth prior to 28 weeks and stillbirths but only those that included results relating to miscarriage, which was defined as pregnancy loss prior to 24 weeks’ gestation.

The citations were examined by two independent reviewers (JB and RA) to produce a list of relevant studies to be included in the systematic review based on the MeSH terms and key words described above. We excluded studies that were duplicates,

those that did not fit selection criteria after review of title and abstract and those that were either case-reports, letters, or review articles. The full-text of the remaining relevant manuscripts was retrieved in full-text to assess suitability for the systematic review. The reference lists of relevant articles and reviews were searched for additional reports and any inconsistencies were discussed to reach a consensus.

Data collection and systematic review

The data from each study included in the systematic review was extracted with regard to the type of procedure, study design, sample size of cases and controls, and miscarriage rate in each study group. Data for cases that had invasive procedure and controls were inputted in contingency tables and risk of miscarriage was estimated for each study. Summary statistics were calculated after taking into account the weighting for each study included in the systematic review. Procedure-related risk of miscarriage was estimated as a weighted risk difference from the summary statistics for cases and controls. The statistical software package StatsDirect version 3.1.11 (StatsDirect Ltd, Cheshire, UK) was used for data analysis.

Results

Data search results

The electronic search from the databases yielded 2,465 potential citations of which 2,431 were excluded as they were duplicates (n=486) or a review of the title or abstract did not meet the inclusion criteria (n=1616), leaving 34 studies for full-text review. After the full manuscript review, we included 10 studies for amniocentesis[7-16] and 6 studies for CVS[7,16,18-20], which were used to estimate the procedure-related risk of miscarriage. The study selection process is shown in the flow chart in Figure 1.

Amniocentesis group

There were a total of 623 miscarriages from 64,901 amniocentesis procedures with a risk of pregnancy loss of 0.95% (95%CI: 0.70 to 1.24). In the control group, there were 1,825 miscarriages in 299,979 pregnancies with a loss rate of 0.60% (95CI%: 0.47 to 0.75). The weighted procedure-related risk of rate of miscarriage was 0.35% (95%CI: 0.07 to 0.63) (Table 1).

Chorionic villus sampling group

There were a total of 327 miscarriages from 19,000 CVS procedures with a risk of pregnancy loss of 1.59% (95%CI: 0.74 to 2.76). In the control group, there were 1,524 miscarriages in 202,706 pregnancies with a loss rate of 1.23% (95CI%: 0.74 to 1.86). The weighted procedure-related risk of miscarriage following CVS was 0.35% (95%CI: -0.31 to 1.00) (Table 2).

Discussion

The results of the systematic review demonstrate that the procedure-related risk of miscarriage from amniocentesis and CVS are lower than currently quoted in literature. The attributable risk for amniocentesis and CVS is similar, which is about 0.35% (95%CI: 0.07 to 0.63) and 0.35 (95% CI: -0.31 to 1.00), respectively.

The strength of this study is a systematic search of published literature to identify manuscripts that reported results from large controlled studies and estimation of weighted summary statistics to calculate the procedure-related risk of miscarriage by taking into account the event rate and sample size in case and control groups. The limitation of such a systematic review study design is the inevitable introduction of

biases introduced due to heterogeneity between studies and although such biases cannot be completely removed but mitigated to an extent by measures undertaken in this study such as inclusion of only controlled studies and those reporting results from experienced centres.

The findings of this systematic review are consistent with results of recent studies which demonstrate that the risks of procedure-related loss are considerably lower than currently quoted and that undergoing an invasive procedure does not significantly increase this risk.[6,7,19] In a recent nationwide population based study of 147,987 women with a singleton pregnancy including 5,072 who underwent CVS and 1,809 who underwent amniocentesis, the authors reported that the procedure-related risk of miscarriage at 21 days following CVS was -0.21% and that at 28 days following amniocentesis was 0.56%. The authors reported that there was no significant difference in the risk of miscarriage in those that had an amniocentesis or CVS compared to those that did not. [7] Similarly, a meta-analysis of large controlled studies reporting results from 324 losses in 42,176 women who underwent amniocentesis and 207 losses in 8,899 women who underwent CVS stated that the procedure-related risk of miscarriage is about 0.1% and 0.2%, respectively.[6] The results are also consistent with another large observational cohort study of 33,856 women including 2,396 that underwent a CVS which reported that there was no significant difference in the risk of miscarriage after adjusting for maternal and pregnancy characteristics in women who had a CVS compared to those that did not. This study highlighted the important fact that although the procedure-related risk of miscarriage associated with CVS could be derived by comparing pregnancy outcome in women undergoing the procedure with those that do 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 (NT), reversed a-wave in the fetal ductus venosus and decreased serum pregnancy associated plasma protein-A (PAPP-A), are also associated with increased risk for miscarriage.[19] Similar results were reported in a recent study by Wah *et al.,* who estimated the risk of miscarriage in 1,906 CVS procedures and 7,634 controls and noted that the procedure-related risks was 0.15%.[20] Another recent study reported their results of a large cohort of women undergoing transabdominal and transvaginal CVS and reported that the procedure-related risks of miscarriage are 1.57% but this includes all operators – experienced and inexperienced. When the risk of miscarriage was assessed based on the level of expertise, the risk of miscarriage dropped from 2.24% for inexperienced operators to 0.42% for experienced operators.

The results of this systematic review as well as those of recently published large population studies and meta-analysis demonstrate that the procedure-related risks of miscarriage following amniocentesis and CVS performed by Fetal Medicine experts in experienced centres is considerably lower than that currently quoted to women. It is important to provide women with accurate information when they consider options for prenatal diagnosis.

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Figure Legends

Figure 1. Flow chart demonstrating process of selection of studies included in the systematic review

Table 1. Procedure-related risk of miscarriage in pregnancies undergoing amniocentesis calculated as a weighted risk difference (95% confidence interval) from miscarriage rate in controlled studies

Author	Amniocentesis group		Control group		Procedure-related loss % (95% CI)	Study weight (%)
	Total	Miscarriage rate n (%, 95% CI)	Total	Miscarriage rate n (%, 95% CI)		
Muller *et al.*, 2002[8]	3472	31 (0.89, 0.61 to 1.27)	47004	197 (0.42, 0.36 to 0.48)	0.47 (0.20 to 0.85)	10.83
Eddleman *et al.,* 2006[9]	3096	31 (1.00, 0.68 to 1.42)	31907	300 (0.94, 0.84 to 1.05)	0.06 (-0.26 to 0.49)	10.36
Kong *et al.,* 2006[10]	3468	39 (1.12, 0.80 to 1.53)	1125	13 (1.16, 0.62 to 1.97)	-0.03 (-0.89 to 0.60)	6.90
Towner *et al.,* 2007[111]	15005	69 (0.46, 0.36 to 0.58)	17045	90 (0.53, 0.42 to 0.65)	-0.07 (-0.22 to 0.09)	12.14
Odibo *et al.,* 2008[12]	11695	113 (0.97, 0.80 to 1.16)	39594	335 (0.85, 0.76 to 0.94)	0.12 (-0.07 to 0.33)	11.85
Pitukkijronnakorn *et al.,* 2011[13]	2990	11 (0.37, 0.18 to 0.66)	1495	3 (0.20, 0.04 to 0.59)	0.17 (-0.25 to 0.49)	10.87
Corrado *et al.,* 2012[14]	2990	30 (1.00, 0.68 to 1.43)	487	4 (0.82, 0.22 to 2.09)	0.18 (-1.12 to 0.86)	5.63
Theodora *et al.,* 2015[15]	12413	155 (1.25, 1.06 to 1.46)	6993	43 (0.61, 0.45 to 0.83)	0.63 (0.36 to 0.90)	11.30
Wulff *et al.,* 2016[7]	1809	20 (1.11, 0.68 to 1.70)	147987	820 (0.55, 0.52 to 0.59)	0.55 (0.16 to 1.15)	9.16
Bakker *et al.,* 2017[16]	7963	124 (1.56, 1.30 to1.85)	6342	20 (0.31, 0.19 to 0.49)	1.24 (0.95 to 1.56)	10.96
Summary statistic	**64901**	**623 (0.95, 0.70 to 1.24)**	**299979**	**1825 (0.60, 0.47 to 0.75)**	**0.35 (0.07 to 0.63)**	**100.00**

CI = Confidence Interval

Table 2. Procedure-related risk of miscarriage in pregnancies undergoing chorionic villus sampling (CVS) calculated as a weighted risk difference (95% confidence interval) from miscarriage rate in controlled studies

Author	CVS group		Control group		Procedure-related loss % (95% CI)	Study weight (%)
	Total	Miscarriage rate n (%, 95% CI)	Total	Miscarriage rate n (%, 95% CI)		
Lau *et al.,* 2005[17]	1355	25 (1.85, 1.20 to 2.71)	1125	13 (1.16, 0.62 to 1.97)	0.69 (-0.30 to 1.69)	13.72
Odibo *et al.,* 2008[18]	5148	138 (2.68, 2.26 to 3.16)	4803	161 (3.35, 2.86 to 3.90)	-0.67 (-1.35 to -0.01)	16.03
Akolekar *et al.,* 2011[19]	2396	44 (1.84, 1.34 to 2.46)	31460	360 (1.14, 1.03 to 1.27)	0.69 (0.21 to 1.32)	16.99
Wulff *et al.,* 2016[7]	5072	17 (0.34, 0.20 to 0.54)	147987	820 (0.55, 0.52 to 0.59)	-0.21 (-0.35 to -0.02)	19.08
Wah *et al*., 2017[20]	1906	16 (0.84, 0.48 to 1.36)	7687	53 (0.69, 0.52 to 0.90)	0.15 (-0.24 to 0.69)	17.70
Bakker *et al.,* 2017[16]	3123	87 (2.79, 2.24 to 3.43)	9644	117 (1.21, 1.00 to 1.45)	1.57 (1.00 to 2.24)	16.48
Summary statistic	**19000**	**327 (1.59, 0.74 to 2.76)**	**202706**	**1524 (1.23, 0.74 to 1.86)**	**0.35 (-0.31 to 1.00)**	**100.00**

CI=Confidence Interval