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Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis

L. J. SALOMON1,2, A. SOTIRIADIS3, C. B. WULFF4, A. ODIBO5 and R. AKOLEKAR6,7

1 Hôpital Necker–Enfants Malades, AP-HP, Université Paris Descartes, Paris, France; 2 Fetus & LUMIERE team, EA7328, Imagine Institute, Paris, France; 3 Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; 4 Center of Fetal Medicine, Department of Obstetrics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; 5 Department of Obstetrics and Gynecology, University of South Florida, Morsani College of Medicine, Tampa, FL, USA; 6 Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK; 7 Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK

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

CONTRIBUTION

What does this work add to what is already known?
The procedure-related risk of miscarriage after CVS and amniocentesis appears to be negligible, especially when such risks are compared between invasive-procedure and control groups with similar background-risk profile for chromosomal abnormalities.

What are the clinical implications of this work?
CVS and amniocentesis are not associated with any significant increase in the risk of miscarriage over the background risk in women undergoing these procedures, and there is no evidence that CVS is less safe than amniocentesis.

ABSTRACT

Objective To estimate the procedure-related risk of miscarriage after amniocentesis and chorionic villus sampling (CVS) based on a systematic review of the literature and an updated meta-analysis.

Methods A search of MEDLINE, EMBASE and The Cochrane Library was carried out to identify studies reporting complications following CVS or amniocentesis. Eligible for inclusion were large controlled studies reporting data for pregnancy loss prior to 24 weeks' gestation. Study authors were contacted when required to identify additional necessary data. Data for cases that had an invasive procedure and controls were inputted into contingency tables and the risk of miscarriage was estimated for each study. Summary statistics based on a random-effects model 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. Subgroup analyses were performed according to the similarity in risk levels for chromosomal abnormality between the invasive-testing and control groups. Heterogeneity was assessed using the $I^2$ statistic. Egger's bias was estimated to assess reporting bias in published studies.

Results The electronic search yielded 2943 potential citations, from which 12 controlled studies for amniocentesis and seven for CVS were selected for inclusion in the systematic review. A total of 580 miscarriages occurred following 63,723 amniocentesis procedures, resulting in a weighted risk of pregnancy loss of 0.91% (95% CI, 0.73–1.09%). In the control group, there were 1726 miscarriages in 330,469 pregnancies with a loss rate of 0.58% (95% CI, 0.47–0.70%). The weighted procedure-related risk of miscarriage following amniocentesis was 0.30% (95% CI, 0.11–0.49%; $I^2 = 70.1\%$). A total of 163 miscarriages occurred following 13,011 CVS procedures, resulting in a risk of pregnancy loss of 1.39% (95% CI, 0.76–2.02%). In the control group, there were 1946 miscarriages in 232,680 pregnancies with a loss rate of 1.23% (95% CI, 0.86–1.59%). The weighted procedure-related risk of miscarriage following CVS was 0.20% (95% CI, −0.13 to 0.52%; $I^2 = 52.7\%$). However, when studies including only women with similar risk profiles for chromosomal abnormality in the intervention and control groups were considered, the procedure-related risk for amniocentesis was 0.12% (95% CI, −0.05 to 0.30%; $I^2 = 44.1\%$) and for CVS it was −0.11% (95% CI, −0.29 to 0.08%; $I^2 = 0\%$).
Conclusions The procedure-related risks of miscarriage following amniocentesis and CVS are lower than currently quoted to women. The risk appears to be negligible when these interventions were compared to control groups of the same risk profile. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

There is considerable evidence suggesting that the procedure-related risk of miscarriage following amniocentesis or chorionic villus sampling (CVS) is much lower than that quoted currently by professional bodies\textsuperscript{1–3}. The pooled summary statistics of this procedure-related risk, based on data reported in large controlled cohort studies published until January 2014, were reported in a systematic review and meta-analysis published in 2015\textsuperscript{4}. Since then, further large studies have been published reporting the procedure-related risk of miscarriage following invasive procedures from large cohort, population-based and randomized controlled studies, with data from more than 20,000 procedures\textsuperscript{5–11}. We aimed to derive updated procedure-related risks of miscarriage following amniocentesis or CVS, by reviewing data from all studies published until 31 January 2019, in order to provide clinicians with the most recent estimates which can be used to counsel women.

METHODS

Data sources and search strategy

This systematic review and meta-analysis was undertaken based on an a-priori designed study protocol and was registered in advance with the PROSPERO international prospective register of systematic reviews (registration number: CRD42019130495). An electronic search of MEDLINE, EMBASE and The Cochrane Library was carried out on 31 January 2019, 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’. The search and selection criteria were restricted to studies reported in English. The citations retrieved from the search were examined for relevance to this study based on the type of invasive prenatal procedure used, study design, sample size of the study, study period and gestational age at pregnancy-outcome assessment. We complemented the searches by perusing the references of retrieved articles and the studies included in previous systematic reviews on the topic.

Eligibility criteria

Articles eligible for inclusion in our study were randomized controlled trials (RCT) and prospective or retrospective cohort or case–control studies reporting on the pregnancy outcome of women who had invasive prenatal testing and that of control pregnancies that did not have an invasive procedure. In view of the improvements and advances in ultrasound resolution and the subsequent improvements in performing CVS and amniocentesis over the last couple of decades, we included only studies published from the year 2000 onwards to ensure uniformity of equipment and techniques utilized in the studies compared. In case of studies reporting data spanning the years before and after 2000, we included only cases that underwent invasive testing from 2000 onwards.

We included studies reporting data on invasive procedures carried out in singleton pregnancy. Studies reporting results from both singleton and multiple pregnancy were deemed eligible if data from multiple pregnancies were < 5% of the total sample size.

We compared outcomes of women who underwent invasive prenatal testing (CVS or amniocentesis) with those of women that did not have any invasive procedure. When data were reported separately for transabdominal and transcervical CVS, only the former group was entered in the analyses.

The primary outcome measure was miscarriage, defined as fetal loss before 24 or 22 weeks’ gestation\textsuperscript{12}. In studies reporting data for miscarriage due to various causes, we included only procedure-related losses, i.e. those not associated with structural anomalies or other factors likely to cause miscarriage independently from invasive testing.

Study selection and data extraction

Search results were screened by two of the authors (R.A. and L.J.S.). The citations were examined to produce a list of relevant studies after excluding: duplicates; studies that did not meet the selection criteria after review of the title and abstract; case reports; letters; or review articles. The same two authors assessed independently the full text of all studies deemed relevant for inclusion. Data were extracted using a prespecified form. Any disagreements were resolved through discussion or, if required, by consulting a third author (A.S.).

For each study, we recorded information about the authors, country of origin, years of enrolment for the intervention and control groups, indications for invasive testing, technique of CVS/amniocentesis, experience of the operators, characteristics of control women and risk level of the two groups. The number of terminations of pregnancy was recorded and these cases were subtracted from the denominator. The authors of primary studies were contacted if further details or clarifications were required.

Quality assessment

The methodological quality of studies included in the systematic review was assessed using the Newcastle–Ottawa Scale (NOS)\textsuperscript{13}. Briefly, NOS assesses the quality of cohort or case–control studies across three domains: selection (including representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure...
and demonstration that the outcome of interest was not already present at the start of the study); comparability; and outcome (including assessment of outcome and adequacy of follow-up length). Evaluation of the domains is performed based on a standardized checklist and indicators of high quality are awarded a star; the number and combination of stars expresses the overall quality of a study in an Agency for Healthcare Research and Quality-compliant way (good, fair or poor).

The study was reported as per the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.

Summary measures and synthesis of results

Data from each study were extracted to note the type of procedure, study design, sample size and miscarriage rate in each study group. Study authors were contacted, if required, to obtain additional necessary data. Data were entered into contingency tables and miscarriage rate (95% CI) was estimated in the invasive-procedure and the control groups, for each study separately and as a pooled estimate weighted by the sample size of each study. The procedure-related risk for amniocentesis and CVS in each study was estimated as a risk difference (RD) based on the miscarriage rates in the invasive-procedure and control groups, which was then used to calculate the weighted pooled-summary estimate (95% CI). Given the non-randomized design of the majority of the included studies, and thus the anticipated heterogeneity between the studies, we calculated the summary effect sizes using random-effects models. The random-effects model assumes that the true effect size varies between the studies, and that included studies represent a random sample of effect sizes that could have been observed. Therefore, we opted to use this model as it not only allows for variation within studies, but also between studies, thus providing a conservative estimate of the summary statistics with wider 95% CI. The procedure-related risks for amniocentesis and CVS were expressed graphically in forest plots. Pooled proportions were calculated using the metaprop command. Heterogeneity between studies was assessed by estimation of the I² statistic; Egger’s meta-regression test was used to assess reporting bias in studies when 10 or more studies were available.

Subgroup analyses

We planned the subgroup analyses according to the similarity in risk levels for chromosomal abnormality in the invasive-testing and control groups, as extracted by their description in the primary studies (similar or dissimilar risk), as this could be related to confounders that can affect the procedure-related risk, and therefore the RD. The risk profile was considered similar when: (1) the study was a RCT; (2) the control group had similar risk level to the intervention group, but controls chose not to have the intervention; or (3) the authors of the primary studies reported that weighing for risk factors had been performed at selection of controls. In all other cases, the risk profile was considered as dissimilar (typically, the intervention group had a high-risk screening result and the control group a low-risk result).

Statistical analyses were carried out using Stata version 14.0 (StataCorp, College Station, TX, USA) software, using the metan and metaprop commands.

RESULTS

Data search results

The electronic search yielded 2943 potentially eligible citations, of which 2911 were excluded because they were a duplicate, case report or letter or they did not meet the inclusion criteria following review of the title or abstract, leaving 32 studies for full-text review. After the full-manuscript review, we finally considered 12 studies for amniocentesis and eight studies for CVS (four studies reported on both procedures). Of those, one study was eventually excluded, as it reported cumulative data for miscarriage and stillbirth, leaving 12 studies for amniocentesis and seven for CVS (Figure 1). The raw data for the study of Wittf et al. were calculated from the published adjusted estimates and were complemented with additional information provided by the authors. Similarly, additional data for amniocentesis and CVS were obtained for the study of Malan et al. by contacting the authors. Characteristics of the included studies are presented in Table 1.

Quality assessment

The methodological quality of each of the included studies was assessed using the NOS. The rating of the studies

![Flowchart showing selection of studies included in systematic review and meta-analysis](image)
Table 1 Characteristics of studies reporting on pregnancy outcome of women who underwent chorionic villus sampling (CVS) or amniocentesis (amnio) and that of control pregnancies that did not have an invasive procedure

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Risk</th>
<th>Operator type</th>
<th>Population</th>
<th>Risk</th>
<th>Outcome explored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller (2002)</td>
<td>France</td>
<td>Retrospective, multicenter</td>
<td>3472 consecutive amnios (singleton pregnancy) offered after second-trimester test risk &gt; 1:250</td>
<td>H</td>
<td>Not specified</td>
<td>47,004 women who did not have amnio after second-trimester screening</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; preterm birth 24–28 weeks</td>
</tr>
<tr>
<td>Eddleman (2006)</td>
<td>USA</td>
<td>Prospective multicenter (FASTER)</td>
<td>3096 consecutive amnios (singleton pregnancy) offered if first-trimester risk &gt; 1:150 or second-trimester risk &gt; 1:300 (1999–2002)</td>
<td>H</td>
<td>Specialists (different levels)</td>
<td>31,907 women who did not have amnio after screening</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks</td>
</tr>
<tr>
<td>Towner (2007)</td>
<td>USA</td>
<td>Retrospective, multicenter</td>
<td>15,005 amnios (singleton pregnancy) offered for abnormal serum screening results (1995–2001)</td>
<td>H</td>
<td>Specialists</td>
<td>17,045 women (singleton pregnancy) who declined amnio after abnormal serum screening result</td>
<td>H</td>
<td>Miscarriage &lt; 24 weeks; miscarriage &lt; 2 weeks after amnio; preterm delivery &lt; 28 weeks</td>
</tr>
<tr>
<td>Odibo (2008)</td>
<td>USA</td>
<td>Retrospective, single-center</td>
<td>11,746 amnios (singleton pregnancy) offered between 1990 and 2006</td>
<td>I</td>
<td>Specialists</td>
<td>39,821 women who did not have invasive testing and had a live fetus at 15–22 weeks</td>
<td>I</td>
<td>Miscarriage &lt; 24 weeks</td>
</tr>
<tr>
<td>Pukkijronnakorn (2011)</td>
<td>Thailand</td>
<td>Retrospective case–control</td>
<td>2990 amnios (singleton pregnancy) offered due to maternal age &gt; 35 years (1997–2006)</td>
<td>I</td>
<td>Specialists</td>
<td>14,955 women ≥ 35 years who declined amnio</td>
<td>I</td>
<td>Miscarriage &lt; 24, &lt; 28 weeks; delivery &lt; 37 weeks</td>
</tr>
<tr>
<td>Corrado (2012)</td>
<td>Italy</td>
<td>Retrospective single-center</td>
<td>2990 consecutive amnios (singleton pregnancy) performed for age, abnormal screening or history (2001–2009)</td>
<td>H</td>
<td>Specialists</td>
<td>499 women (singleton pregnancy) with same indications as study group but who declined amnio</td>
<td>H</td>
<td>Miscarriage &lt; 24 weeks; preterm birth &lt; 37 weeks; PPROM</td>
</tr>
<tr>
<td>Theodora (2015)</td>
<td>Greece</td>
<td>Retrospective single-center</td>
<td>12,413 consecutive amnios (1996–2010), mostly (77%) for advanced maternal age; positive screening result was an indication in 5% of cases</td>
<td>I</td>
<td>Specialists</td>
<td>6,993 women with ultrasound evaluation at 16–20 weeks and low risk for aneuploidy</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; intrauterine death; neonatal death</td>
</tr>
<tr>
<td>Wulff (2016)</td>
<td>Denmark</td>
<td>Registry-based, multicenter</td>
<td>1,009 consecutive amnios (singleton pregnancy) after CFTS (TA, 2008–2010); combined risk &gt; 1:300</td>
<td>H</td>
<td>Specialists (&gt; 90%)</td>
<td>138,820 women (singleton pregnancy) who did not have invasive testing after CFTS</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; stillbirth</td>
</tr>
</tbody>
</table>

*Continued over.*
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Population</th>
<th>Risk</th>
<th>Operator type</th>
<th>Population</th>
<th>Risk</th>
<th>Outcome explored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker (2017)7</td>
<td>The Netherlands</td>
<td>Retrospective, multicenter</td>
<td>7970 consecutive amnios after CFTS (2001–2011)</td>
<td>H</td>
<td>Trainees and specialists</td>
<td>6432 women who had 20-week anomaly scan and did not have amnio</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; preterm labor and loss; stillbirth; neonatal death</td>
</tr>
<tr>
<td>Malan (2018)10</td>
<td>France</td>
<td>RCT, multicenter</td>
<td>577 women randomized to amnio after high-risk CFTS</td>
<td>H</td>
<td>Not stated</td>
<td>1178 women randomized to cfDNA testing after high-risk CFTS</td>
<td>H</td>
<td>Miscarriage &lt; 24 weeks; stillbirth; neonatal death</td>
</tr>
<tr>
<td>Beta (2019)11</td>
<td>UK</td>
<td>Retrospective, single-center</td>
<td>375 consecutive amnios due to high-risk CFTS</td>
<td>H</td>
<td>Trainees and specialists</td>
<td>42 463 women who underwent CFTS and did not have amnio</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks</td>
</tr>
<tr>
<td>Odibo (2008)24</td>
<td>USA</td>
<td>Retrospective, single-center</td>
<td>5148 consecutive CVS cases (1990–2006); CVS performed from 9 weeks until 1995, when limit changed to &gt; 10 weeks; no specific indications for CVS reported</td>
<td>I</td>
<td>Specialists</td>
<td>4803 women with live fetus at 10–14 weeks, who did not have invasive testing</td>
<td>I</td>
<td>Fetal loss &lt; 24, &lt; 28, &lt; 32 weeks; loss within 14, 30, 60 days or 20 weeks from CVS or ultrasound</td>
</tr>
<tr>
<td>Akolekar (2011)27</td>
<td>UK</td>
<td>Prospective, single-center</td>
<td>2396 consecutive cases that had CVS (TA) after first-trimester screening (2006–2009)</td>
<td>H</td>
<td>Trainees and specialists</td>
<td>31 460 women who did not opt for CVS after first-trimester screening</td>
<td>L</td>
<td>Miscarriage &lt; 14, &lt; 24 weeks; stillbirth</td>
</tr>
<tr>
<td>Wulff (2016)6</td>
<td>Denmark</td>
<td>Registry-based, multicenter</td>
<td>5072 consecutive cases (singleton pregnancy) that had CVS (TA) after CFTS (2008–2010); combined risk &gt; 1:300</td>
<td>H</td>
<td>Specialists (&gt; 90%)</td>
<td>138 820 women (singleton pregnancy) who did not have invasive test after CFTS</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; stillbirth</td>
</tr>
<tr>
<td>Bakker (2017)7</td>
<td>The Netherlands</td>
<td>Retrospective, multicenter</td>
<td>4862 consecutive cases that had CVS (TA, n = 2029; TC, n = 2833) after CFTS (2001–2011)</td>
<td>H</td>
<td>Trainees and specialists</td>
<td>96 51 women who underwent CFTS and did not have CVS</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks; preterm labor and loss; stillbirth; neonatal death</td>
</tr>
<tr>
<td>Wah (2017)8</td>
<td>Hong Kong</td>
<td>Retrospective, single-center</td>
<td>1906 consecutive cases (2004–2014) that had CVS (TA) after high-risk CFTS or for single-gene disease</td>
<td>H</td>
<td>Specialists (&gt; 90%)</td>
<td>7687 singleton pregnancies with low-risk first-trimester result and live fetus at 12 weeks (2011–2012)</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks</td>
</tr>
<tr>
<td>Malan (2018)10</td>
<td>France</td>
<td>RCT, multicenter</td>
<td>221 women randomized to CVS after high-risk CFTS</td>
<td>H</td>
<td>Not stated</td>
<td>1178 women randomized to cfDNA testing after high-risk CFTS</td>
<td>H</td>
<td>Miscarriage &lt; 24 weeks; stillbirth; neonatal death</td>
</tr>
<tr>
<td>Beta (2019)11</td>
<td>UK</td>
<td>Retrospective, single-center</td>
<td>861 consecutive cases that had CVS due to high-risk CFTS</td>
<td>H</td>
<td>Trainees and specialists</td>
<td>39 152 women who underwent CVS and did not have CVS</td>
<td>L</td>
<td>Miscarriage &lt; 24 weeks</td>
</tr>
</tbody>
</table>

Only first author is given for each study. Risk levels: low (L), after a low-risk result at screening; intermediate (I), when maternal age was only/main criterion; and high (H), after high-risk result at screening. cfDNA, cell-free DNA; CFTS, combined first-trimester screening; FASTER, first- and second-trimester evaluation risk; PPROM, preterm prelabor rupture of membranes; RCT, randomized controlled trial; TA, transabdominal; TC, transcervical.
based on study type, selection, comparability and outcome are shown in Table S1. Most of the included studies had an overall good score regarding selection and comparability of the study groups, as well as ascertainment of the outcome of interest.

**Amniocentesis group**

A total of 580 miscarriages occurred following 63,723 amniocentesis procedures, resulting in a pooled risk of pregnancy loss after amniocentesis of 0.91% (95% CI, 0.73–1.09%; $I^2 = 88.2\%$). In the control group, there were 1726 miscarriages in 330,469 pregnancies, with a pooled loss rate of 0.58% (95% CI, 0.47–0.70%; $I^2 = 96.1\%$). The pooled procedure-related risk of miscarriage was 0.30% (95% CI, 0.11–0.49%; $I^2 = 70.1\%$) following amniocentesis (Figure 2a).

**CVS group**

In 13,011 women who underwent a CVS procedure, there were a total of 163 miscarriages, resulting in a pooled risk of pregnancy loss of 1.39% (95% CI, 0.76–2.02%; $I^2 = 89.1\%$). In the control group, 1946 miscarriages occurred in 232,680 pregnancies, with a pooled loss rate of 1.23% (95% CI, 0.86–1.59%; $I^2 = 98.1\%$). The pooled procedure-related risk of miscarriage was non-significant (0.20% (95% CI, −0.13 to 0.52%; $I^2 = 52.7\%$)) following CVS (Figure 2b).

**Subgroup analyses**

For each invasive test (amniocentesis or CVS) we examined separately the procedure-related risk of miscarriage for studies with similar and those with dissimilar risk level for chromosomal abnormalities (Table 1). The pooled risk RD (i.e. procedure-related risk) for amniocentesis was

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk difference (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller (2002)</td>
<td>0.0047 (0.0016 to 0.0079)</td>
<td>10.27</td>
</tr>
<tr>
<td>Eddleman (2006)</td>
<td>0.0009 (−0.0029 to 0.0047)</td>
<td>9.21</td>
</tr>
<tr>
<td>Kong (2006)</td>
<td>0.0032 (−0.0030 to 0.0095)</td>
<td>5.59</td>
</tr>
<tr>
<td>Towner (2007)</td>
<td>−0.0007 (−0.0022 to 0.0009)</td>
<td>13.21</td>
</tr>
<tr>
<td>Odibo (2008)</td>
<td>0.0012 (−0.0008 to 0.0032)</td>
<td>12.48</td>
</tr>
<tr>
<td>Pitukkijronnakorn (2011)</td>
<td>0.0017 (−0.0015 to 0.0048)</td>
<td>10.36</td>
</tr>
<tr>
<td>Corrado (2012)</td>
<td>0.0018 (−0.0070 to 0.0106)</td>
<td>3.53</td>
</tr>
<tr>
<td>Theodora (2015)</td>
<td>0.0068 (0.0041 to 0.0095)</td>
<td>11.13</td>
</tr>
<tr>
<td>Wulff (2016)</td>
<td>0.0057 (0.0014 to 0.0100)</td>
<td>8.25</td>
</tr>
<tr>
<td>Bakker (2017)</td>
<td>0.0068 (0.0031 to 0.0105)</td>
<td>9.24</td>
</tr>
<tr>
<td>Malan (2018)</td>
<td>0.0010 (−0.0080 to 0.0101)</td>
<td>3.36</td>
</tr>
<tr>
<td>Beta (2019)</td>
<td>0.0012 (−0.0078 to 0.0103)</td>
<td>3.36</td>
</tr>
<tr>
<td>Overall ($I^2 = 70.1%; P &lt; 0.0001$)</td>
<td>0.0030 (0.0011 to 0.0049)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 2** Forest plots showing procedure-related risk of miscarriage after amniocentesis (a) and chorionic villus sampling (CVS) (b), expressed as risk difference (95% CI) from controls who did not undergo invasive procedure. Weights were calculated using random-effects model.
0.46% (95% CI, 0.25–0.67%; $I^2 = 38.1\%$) when analysis was carried out in studies with dissimilar risk level between the invasive-procedure and control groups. When studies with similar risk levels between the amniocentesis and control groups were analyzed, there was no significant procedure-related risk (pooled RD, 0.12% (95% CI, −0.05 to 0.30%; $I^2 = 44.1\%$)) following amniocentesis (Figure 3a).

The procedure-related risk following CVS was non-significant when studies with similar level of risk between the CVS and the control groups were compared (pooled RD, −0.11% (95% CI, −0.29 to 0.08%);

![Figure 3](https://example.com/figure3.png)

**Figure 3** Forest plots showing subgroup analysis for procedure-related risk of miscarriage after amniocentesis (a) and chorionic villus sampling (CVS) (b), expressed as risk difference (95% CI) from controls who did not undergo invasive procedure. Subgroup 1 includes studies in which intervention and control groups had similar risk profile for chromosomal abnormalities (i.e. they were both of high, intermediate or low risk). Study of Wulff et al. included in Subgroup 1 following risk-level adjustment on propensity analysis. Subgroup 2 includes studies in which intervention and control groups had different risk profile. Weights were calculated using random-effects model.
I² = 0%). In contrast, CVS was associated with a pooled procedure-related risk of 0.48% (95% CI, 0.17–0.78; I² = 0%) when studies with dissimilar level of risk between the intervention and control groups were analyzed (Figure 3b).

Publication bias
We were able to assess the potential for publication bias only for amniocentesis, as fewer than 10 CVS studies were included in the analysis. The Egger’s meta-regression test did not demonstrate presence of small-study effects (P = 0.179; Figure S1).

DISCUSSION
Main findings
The findings of our study demonstrate that the procedure-related risk of miscarriage is considerably lower than is quoted currently in guidelines from professional bodies, and is 0.30% following amniocentesis, whereas there is no significant procedure-related risk associated with CVS, which may be a safer procedure than amniocentesis. Moreover, our results highlight that the point estimates for miscarriage are even lower, with no significant increase in risk of miscarriage, for both amniocentesis and CVS, when the analysis is restricted to studies in which the control population has a similar risk profile for chromosomal abnormalities as the women who underwent invasive prenatal testing.

Strengths and limitations
This is an updated version of our previous meta-analyses, to which we added the only randomized controlled trial to be published in three decades reporting on the risk of miscarriage following invasive procedures, and followed a new approach to address the issue of heterogeneity between the included studies.

The published studies have used different indications for invasive testing and different selection criteria for the control population, culminating in different background risk levels for the compared groups, both within and across studies. The resulting heterogeneity has been the major argument against quantitative synthesis of such studies. To this end, we have taken the following measures: first, we excluded terminations of pregnancy from both the intervention and control groups; second, we excluded cases of miscarriage attributable directly to structural defects or obstetric complications unrelated to invasive testing, if data were available; third, we only analyzed invasive procedures performed from 2000 onwards, if such data were available, to account for the progress in ultrasound resolution and sampling techniques; fourth, we stratified the intervention and control groups according to their risk profiles (as extracted from their inclusion criteria) and we performed subgroup analyses of studies in which the two intervention and control groups had similar risk profiles. This analysis highlighted the impact of dissimilar background risks as a source of risk inflation and statistical heterogeneity; and fifth, anticipating that the studies do not represent random samples from the same population, we used the random-effects model, which does not assume a common underlying effect size and produces more conservative estimates. In any case, as the control groups have usually more favorable risk profiles, any bias would be against invasive procedures, which means that the latter may be even safer than appears in an aggregate analysis.

There are some limitations to our study which could not be overcome despite our robust methodology of well-defined eligibility criteria and inclusion of controlled studies with large sample size, as well as a strict approach to minimizing heterogeneity. A limitation of our study is that the comparison of the risks of miscarriage between the intervention and control pregnancies with similar risk profile and background risks included mainly high-risk populations, preventing us from being able to comment on risk estimates of miscarriage in large low-risk populations. In our study, we did not examine other pregnancy complications, such as preterm birth and stillbirth, nor did we examine the serious but rare outcomes, such as maternal septicemia or amniotic fluid embolism, as they were not reported consistently in the included studies. Another limitation refers to the lack of analyses of data with regard to operator experience, as this is potentially an important factor associated with procedure-related loss. Unfortunately, with the exception of two recent studies with conflicting results (Akolekar et al. and Bakker et al.), the studies did not provide data on the effect of operator experience on the risk of miscarriage, and we were unable to account for this in our analyses.

Interpretation of findings
The first question we aimed to address was whether invasive prenatal diagnosis is a safe procedure. Our results suggest that amniocentesis is associated with a procedure-related risk of 1:300 at most, or more likely, no significant increase in risk if we considered the results from our analysis which included only studies with comparable risk profiles in the intervention and control groups. With regard to CVS, our results demonstrate that there is no significant procedure-related risk associated with undergoing this procedure.

A second related question is: which procedure is safer to undertake, CVS or amniocentesis. There is no statistically appropriate way to answer this through either a direct or network meta-analysis, as the two methods do not have a common comparator. The closest approximation to a valid answer to this question is to estimate a pooled procedure-related risk from those studies which reported results for both amniocentesis and CVS, by comparison with a control group. There were four such studies comparing both CVS and amniocentesis to their corresponding control groups; their pooled procedure-related risk was 0.11% (95% CI, −0.28...
to 0.50; \( I^2 = 42.1\% \) for CVS and 0.55% (95% CI, 0.29 to 0.81; \( I^2 = 0\% \)) for amniocentesis. There are a few hypotheses that can potentially explain the reasons for these differences and the apparent greater safety of CVS compared with amniocentesis. First, CVS is usually performed by specialist and experienced fetal medicine operators whereas this is not always the case with amniocentesis. Second, performing CVS involves introduction of the needle into the placental tissue, which is a highly vascular tissue with blood flow of about 90–100 mL/min/kg at 12 weeks’ gestation\(^{29,30}\), as opposed to introduction of a needle into the amniotic sac, which is a closed cavity and therefore has a higher chance of a potential infection being introduced into the confined intra-amniotic space. Last, in CVS there is the option to reschedule the procedure and undertake amniocentesis if there are technical limitations.

The quest to quantify accurately procedure-related risks for invasive diagnostic procedures in pregnancy may seem trivial. However, we consider it to be quite important and relevant to current clinical practice. A recent systematic review attempted to quantify procedure-related risks of miscarriage following amniocentesis or CVS from published RCTs, and concluded that ‘second-trimester amniocentesis increased the risk of pregnancy loss, but it was not possible to quantify this increase precisely from only one study\(^{31}\). Such conclusions are unhelpful and do not provide women or their clinicians with any clear evidence-based estimates of risks for decision-making. These invasive procedures are carried out routinely for prenatal diagnosis, but instead of accurate and recent estimates of risks from expert operators, these are based on historical and inflated estimates. There are significant advances in cytogenetic analysis and genomic sequencing which are progressing at a rapid pace; pregnant women must receive appropriate counseling to enable them to make informed choices about their options for prenatal testing without being deterred by falsely exaggerated rates of procedure-related risks of miscarriage. Until such a time that non-invasive testing becomes as diagnostic and comprehensive as cytogenetic techniques, the questions about the safety of invasive procedures and the factors affecting it remain topical\(^{32}\).

Comparison with previous studies

In comparison to our previous meta-analyses\(^{4,5}\), this update includes the first RCT published in the last three decades reporting on the risk of miscarriage following invasive procedures, and it addresses the issue of heterogeneity by carefully excluding cases potentially affected by confounders and by accounting for the effect of different background risks. In terms of numerical estimates, the procedure-related risk of amniocentesis seems to stabilize at around 1:300, whereas the RD between CVS and controls still fails to reach significance. The most important novelty is the synthesis of studies in which the intervention and control groups had similar background risks for chromosomal abnormality, as derived from their description. It appears that, when comparing women at a similar risk level (be it high, intermediate or low; Table 1), the procedure-related risk for amniocentesis also fails to reach significance, whereas the statistical heterogeneity decreases substantially. This is a significant finding, supporting the concept that, all other things being equal, an invasive procedure is not associated with a significant increase in the rate of miscarriage. This does not imply that a miscarriage following an invasive procedure cannot occur, but this is more likely to be related to either operator-independent maternal factors\(^{27}\) or to the experience and technique of the operator, rather than the procedure itself. In a large UK study, the authors reported that there was no significant increase in overall procedural risk of miscarriage, regardless of whether the procedure was carried out by fetal medicine experts or trainees under direct supervision of an expert\(^{27}\), whereas the point estimates of procedure-related miscarriage appeared to decrease with operators’ experience, though in a non-significant way in a Dutch study\(^{7}\). As neither of these studies was randomized, there is no reliable way to ascertain how experience may impact on outcomes or whether the effects are subject to modifications by confounders like negative selection bias.

In terms of raw numbers and sample size of the included studies, the evidence is dominated by a large Danish registry study\(^{6}\), which shows that invasive procedures themselves do not carry a significant miscarriage risk. However, the use of the random-effects model reduced the weight (and therefore the dominance) of this single trial, which in any case is in line with the aggregate findings. Similarly, the French multicenter RCT, which aimed to show that there would be a reduction in the risk of miscarriage in the group that was offered invasive testing only for positive cell-free DNA results (\( n = 1034 \)) as opposed to those with direct invasive testing (\( n = 1017 \)), also failed to show a significant difference (RD, –0.03%)\(^{10}\).

Conclusions

The findings of this systematic review and meta-analysis demonstrate that the procedure-related risks of miscarriage from invasive procedures are low, or negligible if groups with similar background risks of chromosomal abnormality are compared. In terms of safety of a prenatal diagnostic procedure, it appears that CVS is potentially safer compared with amniocentesis. Women should be reassured that invasive procedures carried out by experienced operators in specialist centers are not associated with a significant increase in miscarriage rate as compared to not undergoing these procedures.

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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** Methodological assessment of included studies based on Newcastle–Ottawa Scale

**Figure S1** Assessment of presence of small-study effects using Egger’s meta-regression test, in studies evaluating risk of miscarriage following amniocentesis.