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

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CONTRIBUTION

What are the novel findings of this work?
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%; $I^2 = 0\%$).

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SYSTEMATIC REVIEW

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[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[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[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[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)[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[14].

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[15]. 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 I^2 statistic; Egger's meta-regression test was used to assess reporting bias in studies when 10 or more studies were available[16–18].

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[6,7,9–11,19–25] and eight studies for CVS[6–8,10,11,26–28] (four studies[6,7,10,11] reported on both procedures). Of those, one study[26] 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 Wulff *et al.*[6] 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.*[10] by contacting the authors. Characteristics of the included studies are presented in Table 1.
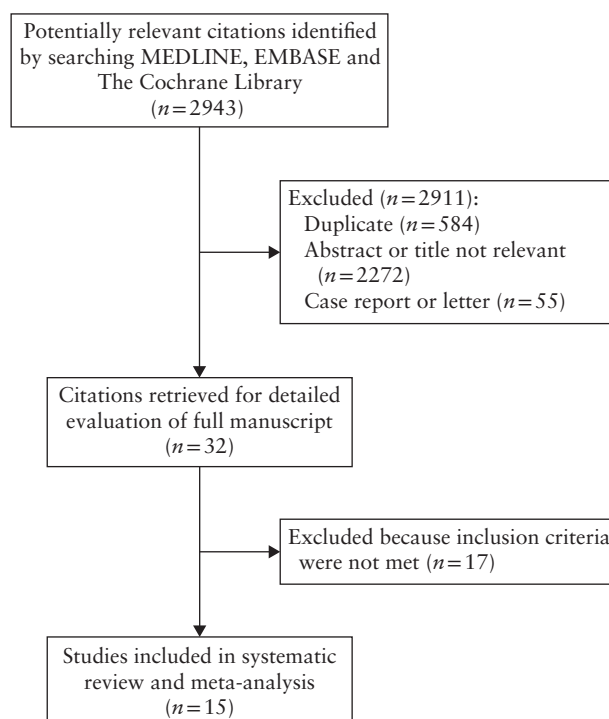

Figure 1 Flowchart showing selection of studies included in systematic review and meta-analysis.

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

Study	Country	Study design	Invasive-procedure group			Controls		Outcome explored
			Population	Risk	Operator type	Population	Risk	
Amniocentesis								
Muller (2002)[19]	France	Retrospective, multicenter	3472 consecutive amnios (singleton pregnancy) offered after second-trimester test risk > 1:250	H	Not specified	47004 women who did not have amnio after second-trimester screening (2418 high-risk but did not opt for amnio)	L	Miscarriage < 24 weeks; preterm birth 24–28 weeks
Eddleman (2006)[20]	USA	Prospective multicenter (FASTER)	3096 consecutive amnios (singleton pregnancy) offered if first-trimester risk > 1:150 or second-trimester risk > 1:300 (1999–2002)	H	Specialists (different levels)	31907 women who did not have amnio after screening	L	Miscarriage < 24 weeks
Kong (2006)[21]	Hong Kong	Retrospective, single-center	3468 amnios (58 sets of twins) offered for maternal age > 35 years (1997–2004)	I	Trainees and specialists	1125 women with low-risk CFTS (2003–2004)	L	Total, unintended and procedure-related losses within 2, 4, 6 and 10 weeks, < 24 weeks and neonatal losses
Towner (2007)[22]	USA	Retrospective, multicenter	15005 amnios (singleton pregnancy) offered for abnormal serum screening results (1995–2001)	H	Specialists	17045 women (singleton pregnancy) who declined amnio after abnormal serum screening result	H	Miscarriage < 24 weeks; miscarriage < 2 weeks after amnio; preterm delivery < 28 weeks
Odibo (2008)[23]	USA	Retrospective, single-center	11746 amnios (singleton pregnancy) offered between 1990 and 2006	I	Specialists	39821 women who did not have invasive testing and had a live fetus at 15–22 weeks	I	Miscarriage < 24 weeks
Pitukkijronnakorn (2011)[24]	Thailand	Retrospective case–control	2990 amnios (singleton pregnancy) offered due to maternal age ≥ 35 years (1997–2006)	I	Specialists	1495 women ≥ 35 years who declined amnio	I	Miscarriage < 24, < 28 weeks; delivery < 37 weeks
Corrado (2012)[25]	Italy	Retrospective single-center	2990 consecutive amnios (singleton pregnancy) performed for age, abnormal screening or history (2001–2009)	H	Specialists	499 women (singleton pregnancy) with same indications as study group but who declined amnio	H	Miscarriage < 24 weeks; preterm birth < 37 weeks; PPROM
Theodora (2015)[9]	Greece	Retrospective single-center	12413 consecutive amnios (1996–2010), mostly (77%) for advanced maternal age; positive screening result was an indication in 5% of cases	I	Specialists	6993 women with ultrasound evaluation at 16–20 weeks and low risk for aneuploidy	L	Miscarriage < 24 weeks; intrauterine death; neonatal death
Wulff (2016)[6]	Denmark	Registry-based, multicenter	1809 consecutive amnios (singleton pregnancy) after CFTS (TA, 2008–2010); combined risk > 1:300	H	Specialists (> 90%)	138820 women (singleton pregnancy) who did not have invasive testing after CFTS	L	Miscarriage < 24 weeks; stillbirth

Continued over.

Table 1 Continued

Study	Country	Study design	Invasive-procedure group		Operator type	Controls		Outcome explored
			Population	Risk		Population	Risk	
Bakker (2017)[7]	The Netherlands	Retrospective, multicenter	7970 consecutive amnios after CFTS (2001–2011)	H	Trainees and specialists	6432 women who had 20-week anomaly scan and did not have amnio	L	Miscarriage <24 weeks; preterm labor and loss; stillbirth; neonatal death
Malan (2018)[10]	France	RCT, multicenter	577 women randomized to amnio after high-risk CFTS	H	Not stated	1178 women randomized to cfDNA testing after high-risk CFTS	H	Miscarriage <24 weeks; stillbirth; neonatal death
Beta (2019)[11]	UK	Retrospective, single-center	375 consecutive amnios due to high-risk CFTS	H	Trainees and specialists	42 463 women who underwent CFTS and did not have amnio	L	Miscarriage <24 weeks
Chorionic villus sampling								
Odibo (2008)[28]	USA	Retrospective, single-center	5148 consecutive CVS cases (1990–2006); CVS performed from 9 weeks until 1995, when limit changed to > 10 weeks; no specific indications for CVS reported	I	Specialists	4803 women with live fetus at 10–14 weeks, who did not have invasive testing	I	Fetal loss < 24, < 28, < 32 weeks; loss within 14, 30, 60 days or 20 weeks from CVS or ultrasound
Akolekar (2011)[27]	UK	Prospective, single-center	2396 consecutive cases that had CVS (TA) after first-trimester screening (2006–2009)	H	Trainees and specialists	31 460 women who did not opt for CVS after first-trimester screening	L	Miscarriage < 14, < 24 weeks; stillbirth
Wulff (2016)[6]	Denmark	Registry-based, multicenter	5072 consecutive cases (singleton pregnancy) that had CVS (TA) after CFTS (2008–2010); combined risk > 1:300	H	Specialists (> 90%)	138 820 women (singleton pregnancy) who did not have invasive test after CFTS	L	Miscarriage < 24 weeks; stillbirth
Bakker (2017)[7]	The Netherlands	Retrospective, multicenter	4862 consecutive cases that had CVS (TA, *n* = 2029; TC, *n* = 2833) after CFTS (2001–2011)	H	Trainees and specialists	9651 women who underwent CFTS and did not have CVS	L	Miscarriage < 24 weeks; preterm labor and loss; stillbirth; neonatal death
Wah (2017)[8]	Hong Kong	Retrospective, single-center	1906 consecutive cases (2004–2014) that had CVS (TA) after high-risk CFTS or for single-gene disease	H	Specialists (> 90%)	7687 singleton pregnancies with low-risk first-trimester result and live fetus at 12 weeks (2011–2012)	L	Miscarriage < 24 weeks
Malan (2018)[10]	France	RCT, multicenter	221 women randomized to CVS after high-risk CFTS	H	Not stated	1178 women randomized to cfDNA testing after high-risk CFTS	H	Miscarriage < 24 weeks; stillbirth; neonatal death
Beta (2019)[11]	UK	Retrospective, single-center	861 consecutive cases that had CVS due to high-risk CFTS	H	Trainees and specialists	39 152 women who underwent CFTS and did not have CVS	L	Miscarriage < 24 weeks

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.

Quality assessment

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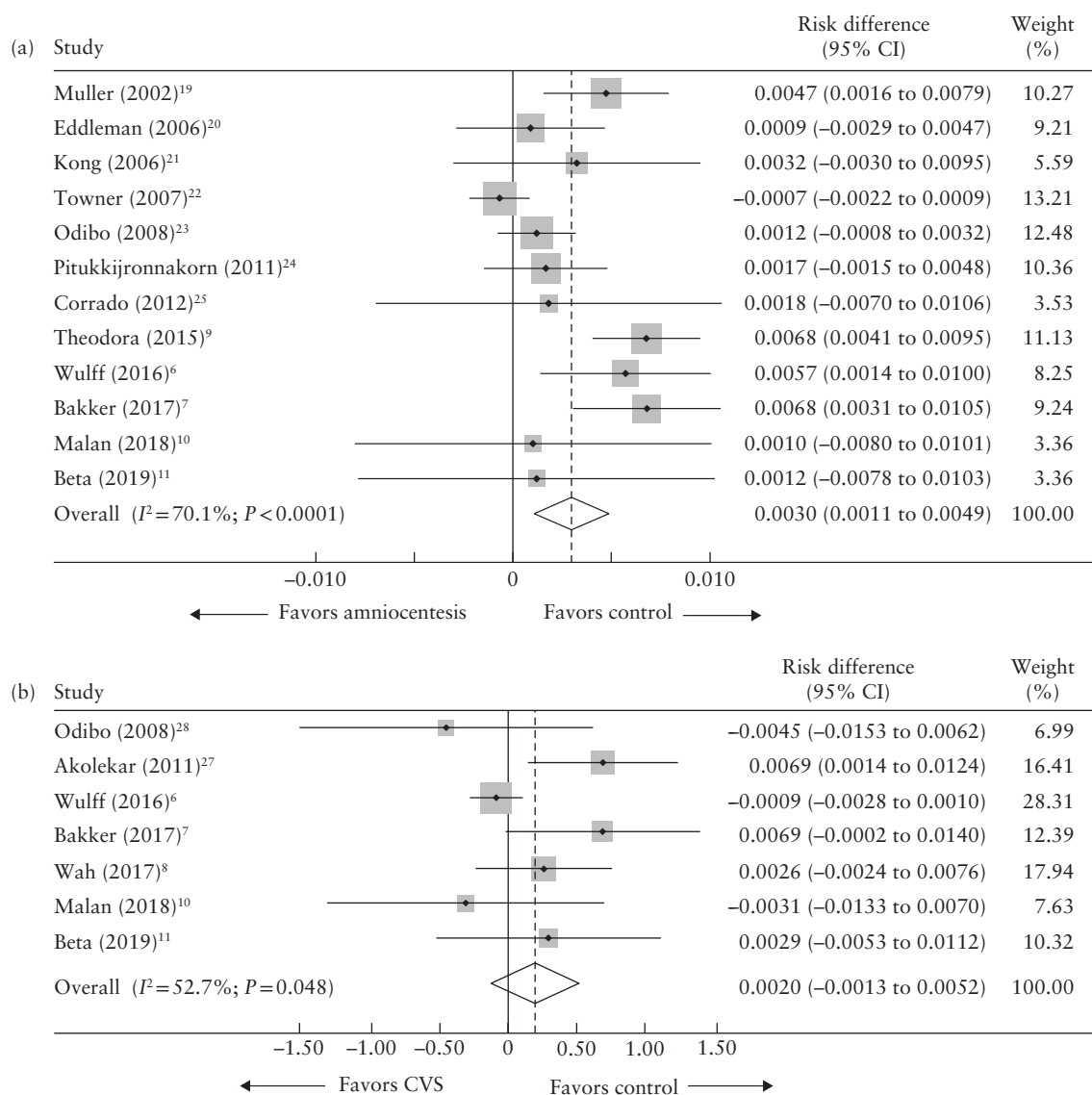

Figure 2 Forest plots showing procedure-related risk of miscarriage after amniocentesis (a) and chorionic villus sampling (CVS) (b), expressed as risk difference (95% CI) from controls who did not undergo invasive procedure. Weights were calculated using random-effects model.

for chromosomal abnormalities (Table 1). The pooled risk RD (i.e. procedure-related risk) for amniocentesis was 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).

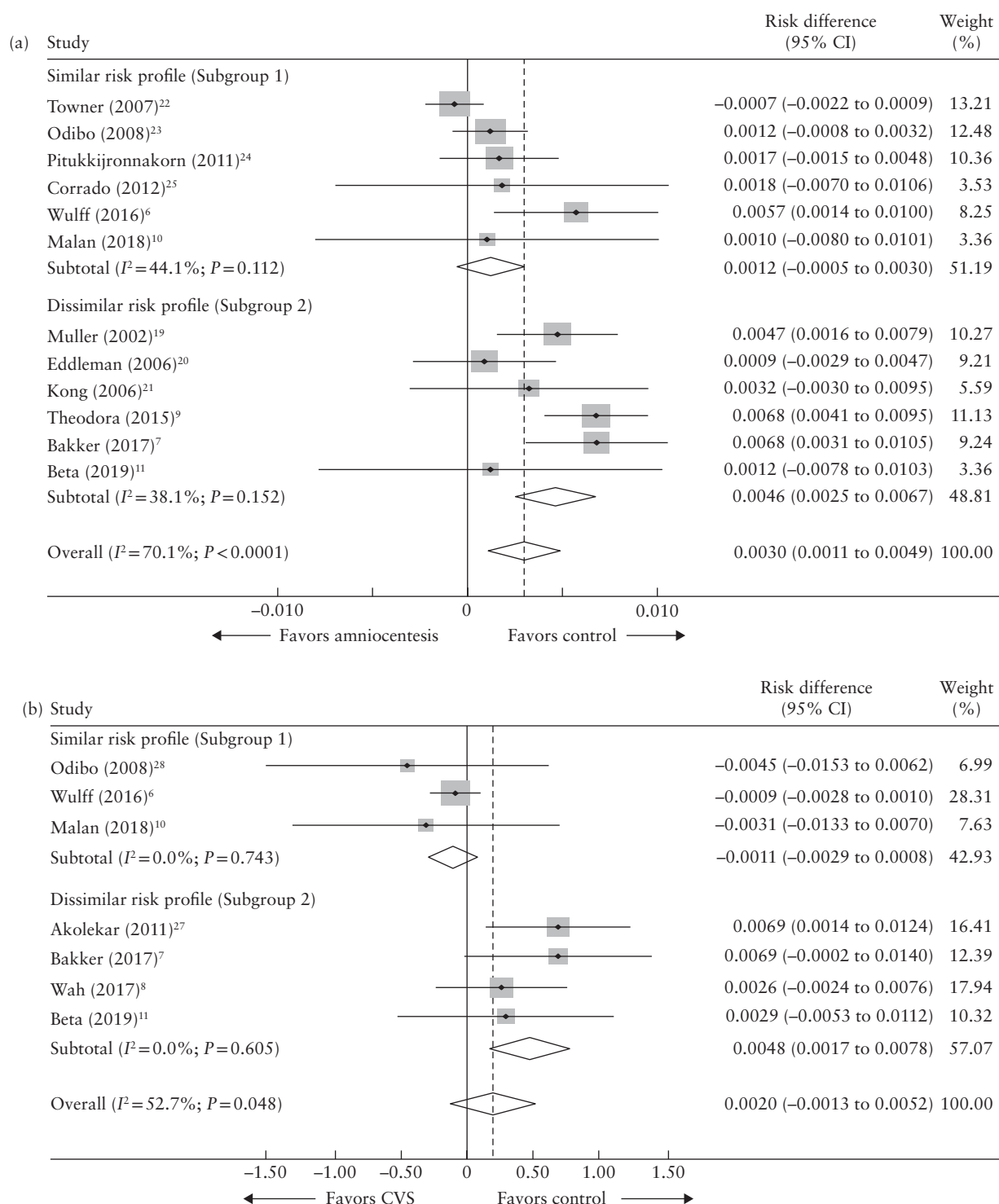The procedure-related risk following CVS was non-significant when studies with similar level of risk

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.

between the CVS and the control groups were compared (pooled RD, −0.11% (95% CI, −0.29 to 0.08%); $I^2 = 0\%$). In contrast, CVS was associated with a pooled procedure-related risk of 0.48% (95% CI, 0.17−0.78; $I^2 = 0\%$) 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[10] 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.*[27] and Bakker *et al.*[7]), 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[6,7,10,11] 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.

REFERENCES

1. Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z, McGillivray G; International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. *Ultrasound Obstet Gynecol* 2016; 48: 256–268.
2. Royal College of Obstetricians and Gynaecologists. Amniocentesis and Chorionic Villus Sampling. *Green-top guideline No.8*. RCOG Press: London, 2010.

3. Invasive prenatal testing for aneuploidy. ACOG Practice Bulletin No. 88, December 2007. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2007; **110**: 1459–1467.

4. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; **45**: 16–26.

5. Beta J, Lesmes-Heredia C, Bedetti C, Akolekar R. Risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review of the literature. *Minerva Ginecol* 2018; **70**: 215–219.

6. Wulff CB, Gerds TA, Rode L, Ekelund CK, Petersen OB, Tabor A; Danish Fetal Medicine Study Group. Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147 987 singleton pregnancies. *Ultrasound Obstet Gynecol* 2016; **47**: 38–44.

7. Bakker M, Birnie E, Robles de Medina P, Sollie KM, Pajkrt E, Bilardo CM. Total pregnancy loss after chorionic villus sampling and amniocentesis: a cohort study. *Ultrasound Obstet Gynecol* 2017; **49**: 599–606.

8. Wah YM, Leung TY, Cheng YKY, Sahota DS. Procedure-Related Fetal Loss following Chorionic Villus Sampling after First-Trimester Aneuploidy Screening. *Fetal Diagn Ther* 2017; **41**: 184–190.

9. Theodora M, Antsaklis A, Blanas K, Antsaklis P, Daskalakis G, Sindos M, Mesogitis S, Papantoniou N. Risk for fetal loss and prematurity after 12 413 second-trimester amniocenteses in a single center. *J Perinat Med* 2015; **43**: 347–351.

10. Malan V, Bussières L, Winer N, Jais JP, Baptiste A, Le Lorc'h M, Elie C, O'Gorman N, Fries N, Houfflin-Debarge V, Sentilhes L, Vekemans M, Ville Y, Salomon LJ; SAFE 21 Study Group. Effect of Cell-Free DNA Screening *vs* Direct Invasive Diagnosis on Miscarriage Rates in Women With Pregnancies at High Risk of Trisomy 21: A Randomized Clinical Trial. *JAMA* 2018; **320**: 557–565.

11. Beta J, Zhang W, Geris S, Kostiv V, Akolekar R. Procedure-related risk of miscarriage following chorionic villus sampling and amniocentesis. *Ultrasound Obstet Gynecol* 2019; **54**: 452–457.

12. Survival of extremely preterm infants: Joint statement from the British Medical Association, the British Association of Perinatal Medicine, the Faculty of Sexual and Reproductive Healthcare, the Royal College of Nursing and the Royal College of Obstetricians and Gynaecologists. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/JointStatementBMABAPMFSRHRCNRCOG24wkMay08.pdf.

13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *BMJ* 2009; **39**: b2535.

15. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.

16. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **10**: 101–129.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.

18. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.

19. Muller F, Thibaud D, Poloce F, Gelineau MC, Bernard M, Brochet C, Millet C, Réal JY, Dommergues M. Risk of amniocentesis in women screened positive for Down syndrome with second-trimester maternal serum markers. *Prenat Diagn* 2002; **22**: 1036–1039.

20. Eddleman KA, Malone FD, Sullivan L, Dukes K, Berkowitz RL, Kharbutli Y, Porter TF, Luthy DA, Comstock CH, Saade GR, Klugman S, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, D'Alton ME. Pregnancy loss rates after mid-trimester amniocentesis. *Obstet Gynecol* 2006; **108**: 1067–1072.

21. Kong CW, Leung TN, Leung TY, Chan LW, Sahota DS, Fung TY, Lau TK. Risk factors for procedure-related fetal losses after mid-trimester genetic amniocentesis. *Prenat Diagn* 2006; **26**: 925–930.

22. Towner D, Currier RJ, Lorey FW, Cunningham GC, Greve LC. Miscarriage risk from amniocentesis performed for abnormal maternal serum screening. *Am J Obstet Gynecol* 2007; **196**: 608.e1–5.

23. Odibo AO, Gray DL, Dicke JM, Stamilio DM, Macones GA, Crane JP. Revisiting the fetal loss rate after second-trimester genetic amniocentesis: a single center's 16-year experience. *Obstet Gynecol* 2008; **111**: 589–595.

24. Pitukkijronnakorn S, Promsonthi P, Panburana P, Udomsubpayakul U, Chittacharoen A. Fetal loss associated with second-trimester amniocentesis. *Arch Gynecol Obstet* 2011; **284**: 793–797.

25. Corrado F, Cannata ML, La Galia T, Magliarditi M, Imbruglia L, D'anna R, Carlo Stella N. Pregnancy outcome following mid-trimester amniocentesis. *J Obstet Gynaecol* 2012; **32**: 117–119.

26. Lau KT, Leung YT, Fung YT, Chan LW, Sahota DS, Leung NT. Outcome of 1355 consecutive transabdominal chorionic villus samplings in 1351 patients. *Chin Med J (Engl)* 2005; **18**: 1675–1681.

27. Akolekar R, Bower S, Flack N, Bilardo CM, Nicolaides KH. Prediction of miscarriage and stillbirth at 11–13 weeks and the contribution of chorionic villus sampling. *Prenat Diagn* 2011; **31**: 38–45.

28. Odibo AO, Dicke JM, Gray DL, Oberle B, Stamilio DM, Macones GA, Crane JP. Evaluating the rate and risk factors for fetal loss after chorionic villus sampling. *Obstet Gynecol* 2008; **112**: 813–819.

29. Acharya G, Sonesson SE, Flo K, Räsänen J, Odibo A. Hemodynamic aspects of normal human feto-placental (umbilical) circulation. *Acta Obstet Gynecol Scand* 2016; **95**: 672–682.

30. Assali, NS, Rauramo, L, Peltonen, T. Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy. *Am J Obstet Gynecol* 1960; **79**: 86–98.

31. Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. *Cochrane Database Syst Rev*. 2017; **9**: CD003252.

32. Salomon LJ, Alfirevic Z, Audibert F, Kagan KO, Paladini D, Yeo G, Raine-Fenning N; ISUOG Clinical Standards Committee. ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice. *Ultrasound Obstet Gynecol* 2017; **49**: 815–816.

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.

A video abstract of this article is available online.

This article has been selected for Journal Club.

A slide presentation prepared by Dr Yael Raz, one of UOG's Editors for Trainees, is available online.

Spanish translation by Dr Rubén D. Fernández Jr.
Chinese translation by Dr Yan Liu and Prof. Qingqing Wu, ISUOG China Task Force.

Riesgo de aborto después de una amniocentesis o una biopsia de vellosidades coriónicas: revisión sistemática de bibliografía y metaanálisis actualizado

RESUMEN

Objetivo Estimar el riesgo de aborto relacionado con el procedimiento de la amniocentesis o la biopsia de vellosidades coriónicas (BVC) mediante una revisión sistemática de bibliografía y un metaanálisis actualizado.

Métodos Se realizó una búsqueda en MEDLINE, EMBASE y The Cochrane Library para identificar estudios que reportaron sobre complicaciones después de una BVC o amniocentesis. Se consideraron elegibles para su inclusión los estudios controlados de gran tamaño que reportaron datos sobre la pérdida del embarazo antes de las 24 semanas de gestación. Se estableció contacto con los autores de los estudios cuando fue necesario para identificar datos adicionales necesarios. Se introdujeron en tablas de contingencia los datos de los casos que se sometieron a un procedimiento invasivo y controles y se estimó el riesgo de aborto para cada estudio. Las estadísticas resumen basadas en un modelo de efectos aleatorios se calcularon después de tener en cuenta la ponderación para cada estudio incluido en la revisión sistemática. El riesgo de aborto relacionado con cada procedimiento se estimó como una diferencia de riesgo ponderada de las estadísticas resumen para los casos y controles. Los análisis de subgrupos se realizaron de acuerdo con la similitud en los niveles de riesgo de anomalías cromosómicas entre los grupos de prueba invasiva y de control. La heterogeneidad se evaluó mediante el test estadístico I^2. Se estimó el sesgo de Egger para evaluar el sesgo de información reportada en los estudios publicados.

Resultados La búsqueda electrónica arrojó 2943 citas potenciales, de las cuales se seleccionaron para su inclusión en la revisión sistemática 12 estudios controlados para la amniocentesis y siete para la BVC. Después de los 63723 procedimientos de amniocentesis sucedieron un total de 580 abortos, lo que resultó en un riesgo ponderado de pérdida de embarazo del 0,91% (IC 95%, 0,73–1,09%). En el grupo de control hubo 1726 abortos en 330469 embarazos, con una tasa de pérdida del 0,58% (IC 95%, 0,47–0,70%). El riesgo ponderado de aborto relacionado con el procedimiento de amniocentesis fue del 0,30% (IC 95%, 0,11–0,49%; I^2 = 70,1%). Después de 13011 procedimientos de BVC se produjeron un total de 163 abortos, lo que resultó en un riesgo de pérdida de embarazo del 1,39% (IC 95%, 0,76–2,02%). En el grupo de control hubo 1946 abortos en 232680 embarazos, lo que supuso una tasa de pérdida del 1,23% (IC 95%, 0,86–1,59%). El riesgo ponderado de aborto relacionado con el procedimiento de BVC fue de 0,20% (IC 95%, -0,13–0,52%; I^2 = 52,7%). Sin embargo, cuando se consideraron los estudios que incluyeron sólo mujeres con perfiles de riesgo similares para la anomalía cromosómica en los grupos de intervención y control, el riesgo relacionado con el procedimiento de la amniocentesis fue de 0,12% (IC 95%, -0,05–0,30%; I^2 = 44.1%) y para el MVC fue de -0,11% (IC 95%, -0,29–0,08%; I^2 = 0%).

Conclusiones Los riesgos de aborto relacionados con el procedimiento de la amniocentesis y la BVC son menores que los actualmente mencionados a las mujeres. El riesgo parece ser insignificante cuando estas intervenciones se compararon con grupos de control del mismo perfil de riesgo. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

羊膜穿刺术或绒毛膜绒毛取样后的流产风险：相关文献的系统评估及最新的元分析

摘要

目标：依据相关文献的系统评估及最新的元分析，估算羊膜穿刺术与绒毛膜绒毛取样（CVS）后的程序相关性流产风险。

方法：检索了 MEDLINE、EMBASE 及科克伦图书馆藏文献（Cochrane Library），寻找一些报告 CVS 或羊膜穿刺术之后出现并发症的研究案例。符合纳入标准的是妊娠 24 周前报告妊娠失败数据的大型对照研究。需要时联系了研究作者，以确定其他必要的数据。将几个侵入性程序与对照案例的数据输入了列联表，估算了每项研究的流产风险。考虑了系统评估中包括的每项研究的权重后，计算了基于随机效应模型的汇总统计。针对相关案例和对照组汇总统计数据，以加权风险差异的形式估算了程序相关性流产风险。根据侵入性测试组和对照组之间的染色体异常风险水平相似性，进行了亚组分析。通过 I^2 统计进行了异质性评估。估算了艾格偏差，以评估已发表的研究报告中的报告偏差。

结果：在线检索发现了 2943 例潜在的引述案例，从中选出 12 例羊膜穿刺术对照研究案例和 7 例 CVS 案例，纳入系统评估范畴。63 723 例羊膜穿刺术之后，总共有 580 例流产案例，相应的妊娠失败加权风险为 0.91%（95% CI, 0.73-1.09%）。在对照组中，330 469 例妊娠中有 1726 例流产案例，妊娠失败率为 0.58%（95% CI, 0.47-0.70%）。羊膜穿刺术之后的程序相关性加权流产风险为 0.30%（95% CI, 0.11-0.49%; I^2=70.1%）。13 011 CVS 程序之后总共发生了 163 例流产，相应的妊娠失败风险为 1.39%（95% CI, 0.76-2.02%）。在对照组中，232 680 例妊娠中有 1946 例流产案例，妊娠失败率为 1.23%（95% CI, 0.86-1.59%）。CVS 之后的程序相关性加权流产风险为 0.20%（95% CI, 0.13-0.52%; I^2=52.7%）。但在考虑一些只在干预组和对照组中纳入相似染色体异常风险特征的女性受试者的研究项目时，羊膜穿刺术的程序相关性风险为 0.12%（95% CI, 0.05-0.30%; I^2=44.1%），CVS 则为 0.11%（95% CI, 0.29-0.08%; I^2=0%）。

结论：羊膜穿刺术和 CVS 之后的程序相关性流产风险低于当前引述的水平。将这些干预组和具有相同风险特征的对照组进行比较后发现，风险似乎可以忽略不计。© ISUOG 2019 版权所有。John Wiley & Sons Ltd. 出版