Risk of fetal loss following amniocentesis or chorionic villous sampling in twin pregnancies: a systematic review and meta-analysis

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Contribution

What are the novel findings of this work?

The risk of fetal loss after amniocentesis or CVS in twin pregnancies is lower than previously reported, and there is no significant difference when comparing fetal loss before 24 weeks of gestation or within 4 weeks from the procedure in twin pregnancies undergoing with those not undergoing invasive prenatal testing.

What are the clinical implications of this work?

These data are intuitively helpful when counselling parents about the safety of the procedure, as a woman can be reassured that the overall risk of fetal loss is low, although clinicians should still highlight the higher rate of fetal loss in twins compared to singletons.

ABSTRACT

Objectives: To assess the rate of fetal loss following amniocentesis and chorionic villous sampling (CVS) in twin pregnancies.

Methods: Medline, Embase and Cochrane databases were searched for studies reporting procedure-related complications following amniocentesis or chorionic villous sampling in twin pregnancies. The primary outcome was the rate of procedure-related fetal loss. The secondary outcomes were fetal loss occurring before the 24th week of gestation and fetal loss occurring within 4 weeks after the procedure. Head-to-head meta-analyses were used to directly compare, for each outcome: (a) women undergoing amniocentesis versus women not undergoing amniocentesis, and (b) women undergoing CVS versus women not undergoing CVS, and to compute pooled risk differences between women exposed and not exposed to each invasive procedure. Additionally, meta-analyses of proportions were used to estimate the pooled rates of each of the three outcomes among women undergoing amniocentesis or CVS, and among controls, and head-to-head meta-analyses to directly compare, for each outcome: women undergoing amniocentesis versus women not undergoing amniocentesis; women undergoing CVS versus women not undergoing CVS.

Results: Sixteen studies (3419 twin pregnancies undergoing and 2517 twin pregnancies not invasive procedures) were included. *In twin pregnancies undergoing amniocentesis*, head-to-head meta-analyses directly comparing women undergoing amniocentesis versus women not undergoing amniocentesis found a higher risk for overall fetal loss (OR 1.46, p=0.04; RD 0.013, p=0.04), while there was no difference when focusing on either fetal loss before 24 weeks of gestation (OR 1.59, p=0.06; RD 0.010, p=0.11) or fetal loss within 4 weeks from the procedure (OR 1.38, p=0.3; RD 0.003, p=0.8).

In twin pregnancies undergoing CVS, head-to-head meta-analyses directly comparing women undergoing CVS versus women not undergoing CVS found no significant difference either when investigating overall fetal loss (OR 1.61, p=0.5; RD 0.003, p=0.8) or fetal loss before 24 weeks of gestation (OR 1.61, p=0.5; RD 0.003, p=0.8).

Conclusion: The risk of fetal loss following amniocentesis and CVS in twins is lower than the one previously reported, and the rate of fetal loss before 24 weeks of gestation or

within 4 weeks from the procedure did not differ from the background risk of a twin pregnancy not undergoing invasive prenatal testing. These data can guide prenatal counselling for twin pregnancies undergoing invasive procedures.

INTRODUCTION

Prenatal diagnostic invasive procedures, such as amniocentesis or chorionic villous sampling (CVS), are usually performed to rule out fetal chromosomal or biochemical anomalies, maternal transmittable infectious disease, and sometimes also performed for maternal request, when parental anxiety might significantly affect the pregnancy.[1]

The main concern for prenatal invasive testing is the risk of procedure-related fetal loss.[1] In singleton pregnancies, the risk of miscarriage after amniocentesis or CVS is low, ranging from 0.2% to 0.3%.[2]

Twin pregnancies are at increased risk of perinatal mortality and morbidity compared to singletons,[3-7] but the exact rate of procedure-related complications after invasive testing is still uncertain, with an estimated risk of fetal loss ranging from 2-4% in case of both amniocentesis and CVS, according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[1]

The most recent systematic review on this topic reported that the risk of pregnancy loss is likely to be increased by approximately 1% above the background risk in twin pregnancies following either amniocentesis or CVS, but this analysis dates back to almost ten years.[8] In the meantime, other studies were published, also evaluating the association between the risk of fetal loss and chorionicity[9] or entry technique[10] (whether to perform amniocentesis through a single uterine entry, passing through the inter-twin membrane or through two different entries into the two amniotic sacs) and the risk appears to be lower than previously reported.

The aim of this systematic review was to ascertain the actual rate of fetal loss following amniocentesis and CVS in twin pregnancies.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol recommended for systematic reviews and meta-analysis.[11-13] Medline, Embase and Cochrane databases were searched electronically on February 12, 2020 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “amniocentesis”, “chorionic villous sampling”, “miscarriage”, “fetal loss” and “twins”. The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed.[14-16] The study was registered with the PROSPERO database (registration number CRD42020159940).

Outcomes measures, study selection and data collection

The primary outcome was the rate of overall fetal loss following amniocentesis or CVS in twin pregnancies, as defined by each author. Secondary outcomes were fetal loss occurring before the 24th week of gestation and fetal loss occurring within 4 weeks after the procedure.

We also planned to perform sub-group analyses according to chorionicity (dichorionic vs monochorionic) and entry technique (single versus double).

Only prospective and retrospective studies reporting data on amniocentesis or CVS in twin pregnancies were considered suitable for the inclusion. Studies reporting the outcome of invasive procedures in high order multiple gestations and those reporting the outcome of invasive procedures performed for fetal reduction were excluded. Pregnancies affected by chromosomal anomalies were also excluded from the analysis. Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than five cases were excluded to avoid publication bias. Furthermore, studies published before 2000 were not included as advances in the field of invasive procedures and in the management of twin pregnancies make them less relevant.

Two authors (DDM, FDA) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment, risk of bias and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.[17] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at beginning of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[17]

In a sample of women with twin pregnancies, we evaluated the risk of fetal loss among women who underwent amniocentesis (vs no amniocentesis) or CVS (vs no CVS). Fetal loss was evaluated using three different approaches: (1) considering all cases of fetal loss (overall fetal loss); (2) considering only fetal losses occurring before the 24th week of gestation; (3) including only the cases occurring within 4 weeks after the procedure.

First, we set six head-to-head meta-analyses to directly compare, for each outcome: (1) women undergoing amniocentesis versus women not undergoing amniocentesis; (2) women undergoing CVS versus women not undergoing CVS. For this purpose, we included only studies having both arms of women undergoing versus not undergoing prenatal invasive testing, and we excluded those having only single-arm (i.e. only prenatal invasive testing). Furthermore, in these meta-analyses we included some cohort studies in which exposed and unexposed group sizes were severely unbalanced, and some studies that reported zero events in one or both of the compared groups. When the events are rare, many of the most commonly used meta-analytical methods may produce biased estimates.[18-19] When the studies are also substantially imbalanced, the best performing methods are the Mantel-Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method.[20-21] Mantel-Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, the exclusion of which may however cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect.[18] Therefore, to keep all studies into the analyses, the six head-to-head meta-analyses were carried out using individual data random-effect logistic regression, with single study as the cluster unit, and the pooled datasets with individual data were reconstructed using published 2X2 tables.

Second, we used the Mantel-Haenszel type method of Greenland and Robins[22] to estimate, for each outcome, the pooled risk difference (and 95% confidence interval - CI) between the women undergoing and those not undergoing each invasive procedure.

Providing pooled rates of fetal loss may be useful as introductory information to women contemplating having an invasive test. Therefore, as additional analyses, we performed meta-analyses of proportions to estimate the pooled rates of each of the three outcomes among women undergoing amniocentesis or CVS, and among controls. Proportion meta-analyses were not used when only one study could be included (raw proportions and 95% confidence interval - CI - were reported in such cases), and a random-effect model was adopted to account for the inter-study heterogeneity. Additionally, all proportion meta-analyses were first carried out including all pregnancies, then stratified according to

chorionicity - separately analyzing monochorionic (MC) and dichorionic twins (DC) - and number of needle insertions during the procedure (single- or double-needle).

For each outcome, the total number of publications included in the meta-analyses was <10. We were thus unable to assess publication bias, either graphically, through funnel plots, or formally, through Egger's regression asymmetry test (in such cases, the power is too low to distinguish chance from real asymmetry).[21] All analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2013), and StatsDirect Ltd. (StatsDirect statistical software. England: StatsDirect Ltd. 2013).

RESULTS

Study selection and characteristics

319 articles were identified, 27 were assessed with respect to their eligibility for inclusion and 16 studies[9,10,23-36] were included in the systematic review (Table 1, Figure 1, Supplementary Table 1).

Table 2 shows the definition of overall fetal loss provided by each author, the indication for invasive prenatal diagnosis and the exclusion criteria of each of the included studies.

These sixteen studies[9,10,23-36] included 3419 twin pregnancies undergoing invasive procedures and 2517 twin pregnancies not undergoing invasive prenatal diagnosis.

Twin pregnancies included both DC and MC pregnancies, while we could not find any study reporting the occurrence of fetal loss exclusively in monoamniotic gestations.

The results of the quality assessment of the included studies using the NOS scale are presented in Table 3. Most of the included studies showed an overall good score regarding the selection and comparability of study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and heterogeneity of the outcomes observed.

Synthesis of the results

Amniocentesis

Thirteen studies[9,10,23,25-33,36] (5012 pregnancies) reported the occurrence of fetal loss in twin pregnancies undergoing amniocentesis.

Head-to-head meta-analyses directly comparing women undergoing amniocentesis versus women not undergoing amniocentesis found a higher risk of overall fetal loss (6 studies[9,25-26,32-33,36]: 60/1538 vs 71/2299; OR 1.46, p=0.04; RD 0.013, p=0.04), while there was no difference when focusing on either fetal loss before 24 weeks of gestation (5 studies[25-26,32-33,36]: 36/1264 vs 31/1712; OR 1.59, p=0.06; RD 0.010, p=0.11) and fetal loss within 4 weeks from the procedure (3 studies[25-26,36]: 25/977 vs 22/1172; OR 1.38, p=0.3; RD 0.003, p=0.8) (Table 4).

Overall, the rate of fetal loss was 2.4% (95% CI 1.4-3.6; 83/2713) compared with 2.4% (95% CI 0.9-4.6; 71/2299) for twin pregnancies not undergoing amniocentesis (Table 5; Figure 2). Eight[9,23,25-27,31,32,36] (2383 pregnancies) and five[9,25,26,32,33] (475 pregnancies) studies reported the occurrence of fetal loss in DC and MC twin pregnancies after amniocentesis, respectively. In DC pregnancies, the occurrence of fetal loss was 2.3% (95% CI 0.9-4.1, 38/1431); in MC gestations, fetal loss occurred in 2.3% (95% CI 0.1-6.4, 12/278). When considering the number of needle insertions during the procedure, the rate of overall fetal loss in double needle insertion was 2.0% (95% CI 0.8-3.7, 59/2439), while the small number of studies reporting data on single needle insertion made it impossible to draw any convincing evidence for this subgroup analysis.

The rate of fetal loss before 24 weeks of gestation was 2.1% (95% CI 1.4-2.9, 59/2439) in pregnancies undergoing amniocentesis compared with 1.7% (95% CI 0.8-2.9, 31/1712) in twin pregnancies not undergoing amniocentesis (Figure 3). When stratifying according to chorionicity, the rate of fetal loss before 24 weeks of gestation was 1.7% (95% CI 0.8-2.8, 26/1237) in DC and 1.2% (95% CI 0.0-4.9, 7/155) in MC pregnancies.

The rate of fetal loss occurring within 4 weeks from the procedure was 2.1% (95% CI 1.5-2.9, 45/1932) in twin pregnancies undergoing amniocentesis compared with 1.8% (95% CI 0.5-3.8, 22/1172) in twin pregnancies not undergoing amniocentesis (Figure S1).

CVS

Four studies[24,28,34,35] (567 pregnancies) reported the overall risk of fetal loss in twin pregnancies undergoing CVS.

Head-to-head meta-analyses directly comparing women undergoing CVS versus women not undergoing CVS found no significant difference either when focusing on overall fetal loss (2 studies[24,35]: 3/201 vs 5/218; OR 1.61, p=0.5; RD 0.003, p=0.8) and fetal loss before 24 weeks of gestation (2 studies[24,35]: 3/201 vs 5/218; OR 1.61, p=0.5; RD 0.003, p=0.8) (Table 4).

Overall, the rate of fetal loss was 2.0% (95% CI 0.0-6.5; 8/349) compared with 1.8% (95% CI 0.3-4.2; 5/218) for twin pregnancies not undergoing CVS (Table 6; Figure 4). Two[24,35] (419 pregnancies) studies reported the occurrence of fetal loss in DC twin pregnancies,

while no study was found for MC pregnancies after CVS. In DC pregnancies, the occurrence of fetal loss was 0.5% (95% CI 0.0-2.2, 3/201). CVS in DC pregnancies was always performed with double needle insertion technique – thus leading to the same results (0.5%) - while no study reported data on single needle insertion.

The rate of fetal loss before 24 weeks of gestation was 2.0% (95% CI 10.0-6.5; 8/349) compared with 1.8% (95% CI 0.3-4.2; 5/218) in twin pregnancies not undergoing CVS (Figure 5). When stratifying according to chorionicity, the rate of fetal loss before 24 weeks of gestation was 0.5% (95% CI 0.0-2.2, 3/201) in DC twin pregnancies.

The rate of fetal loss occurring within 4 weeks from the procedure was 2.2% (95% CI 0.4-11.8, 1/44), although this evidence comes from a single study (Figure S2).[34]

DISCUSSION

Main findings

Our findings show that the risk of fetal loss following amniocentesis and CVS in twin pregnancies is lower than previously reported in observational studies and guidelines.[1,8] In particular, head-to-head meta-analyses showed that there is no significant difference in terms of fetal loss before 24 weeks of gestation or within 4 weeks from the procedure when directly comparing twin pregnancies which had invasive procedures (either amniocentesis or CVS) versus those which did not.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, lack of standardized criteria for the surveillance after the procedure, the heterogeneity in the definition of fetal loss and the different indications for invasive prenatal testing represent the major limitations of this systematic review. Furthermore, some of the included studies also reported data of twin pregnancies complicated by structural anomalies, thus potentially increasing the rate of fetal loss, although lethal abnormalities were usually excluded. Moreover, the stratification according to chorionicity (dichorionic vs monochorionic twin pregnancies) included a lower number of cases, compared with the analysis including all twin pregnancies. Finally, some of the studies include also old data, and it is likely that some of the selection criteria for invasive testing are not comparable to our clinical setting. For this reason, we planned to perform a subgroup analysis on the last ten years, but the robustness of the results was significantly limited by the small number of studies and cases included. Despite these limitations, the present study represents the most up-to-date and comprehensive published review investigating the rate of fetal loss following amniocentesis and CVS in twin pregnancies.

Comparison with other published evidence

In 2012, a large systematic review by Argawal and Alfirevic reported higher rates of fetal loss after both amniocentesis and CVS which were estimated at 3.07% and 3.84%, respectively.[8] In contrast to our findings, the authors also found a significantly higher risk

of pregnancy loss before 24 weeks when evaluating twin pregnancies undergoing or not amniocentesis, with an added risk of around 1% above the background risk.[8] These data were also reported by the 2016 ISUOG guidelines on invasive procedures for prenatal diagnosis that describe a risk of fetal loss between 2.5% and 3.2% after amniocentesis and higher than 3% after CVS.[1]

Similarly, another systematic review of 17 observational studies found that the pooled procedure-related loss rate before 24 weeks was 3.5% after amniocentesis, and the risk was 1.8 times higher, compared with women not undergoing amniocentesis.[37]

The findings from this study show that the rate of fetal loss following amniocentesis and CVS is lower than currently stated and are quite consistent with the American College of Obstetricians and Gynecologists Practice Bulletin on prenatal diagnostic testing for genetic disorders where the attributable pregnancy loss rate of amniocentesis in twins is reported to be approximately 2%.[38]

Clinical and research implications

In the last decade, the spread of cell-free DNA (cfDNA) of maternal blood has significantly reduced the number of invasive procedures for prenatal genetic testing.[1] cfDNA is the most sensitive screening method for common chromosomal anomalies (trisomy 21, 18, 13), with a detection rate of 99.7% for trisomy 21 and 97.9% for trisomy 18 in singleton pregnancies.[39] Despite its excellent performance, cfDNA is still considered as a screening tool and a confirmatory invasive testing is needed in case of abnormal findings.[40]

Furthermore, when focusing on twin pregnancies, the evidence on the accuracy on cfDNA is still an object of debate. A recent meta-analysis found that the detection rate for trisomy 21 in twin pregnancies was 98.2%, and it was similar to what previously reported for singletons;[41] conversely, the detection rate for trisomy 18 was 88.9% and it was lower compared with singleton pregnancies.[41] However, the number of studies assessing the accuracy of cfDNA in twin pregnancies was limited and therefore the number of affected cases included in the analysis was significantly lower. For these reasons, international societies do not currently recommend cfDNA as a non-invasive prenatal testing in twin pregnancies.[40,42]

In this scenario, both amniocentesis and CVS play a fundamental role in prenatal genetic diagnosis in twin pregnancies, regardless of chorionicity.

It is well known that in twin pregnancies, fetal morbidity and mortality are significantly higher than those of singletons[3-7,43-47] – mostly depending on chorionicity and amnionicity – and a recent study showed that in gestations with two live fetuses at the end of the first trimester, the risk of pregnancy loss before 24 weeks was 2.2% in DC and 7.7% in MC diamniotic pregnancies,[48] while the rate of intrauterine death of one fetus after week 22 was 1.7% in MC diamniotic and 0.6% in DC twins.[49]

Of note, in our meta-analysis the rate of fetal loss before 24 weeks of gestation or within 4 weeks from the procedure did not differ from the background risk of a twin pregnancy not undergoing invasive prenatal testing.

These data are intuitively helpful when counselling parents about the safety of the procedure, as a woman can be reassured that the overall risk of fetal loss is low, although clinicians should still highlight the higher rate of fetal loss in twins compared to singletons.

Conclusion

The risk of fetal loss after amniocentesis or CVS in twin pregnancies is lower than previously reported, and there is no significant difference when comparing fetal loss before 24 weeks of gestation or within 4 weeks from the procedure in twin pregnancies undergoing with those not undergoing invasive prenatal testing. Future large prospective studies sharing objective protocols might be useful to elucidate better the actual rates of miscarriage, short and long term procedure-related complications stratified according to chorionicity, single and double entry, number of attempts and indication for invasive testing.

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Figure legends

Figure 1. Systematic review flowchart

Figure 2. Pooled rates of fetal loss (overall) in women with twin pregnancies undergoing amniocentesis

Figure 3. Pooled rates of fetal loss occurring before 24 weeks in women with twin pregnancies undergoing amniocentesis

Figure 4. Pooled rates of fetal loss (overall) in women with twin pregnancies undergoing chorionic villus sampling

Figure 5. Pooled rates of fetal loss occurring before 24 weeks in women with twin pregnancies undergoing chorionic villus sampling

Supplementary Figure S1. Pooled rates of fetal loss occurring within 4 weeks from the procedure in women with twin pregnancies undergoing amniocentesis.

Supplementary Figure S2. Pooled rates of fetal loss occurring within 4 weeks from the procedure in women with twin pregnancies undergoing chorionic villous sampling.

Supplementary Table S1. Excluded studies and reason for the exclusion

Table 1. General characteristics of the included studies

Author	Year	Country	Period analyzed	Study design	Pregnancies (n)	Undergoing invasive (n)	Not undergoing invasive (n)	CVS (n)	Amniocentesis (n)	Operators' experience specified	Stratification according to chorionicity	Stratification according to single or double entry	Structural anomalies excluded
Kim	2019	Korea	2006-2017	Retrospective	170	170	0	0	170	Yes	No	No	Yes
Kim	2019	Korea	2006-2017	Retrospective	54	54	155	54	0	Yes	No	No	Yes
Krispin	2019	Israel	2002-2016	Retrospective	212	212	0	0	212	Yes	No	Yes	No
Sperling	2019	USA	2009-2015	Retrospective	861	274	587	0	274	Yes	Yes	No	Yes
Tenis-Cordoba	2013	Spain	1990-2010	Prospective	661	396	265	0	396	Yes	Yes	No	NR
Kan	2012	China	1997-2006	Prospective	535	105	430	0	105	Yes	Yes	Yes	Yes
Kalogiannidis	2011	Greece	1993-2009	Retrospective	120	120	0	0	120	Yes	No	No	NR
Simonazzi	2010	Italy	2002-2007	Retrospective	204	204	0	104	100	NR	No	Yes	Yes
Daskalakis	2009	Greece	1993-2006	Prospective	442	442	0	0	442	Yes	No	No	Yes
Supadilokluck	2009	Thailand	1992-2006	Retrospective	87	87	0	0	87	Yes	No	No	NR
Hanprasertpong	2008	Thailand	1998-2006	Prospective	66	66	0	0	66	NR	Yes	No	No
Millaire	2006	Canada	1990-2004	Retrospective	380	132	248	0	132	NR	Yes	No	Yes
Toth-Pal	2004	Hungary	1990-2001	Retrospective	447	155	292	0	155	NR	No	No	Yes
Antsaklis	2002	Greece	1977-2000	Retrospective	379	379	0	44	335	Yes	No	No	No

Brambati	2001	Italy	1991-1998	Retrospective	210	147	63	147	0	NR	No	No	No
Yukobowich	2001	Israel	1990-1997	Retrospective	953	476	477	0	476	NR	No	No	Yes

CVS: chorionic villous sampling; NR: not reported.

Table 2. Definition of fetal loss, indication for invasive prenatal diagnosis and exclusion criteria of each study

Author	Year	Definition of fetal loss	Indication for invasive procedure	Exclusion criteria
Kim	2019	Loss of one or two fetuses within 4 weeks	Maternal age ≥ 35 years; abnormal maternal serum screening test results; increased NT; abnormal sonographic findings; chromosomal malformations in parents or previous pregnancies; psychological indications; ICSI pregnancies.	Known chromosome anomaly or lethal anatomical defects; demise of one twin at the time of the procedure; monochorionic or monoamniotic twin; repeated invasive procedure; pregnancies in which selective feticide was carried out
Kim	2019	Miscarriage < 24 weeks	Maternal age ≥ 35 years; abnormal maternal serum screening test results; increased NT; abnormal sonographic findings; chromosomal malformations in parents or previous pregnancies; psychological indications; ICSI pregnancies.	Known chromosome anomaly or lethal anatomical defects; demise of one twin at the time of the procedure; monochorionic or monoamniotic twin; repeated invasive procedure; pregnancies in which SF was carried out; after abnormal karyotyping results of CVS
Krispin	2019	Fetal loss within 4 weeks	Maternal age > 35 years; suspected anatomical anomalies; Cytomegalovirus seroconversion diagnosed during pregnancy	Method of amniocentesis not clear or puncture made only in a single sac; termination of pregnancy; feticide of a single embryo; fetal chromosomal anomalies; monochorionic monoamniotic twins; missing data
Sperling	2019	Fetal loss at any gestational age	Pregnancies positive at the California Prenatal Screening Program; other unspecified indications	Chromosomal/structural abnormalities; selective fetal reduction; terminations of pregnancy; neonatal deaths; ovum donation; incomplete data
Lenis-Cordoba	2013	Fetal loss within 4 weeks	Maternal age; abnormal maternal serum test screening; abnormal NT	Elective termination of pregnancy; previous CVS, AC performed earlier in gestation; selective reduction of triple gestation, monoamniotic twin pregnancies
Kan	2012	Fetal loss within 4 weeks	maternal age over 35 years; history of abnormal babies; chromosomal anomalies; risk of hereditary disease in the fetuses	Abnormal karyotype; structural anomalies; TTTS; missing data

Kalogiannidis	2011	Miscarriage < 24 weeks	Advanced maternal age; abnormal serum markers; ultrasound findings; family or previous history; infection; maternal anxiety; NTDs; carriers of thalassemia; others	Monoamniotic twin pregnancy; previous CVS; embryo reduction in multiple gestations
Simonazzi	2010	Loss of one or two fetuses < 24 weeks	Advanced maternal age; chromosomal anomalies in previous pregnancy; maternal request	Triplet pregnancies; embryo reduction; selective termination
Daskalakis	2009	Fetal loss within 4 weeks	Fetal karyotyping; DNA analysis for b thalassemia; congenital infection	Chromosomal/structural abnormalities; selective fetal reduction; previous CVS; death of one fetus at the time of procedure; monochorionic pregnancy
Supadilokluck	2009	Fetal loss within 2 weeks	Advanced maternal age; history of NTDs; history of chromosomal anomaly; maternal request	NR
Hanprasertpong	2008	Fetal loss within 2 weeks	Advanced maternal age; previous abnormal child; abnormal US findings	NR
Millaire	2006	Loss of one or two fetuses < 24 weeks	NR	Women who underwent amniocentesis before 15 or after 17 weeks; previous CVS; higher order pregnancies; TTTS; early IUGR; lethal fetal anomalies; abnormal karyotype; monoamniotic twins
Toth-Pal	2004	Miscarriage < 24 weeks	Advanced maternal age; US suspicious findings; ICSI pregnancy; parental concern; history of a child born with chromosomal anomalies; abnormal maternal serum testing results; history of Duchenne's muscular dystrophy; suspicion of Toxoplasma infection	Structural or chromosomal anomalies; death of one fetus before amniocentesis
Antsaklis	2002	Fetal loss within 4 weeks	advanced maternal age; history of chromosomal anomaly; abnormal serum biochemistry; abnormal US findings; congenital infections	Chromosomal anomalies; monoamniotic pregnancy
Brambati	2001	Fetal loss < 20 weeks	Fetal karyotyping	NR
Yukobowich	2001	Fetal loss within 4 weeks	Advanced maternal age; abnormal serum biochemistry; maternal request; US suspicious	structural anomalies, death of one fetus before the procedure; selective feticide

			findings	

NT, nuchal translucency; CVS, chorionic villous sampling; NR, not reported; TTTS, twin-twin transfusion syndrome; NTDs, neural tube defects; IUGR, intrauterine growth restriction; US, ultrasound

Table 3. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Author	Year	Selection	Comparability	Outcome
Kim	2019	☐☐☐	☐	☐☐
Kim	2019	☐☐☐	☐	☐☐
Krispin	2019	☐☐☐	☐	☐☐
Sperling	2019	☐☐☐	☐	☐☐
Lenis-Cordoba	2013	☐☐☐	☐	☐☐
Kan	2012	☐☐☐	☐	☐☐
Kalogiannidis	2011	☐☐☐	☐	☐☐
Simonazzi	2010	☐☐☐	☐	☐☐
Daskalakis	2009	☐☐☐	☐	☐☐
Supadilokluck	2009	☐☐☐	☐	☐☐
Hanprasertpong	2008	☐☐☐	☐	☐☐
Millaire	2006	☐☐☐	☐	☐☐
Toth-Pal	2004	☐☐☐	☐	☐☐
Antsaklis	2002	☐☐☐	☐	☐☐
Brambati	2001	☐☐☐	☐	☐☐
Yukobowich	2001	☐☐☐	☐	☐☐

Table 4. Results of the meta-analyses evaluating the association between each invasive procedure (amniocentesis and chorionic villus sampling) and fetal loss in twin pregnancies. For each outcome, pooled risk differences between women undergoing and not undergoing invasive procedures were also computed

	A. Amniocentesis					**B. Chorionic villus sampling**			
Outcomes	**N. of studies (total sample)**	**Raw data***	**Pooled OR (95% CI)**	**Pooled RD (95% CI)**		**N. of studies (total sample)**	**Raw data***	**Pooled OR (95% CI)**	**Pooled RD (95% CI)**
1. Fetal loss (overall)	6 (3837)	60/1538 vs 71/2299	1.46 (1.02-2.10) P=0.04	0.013 (0.001; 0.025) p=0.037		2 (419)	3/201 vs 5/218	1.61 (0.36-7.26) p=0.5	0.003 (-0.019; 0.025) p=0.8
2. Fetal loss <24th gestational week	5 (2976)	36/1264 vs 31/1712	1.59 (0.98-2.59) p=0.06	0.010 (-0.002; 0.023) p=0.11		2 (419)	3/201 vs 5/218	1.61 (0.36-7.26) p=0.5	0.003 (-0.019; 0.025) p=0.8

3. Fetal loss within 4 weeks from the procedure	3 (2149)	25/977 vs 22/1172	1.38 (0.77-2.47) p=0.3	0.003 (-0.020; 0.027) p=0.8		--	--	--	

OR = Odds ratio. CI = Confidence Interval. RD = Risk difference.
* Number of events / Total n. of subjects in the exposed group (women undergoing A. amniocentesis or B. chorionic villus sampling) versus Number of events / Total n. of subjects in the unexposed group (women not undergoing invasive procedures).

Table 5. Pooled rates of each outcome in twin pregnancies which had amniocentesis versus those which did not. Data from single studies have been combined using proportion meta-analysis (random-effect model)

	Amniocentesis			**No amniocentesis**	
Outcomes	**n / N[a]**	**Pooled % (95% CI)**		**n / N[a]**	**Pooled % (95% CI)**
1. Overall fetal loss					
- All twins	83 / 2713	2.4 (1.4-3.6)		71 / 2299	2.4 (0.9-4.6)
- Dichorionic twins only	38 / 1431	2.3 (0.9-4.1)		19 / 952	1.9 (0.1-6.0)
- Monochorionic twins only	12 / 278	2.3 (0.1-6.4)		16 / 197	7.9 (4.4-12.2)
- Single needle insertion only	0 / 65	0.0 (0.0-0.4)*		--	--
- Double needle insertion only	16 / 591	2.0 (0.8-3.7)		7 / 265	2.6 (1.3-5.4)*
2. Fetal loss <24th gestational week					
- All twins	59 / 2439	2.1 (1.4-2.9)		31 / 1712	1.7 (0.8-2.9)
- Dichorionic twins only	26 / 1237	1.7 (0.8-2.8)		5 / 740	0.7 (0.2-1.4)
- Monochorionic twins only	7 / 155	1.2 (0.0-4.9)		5 / 97	5.2 (2.2-11.5)*
3. Fetal loss occurring within 4 weeks from the	45 / 1932	2.1 (1.5-2.9)		22 / 1172	1.8 (0.5-3.8)

procedure					

CI = Confidence Interval. [a] Number of women with the outcome / Total number of women. * Only one study available.

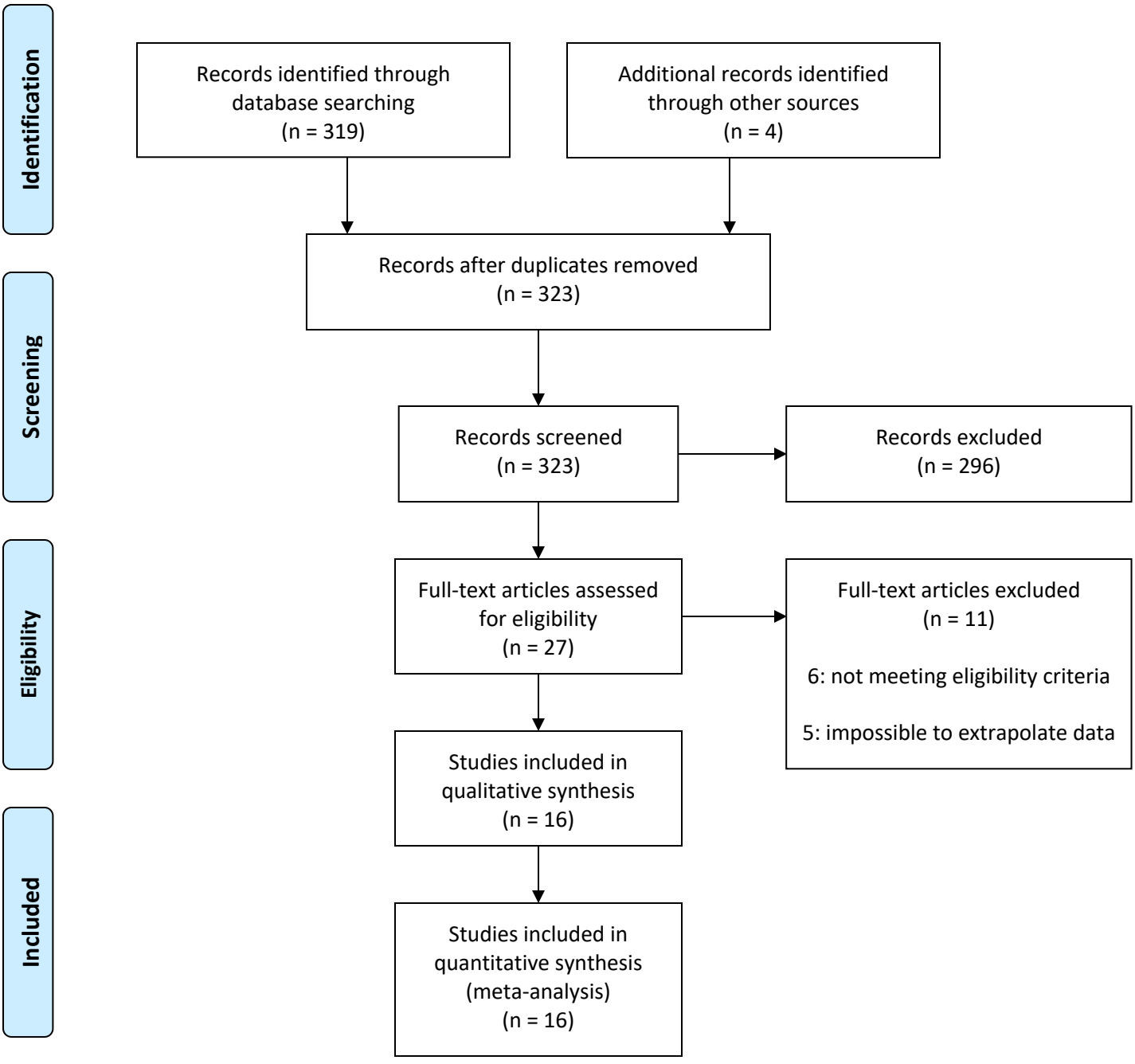
Table 6. Pooled rates of each outcome in twin pregnancies which had chorionic villus sampling versus those which did not. Data from single studies have been combined using proportion meta-analysis (random-effect model)

	Chorionic villus sampling			**No chorionic villus sampling**	
Outcomes	**n / N[a]**	**Pooled % (95% CI)**		**n / N[a]**	**Pooled % (95% CI)**
1. Overall fetal loss					
- All twins	8 / 349	2.0 (0.0-6.5)		5 / 218	1.8 (0.3-4.2)
- Dichorionic twins only	3 / 201	0.5 (0.0-2.2)		5 / 218	1.8 (0.3-4.2)
- Monochorionic twins only	--	--		--	--
- Single needle insertion only	--	--		--	--
- Double needle insertion only	3 / 201	0.5 (0.0-2.2)		5 / 218	1.8 (0.3-4.2)
2. Fetal loss <24th gestational week					
- All twins	8 / 349	2.0 (0.0-6.5)		5 / 218	1.8 (0.3-4.2)
- Dichorionic twins only	3 / 201	0.5 (0.0-2.2)		5 / 218	1.8 (0.3-4.2)
- Monochorionic twins only	--	--		--	--

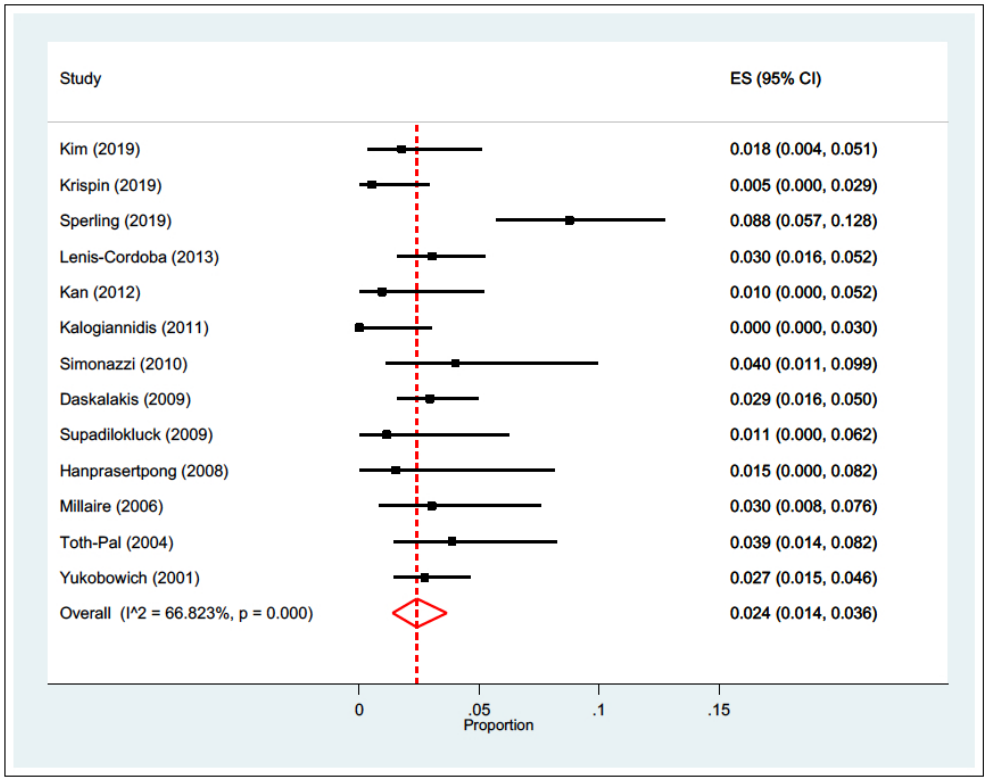
3. Fetal loss occurring within 4 weeks from the procedure	1 / 44	2.2 (0.4-11.8)*		0 / 0	--

CI = Confidence Interval. [a]Number of women with the outcome / Total number of women. * Only one study available

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



Pooled rates of fetal loss (overall) in women with twin pregnancies undergoing amniocentesis

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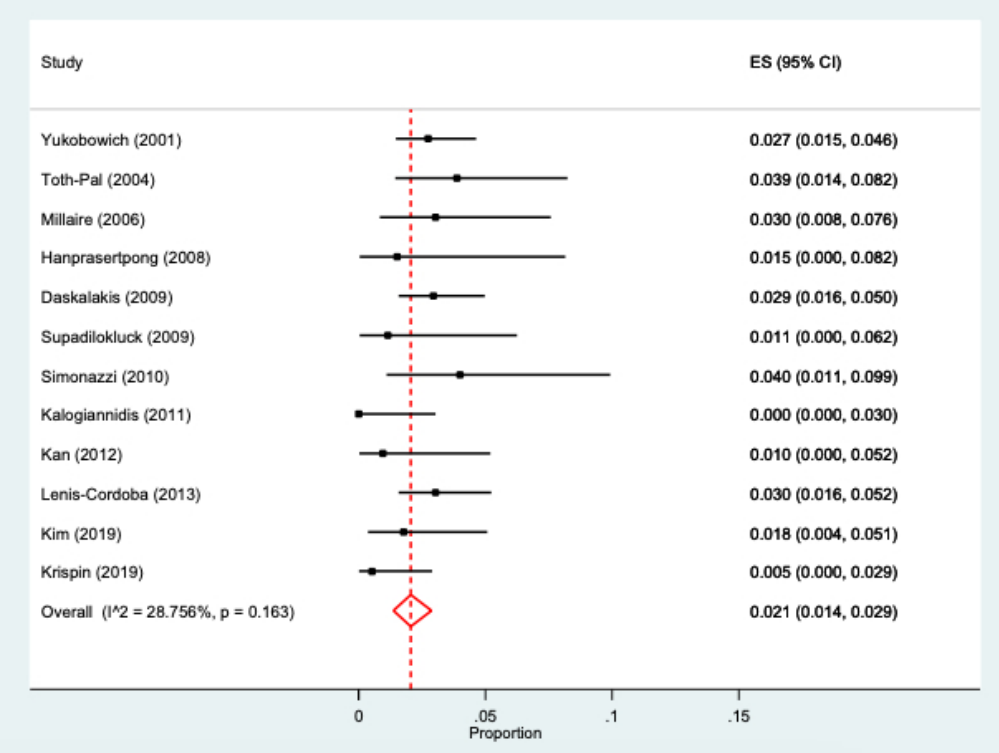

Pooled rates of fetal loss occurring before 24 weeks in women with twin pregnancies undergoing amniocentesis

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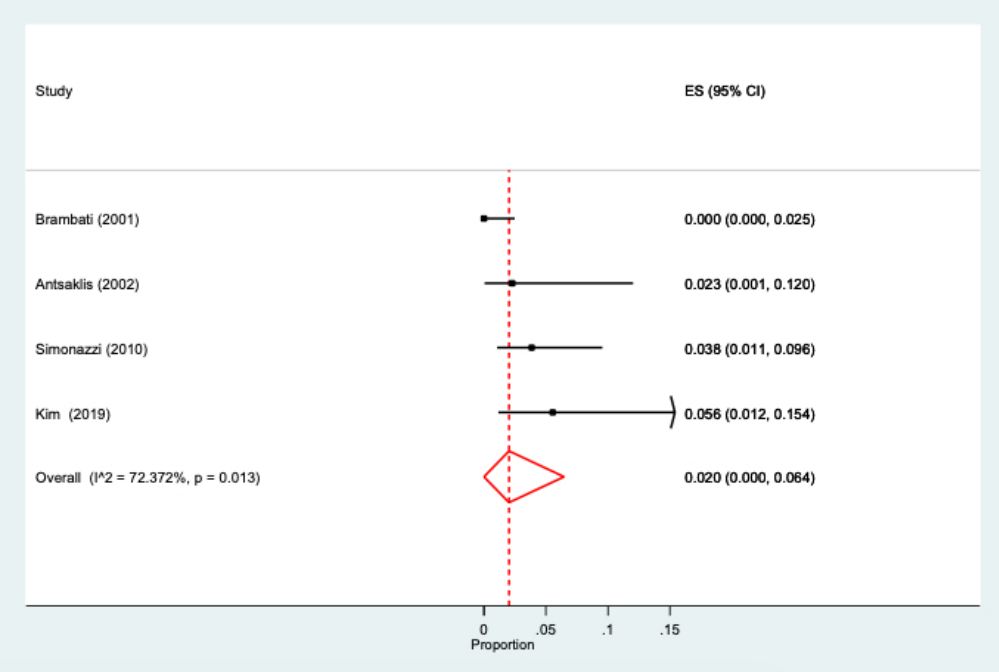

Pooled rates of fetal loss (overall) in women with twin pregnancies undergoing chorionic villus sampling

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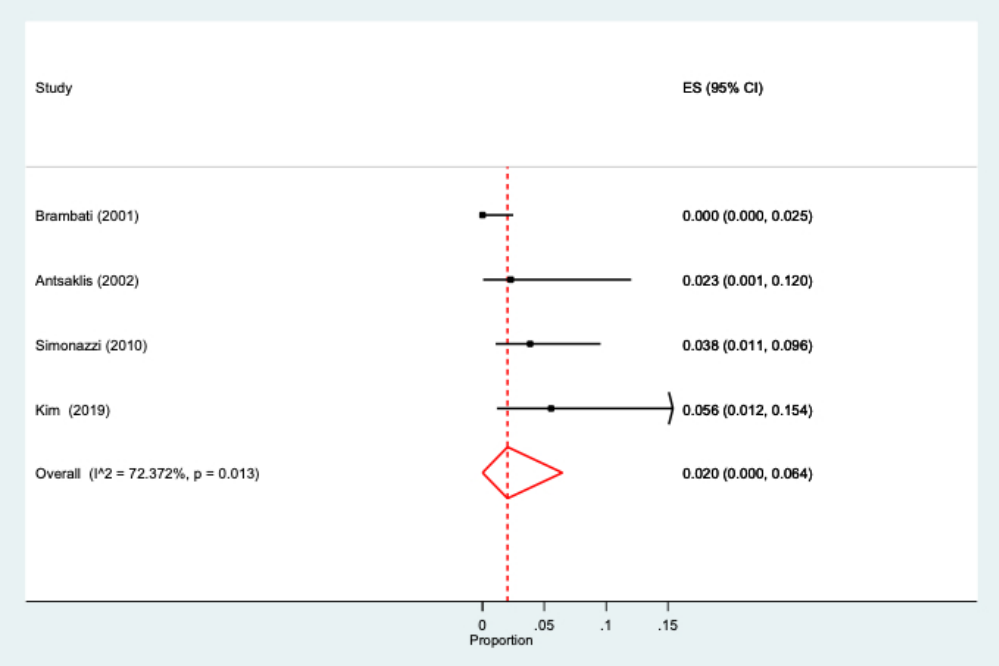

Pooled rates of fetal loss occurring before 24 weeks in women with twin pregnancies undergoing chorionic villus sampling

239x159mm (72 x 72 DPI)