Amniocentesis and chorionic villus sampling for prenatal diagnosis (Review)

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ABSTRACT

Background
A major disadvantage of second trimester amniocentesis is that the result is usually available only after 18 weeks' gestation. Chorionic villus sampling (CVS) and early amniocentesis can be done between 9 and 14 weeks and offer an earlier alternative.

Objectives
The objective was to assess comparative safety and accuracy of second trimester amniocentesis, early amniocentesis, transcervical and transabdominal CVS.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group trials register (March 2003) and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 1, 2002).

Selection criteria
All randomised trials comparing amniocentesis and CVS.

Data collection and analysis
Two reviewers assessed eligibility and trial quality and performed data extraction. We analysed the data using RevMan software.

Main results
A total of 14 randomised studies have been included. In a low risk population with a background pregnancy loss of around 2%, a second trimester amniocentesis will increase this risk by another 1%. This difference did not reach statistical significance, but the increase in spontaneous miscarriages following second trimester amniocentesis compared with controls (no amniocentesis) did (2.1% versus 1.3%; relative risk (RR) 1.02 to 2.52). Early amniocentesis is not a safe early alternative to second trimester amniocentesis because of increased pregnancy loss (7.6% versus 5.9%; RR 1.29, 95% CI 1.03 to 1.61) and higher incidence of talipes compared to CVS (1.8% versus 0.2%; RR 6.43, 95% CI 1.68 to 24.64).

Compared with second trimester amniocentesis, transcervical CVS carries a significantly higher risk of pregnancy loss (14.5% versus 11%; RR 1.40, 95% CI 1.09 to 1.81) and spontaneous miscarriage (12.9% versus 9.4%; RR 1.50, 95% CI 1.07 to 2.11). One study compared transabdominal CVS with second trimester amniocentesis and found no significant difference in the total pregnancy loss between the two procedures (6.3% versus 7%). Transcervical CVS is more technically demanding than transabdominal CVS with more failures to obtain sample and more multiple insertions.

Authors' conclusions
Second trimester amniocentesis is safer than transcervical CVS and early amniocentesis. If earlier diagnosis is required, transabdominal CVS is preferable to early amniocentesis or transcervical CVS. In circumstances where transabdominal CVS may be technically difficult the preferred options are transcervical CVS in the first trimester or second trimester amniocentesis.

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PLAIN LANGUAGE SUMMARY

Amniocentesis is safer after 16 weeks' gestation, and chorionic villus sampling is better done through the wall of the womb

Some parents want reassurance that their baby is all right genetically. This involves taking a sample either of the waters surrounding the baby (amniocentesis) or from the placenta (chorionic villus sampling (CVS) then testing it. The review of studies on ways of taking the sample found a small increase in the risk of miscarriage. Amniocentesis done at 16 to 18 weeks was the safest procedure. CVS is done earlier (about 10 to 13 weeks) and taking the sample through the wall of the womb was safer for the baby than through the vagina and cervix.

BACKGROUND

Most women wish to be reassured that their unborn baby is healthy. Inevitably, any screening programme that aims to provide such reassurance will cause anxiety while waiting for the test results. The additional problems are the relatively high risk of 'false positive' screening test (maternal serum screening and ultrasound) and lack of therapeutic options for chromosomal abnormalities. The aim is, therefore, to select screening and diagnostic tests that are accurate and safe and can be done as early in pregnancy as possible to allow the choice of termination of pregnancy.

Ultrasound is the method of choice for detection of anatomical problems (e.g. absent kidneys, spina bifida), but provides no information on the genetic constitution of a fetus. Maternal serum screening, alone or in combination with ultrasound, is often used to identify fetuses at risk of Down's syndrome, but the definitive chromosomal diagnosis can only be made from fetal cells.

Fetal cells suitable for genetic testing could be obtained from maternal blood or preimplantation embryos. However, the former test is still being developed, while the latter requires 'in vitro fertilisation', which is often not feasible. At present, analysing fetal cells from amniotic fluid, placenta (chorionic villus tissue) or fetal blood can only make an accurate prenatal diagnosis .

Second trimester amniocentesis, a needle puncture through the overlying skin into the uterus and amniotic cavity followed by aspiration of amniotic fluid, is traditionally performed around 16 weeks' gestation. Observational data from the 1970s suggested that, at this gestation, relatively large amounts of amniotic fluid (up to 20 ml) could be aspirated without significant technical difficulties. This amount of amniotic fluid was needed to yield a sufficient number of viable fetal cells to minimise the risk of laboratory failure. In 1977 the MRC Canadian Study reported a rate of successful culture of only 82% below 15 weeks compared to 94% at 16 weeks or above. Another disincentive to perform earlier sampling was a belief that aspiration of large amounts of amniotic fluid earlier in gestation would be more likely to cause neonatal orthopaedic and respiratory complications (respiratory distress syndrome) compared with later sampling.

A major disadvantage of second trimester amniocentesis is that a final result is usually available only after 18 weeks' gestation. Such a long waiting period for a diagnosis can be very distressing for couples, particularly when most obstetricians are reluctant to offer a surgical termination late in pregnancy. Alternatively, earlier options include chorionic villus sampling (CVS) and early amniocentesis.

CVS was developed during the 1980s and involves aspiration of placental tissue rather than amniotic fluid. Ultrasound guided aspiration can be performed using either percutaneous transabdominal or the transvaginal/transcervical approach. Currently, the choice of the approach and the choice of instruments tend to be based upon the operator's personal preference (Alfirevic 2002).

There is an understandable desire to perform CVS as early as possible. Technically, this can be done successfully as early as 6 weeks' gestation. However, a few clusters of limb reduction defects have been reported following CVS with a trend toward an increased incidence of these defects when CVS was done before 9 weeks' gestation (for review of the evidence see: Jackson 1993). Subsequent, large epidemiological follow-up studies failed to confirm this association (Froster 1996), but most clinicians delay this procedure until after 10 weeks' gestation.

Early amniocentesis (9 to 14 weeks' gestation), which was introduced in the late 1980s, is technically the same as a 'late' procedure except that less amniotic fluid is removed. Ultrasound needle guidance is considered to be an essential part of the procedure because of the relatively small target area. The presence of two separate membranes (amnion and chorion) until 15 weeks' gestation creates an additional technical difficulty. Only the amniotic (inner) sac should be aspirated, because the outer sac does not contain sufficient numbers of living fetal cells. Sundberg 1995 reviewed observational studies of early amniocentesis and found 12 published series with more than 100 pregnancies per study (5242 pregnancies in total). Unintended pregnancy loss varied between 1.9% and 4.7% and laboratory failure varied between 0% and 20%. The karyotyping success rate may be increased by using filter techniques in which amniotic cells are retained on a filter after aspiration while the rest of the amniotic fluid (cell free) is reinjected into the amniotic cavity (Sundberg 1991).

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OBJECTIVES

The objective of this review is to compare the safety and accuracy of all types of amniocentesis (i.e. early and late) and chorionic villus sampling (e.g. transabdominal, transcervical) for prenatal diagnosis.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised comparisons of late amniocentesis (after 15 weeks' gestation), early amniocentesis (before 15 weeks' gestation) and chorionic villus sampling (either transabdominally or transvaginally) with each other or with no testing have been included. Quasi-randomised studies (e.g. alternate allocation) are excluded.

Types of participants

Pregnant women requesting invasive prenatal diagnostic testing for fetal chromosomal or genetic disorders.

Types of intervention

Second trimester amniocentesis (after 15 completed weeks of gestation).
Early amniocentesis (before 15 completed weeks of gestation (i.e. 14 weeks and 6 days or less).
Transabdominal, transcervical or transvaginal chorionic villus sampling.

Types of outcome measures

All the sought outcomes can be divided into the following groups:
(i) Outcomes related to technical difficulties in sampling:

- non-compliance with allocated procedure;
- sampling failure;
- multiple insertions;
- second test performed.

(ii) Outcomes related to cytogenetic analysis:

- laboratory failure;
- all non-mosaic abnormalities;
- all mosaics (karyotypes with two or more cell lines);
- true mosaics;
- confined mosaics (two or more cell lines present in the placenta but not in the fetus);
- maternal contamination;
- known false positive after birth;
- known false negative after birth;
- reporting time (interval between sampling and result).

(iii) Pregnancy complications:

- vaginal bleeding after test;
- amniotic leakage after test;
- vaginal bleeding after 20 weeks;
- prelabour ruptured membranes less than 28 weeks;
- antenatal hospital admission;
- delivery less than 37 weeks;
- delivery less than 33 weeks.

(iv) Pregnancy outcome:

- all known pregnancy losses (including terminations of pregnancy)
- termination of pregnancy (all);
- spontaneous miscarriage (pregnancy loss before viability - usually 24 weeks of pregnancy);
- spontaneous miscarriage after test (pregnancy loss in women who had the test actually performed);
- perinatal mortality (stillbirths and neonatal deaths in the first week of life);
- stillbirths;
- neonatal death (death in the first week of life);
- all recorded deaths after viability.

(v) Neonatal complications:

- anomalies (all recorded);
- talipes (clubfoot);
- talipes equinovarus (the foot is plantar flexed, inverted and markedly adducted);
- hemangiomas (localised vascular lesions of the skin and subcutaneous tissue);
- limb reduction defects;
- admission to special care baby unit;
- neonatal respiratory distress symptom (defined by authors);
- birthweight less than the 10th centile;
- birthweight less than the 5th centile.

While all the above outcomes have been sought, only those with data appear in the analysis table. The data that were not prespecified by the reviewers, but reported by the authors, have been clearly labelled as such ('not prespecified').

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SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group trials register (March 2003).

The Cochrane Pregnancy and Childbirth Group's trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, The Cochrane CENTRAL Register (The Cochrane Library, Issue 1, 2003) has been searched using the terms 'amniocentesis*ME', 'amniocentes*', 'chorionic-villi-sampling*ME' and 'chorion*vill*'.

METHODS OF THE REVIEW

All trials have been assessed for methodological quality using the criteria in the Cochrane Handbook (Clarke 2000), with a grade allocated to each trial on the basis of allocation concealment. Allocation concealment has been scored as A (adequate) for telephone randomisation and the use of consecutively numbered sealed envelopes; B (unclear) for trials where randomisation is not clearly described or prone to bias (e.g. open cards, toss of a coin). quasi-randomised designs (C), such as alternate allocation and the use of record numbers, have been excluded. No other formal or informal qualitative analysis was planned as there were no planned exclusions based on quality.

The data were extracted onto 'hard-copy' data sheets, entered onto the RevMan computer software (RevMan 2000), checked for accuracy by another co-reviewer, and analysed using the RevMan software. The data were extracted by allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an 'intention-to-treat' analysis. Where appropriate, the dominators were adjusted to include only those women who could have had the outcome. Women, who were randomised and subsequently either excluded or lost to follow up, were assumed to have had 'no event' in the outcome analyses and have not been included in the denominator data.

We calculated a weighted estimate of relative risk for each outcome. Most of the outcomes were uncommon, therefore, odds ratios were similar to relative risks for most analyses. We tested for heterogeneity between the trials using a standard Chi-squared test. In the absence of heterogeneity, the results were pooled using a fixed effects model. In the presence of significant heterogeneity, we planned a subgroup analysis based on the quality of allocation concealment (A (adequate) versus B (unclear)), various modifications of the techniques used (e.g. filter technique for early amniocentesis, biopsy forceps for chorionic villus sampling) and timing of the procedure. When significant ($p < 0.05$), unexplained heterogeneity was found we used more conservative random effects model.

The data that were not prespecified were collected, reported and clearly labelled as such ('not prespecified'). The possibility that these outcomes are often reported only if they reach statistical significance after a 'post-hoc' data dredging had to be borne in mind. In order to minimise the risk of biased reporting of 'soft outcomes', particularly when clinicians are not blinded to the allocation as is the case in evaluation of invasive procedures, we based our conclusions on the prespecified outcomes.

DESCRIPTION OF STUDIES

(1) SECOND TRIMESTER AMNIOCENTESIS VERSUS CONTROL (NO TESTING)

Tabor 1986 was a multicentre study that included low risk Danish women aged 25 to 34 years between 1980 and 1984. Seventy three per cent (4606/6305) of all eligible women took part. Five doctors, 54% of them by the most experienced operator, performed all procedures. Amniocentesis was performed with a full bladder using a linear 3.5 MHz transducer with a channel guide for the needle in the middle of the probe. A 20-gauge needle (0.9 mm outer diameter) was passed through the channel creating an angle of 90º between the needle and the linear probe.

(2) EARLY VERSUS SECOND TRIMESTER AMNIOCENTESIS

CEMAT 1998 was a multicentre trial carried out under the auspices of the Medical Research Council of Canada. Both early and mid-trimester amniocentesis were done with a free hand technique using a 22 gauge needle under continuous ultrasound guidance. Each operator had done at least 30 early amniocenteses before participating. Eleven millilitres of amniotic fluid were aspirated during early amniocentesis and 20 ml during second trimester am-

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niocentesis. No more than two attempts were carried out on the same day.

(3) CHORIONIC VILLUS SAMPLING (CVS) VERSUS AMNIOCENTESIS

In the Canada 1992 trial, women allocated to have CVS had the transcervical procedure, while in the MRC 1991 trial CVS was carried out in whatever was deemed suitable by the obstetrician (72% by the transcervical and 28% by the transabdominal approach). In the MRC 1991 trial of the 1592 women randomised to amniocentesis with follow-up data, 1417 (89%) are known to have had an amniocentesis. In the Finnish arm of the MRC trial, all CVS procedures were carried out by transcervical approach. In the Canada 1992 trial, a pre-entry ultrasound could not be performed in all centres. As a consequence, 14.2% of women with non-viable, multiple or advanced pregnancies were subsequently excluded, after randomisation, from some analyses. The Denmark 1992 trial was designed as a three-way randomisation of women classified as low genetic risk (transabdominal CVS versus transcervical CVS versus amniocentesis). Borrell 1999 randomised women to transcervical CVS (9 to 13 weeks) or amniocentesis (15 to 18 weeks). This trial was stopped prematurely when second trimester biochemistry screening was introduced.

(4) CVS TRIALS

USNICHD 1992 was a large multicentre collaborative study under the auspices of the US National Institute of Child Health. In total 3999 women were randomised. Transcervical CVS were performed with a 1.5 mm plastic catheter and abdominal procedure with a spinal needle (18 to 22 gauge). Brambati 1991 randomised 78.6% of eligible women referred for genetic counselling at 6 to 8 weeks' gestation. A single operator performed all procedures (both transabdominal and transcervical). Transcervical CVS was performed using a cannula with an outer diameter of 1.45 mm and the transabdominal procedure was done with a spinal needle (1.1 mm outer diameter). A maximum of two passes were allowed in one sampling session. Bovicelli 1986 reported the results of his study in a letter to the Lancet. Transcervical CVS was performed using a flexible 16 gauge silver cannula. The transabdominal procedure was carried out with a double needle system with an 18-gauge guide needle and an aspiration needle of gauge 21. Tomassini 1988 was a single centre trial from Varese (Italy) where 44 women were assigned to transcervical or transabdominal procedure by "random selection". Denmark 1992 randomised women at high genetic risk to either transabdominal or transcervical CVS.

(5) EARLY AMNIOCENTESIS VERSUS TRANSABDOMINAL CVS

Four completed randomised controlled trials have been identified so far. The trial from Uppsala, Sweden by Cederholm and Axelsson (Uppsala 1997) randomised 86 women to early amniocentesis or CVS. The data for 86 randomised women are 'lumped together' with the data for 235 women who selected the procedure 'by choice'. We are therefore, at present, unable to include the randomised data set in the 'intention to treat' analysis. Interestingly, all included studies (King's 1996; Copenhagen l997; Leiden 1998) were stopped before the intended sample size was reached. King's 1996 aimed to recruit 4400 women. However, by March 1993 recruitment was collapsing because of "...widespread publicity that CVS can cause fetal limb abnormalities and is associated with a high risk of spontaneous abortion, and that non-invasive screening by ultrasonography and maternal serum biochemistry can provide sufficient reassurance to avoid invasive testing". The final report of the trial published in 'Fetal Diagnosis and Therapy' in 1996 stated that 840 women had early amniocentesis (278 after randomisation) and 652 women had CVS (277 after randomisation). Leiden 1998 was stopped after the interim data-analysis that was prompted by the first report of the King's 1996 trial in the Lancet in 1994. Copenhagen l997 aimed to recruit more than 3000 women in each group. The combination of slow recruitment and observed clustering of talipes equinovarus cases in the early amniocentesis group prompted the trialists to stop the trial early.

In the King's 1996 and the Leiden 1998 trials, recruited women were given the choice between early amniocentesis, transabdominal CVS or randomisation. In the King's 1996 trial, 37% opted for randomisation (555/1492), 38% for early amniocentesis (562/1492), and 25% for CVS (375/1492). In the Leiden 1998 trial, 55% of women were randomised (115/210), 33% chose early amniocentesis and 12% chose CVS.

The procedure for transabdominal CVS was similar in three included trials. King's 1996 and Leiden 1998 used a 20-gauge needle. The tip of the needle was moved 5 to 10 times while applying negative pressure by manual aspiration through a 20 ml syringe. In the Copenhagen l997 trial, a double-needle technique was used with a guide needle of 1.2 mm (18 gauge) and an aspiration needle of 0.8 mm (21 gauge).

There were important differences in the early amniocentesis technique used in Copenhagen l997 compared to King's 1996 and Leiden 1998. In Copenhagen l997, the filter system was used which allowed re-injection of the majority of the entire aspirated volume back into the amniotic cavity. Early amniocentesis in the King's 1996 and the Leiden 1998 trials was done by straightforward aspiration of 11 ml of amniotic fluid of which the first 1 ml was discarded. King's 1996 and Leiden 1998 used a 20-gauge and a 22-gauge needle, respectively.

(6) USE OF ULTRASOUND

Nolan 1981 compared ultrasound directed taps with taps without benefit of ultrasound scans. Amniocenteses in the 'experimental' group were not 'ultrasound-guided' in the true meaning of this term. Today, the term 'ultrasound guided procedure' is used to describe needle insertion under simultaneous ultrasound guidance using either 'free hand' technique or a needle guide mounted on the ultrasound probe. In the study by Nolan 1981, scans were performed before the procedure with the main aim to inform the

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operator on the placental position. The physician who had benefit of the ultrasound report made attempts to avoid the placenta. In the control group, the physician selected 'what was considered the best site for introduction of the needle'.

STUDIES AWAITING ASSESSMENT

Apart from the Uppsala 1997 trial described above, three other trials have been reported only as abstracts with incomplete information for critical appraisal and data extraction (Horovitz 1994; Ketupanya 1997; Fischer 2000b). Horovitz 1994 compared transabdominal CVS with amniocentesis in 56 multiple pregnancies. It is not clear from the abstract whether this was a randomised study or not. Ketupanya 1997 compared early amniocentesis (12 to 14 weeks) performed with or without amniofiltration technique (29 women in each group). The culture failure was 13.8% in the amniofiltration group compared with 10.3% in the control group. However, the method of randomisation was not described. Fischer 2000b evaluated the effect of leg rubbing by the assisting nurse during genetic amniocentesis with regard to pain perception and patient anxiety. Two hundred women were randomised using sealed envelopes, but the number of women per randomised group was not stated in the abstract.

METHODOLOGICAL QUALITY

(1) SECOND TRIMESTER AMNIOCENTESIS VERSUS CONTROL

The trial by Tabor 1986 is of high quality and remains a gold standard in the field of fetal medicine. For the majority of women, a secretary using a table of random numbers did randomisation. Some women were randomised using sequentially numbered sealed envelopes. The compliance with allocated procedure was 98.3% in the study group. Only 22 women in the control group had an amniocentesis (1%). Most procedures were performed at or beyond 16 weeks gestation; 17% of amniocenteses were performed at 15 weeks' gestation and 3.6% at earlier gestations.

(2) EARLY VERSUS SECOND TRIMESTER AMNIOCENTESIS

Given the size of the study (n = 4374), CEMAT 1998 had a very high follow-up rate (99.2%). In the early amniocentesis group, 87.8% of the procedures were performed before 13+0 weeks of gestation. Only 3.5% of women had 'early amniocentesis' after 14+0 weeks. Most mid-trimester amniocenteses were performed between 15+0 and 15+6 weeks (68.8%) with 10.3% before 15 weeks and 0.8% before 14 weeks.

(3) CVS VERSUS SECOND TRIMESTER AMNIOCENTESIS

Randomisation was organised by telephone in all four trials (MRC 1991; Canada 1992; Denmark 1992; Borrell 1999), apart from the Finnish arm of the MRC trial MRC (Finland) 1993 where sequentially numbered sealed envelopes were used. The outcome of pregnancy is reported for all women in the Canada 1992 trial, 99% of women in the MRC 1991 trial, and 93% in the Denmark 1992 trial.

Denmark 1992 had quite a complex three-arm design with the amniocentesis arm performed only in 'low risk' women. Three thousand three hundred and two low risk women took part in the direct comparison between transabdominal CVS (n = 1076), transcervical CVS (n = 1068) and amniocentesis (n = 1158) and a further 897 in the comparison between two CVS techniques (493 high risk and 404 low risk women). Two reports from this trial were published after the randomisation was stopped in November 1990 with a marked difference in the total number of randomised women (3407 in the report published in Ultrasound in Obstetrics and gynaecology and 4199 women in the Lancet). For the comparison between CVS and amniocentesis only the data on total pregnancy loss have been reported according to 'intention to treat'. The type of pregnancy loss has been reported only for subgroups of women who 'completed the study' (93.2%).

There was a significant 'drop out' rate in Borrell 1999 (33.5%) due to pre-procedure miscarriages and failure to attend allocated procedure. Also, 43 women in the CVS group and seven women in the amniocentesis groups changed the allocated procedure and were 'excluded' from the final analysis. This resulted in an uneven number of women for whom the outcome of pregnancy was reported (314 with CVS and 358 with amniocentesis). A large and uneven 'drop out' rate may be a source of significant bias and data from this trial have to be interpreted with caution.

None of the trials was designed to assess the diagnostic accuracy of prenatal testing adequately. A complete follow up of all randomised pregnancies with cytogenetic confirmation would be necessary to determine the accurate number of false positive and false negative results.

Due to the different timing of the tested procedures adequate blinding of women, investigators and outcome assessors was virtually impossible. However, the type of main outcome measures makes significant bias unlikely.

(4) CVS TRIALS

USNICHD 1992 included only women in whom placental position 'allowed' both transabdominal and transcervical approach. Around 70% of potentially eligible women were excluded because of placental position, thus reducing external validity (generalisibility) of this study. The description of the randomisation procedure has not been included in the trial reports of USNICHD 1992. The outcome data were not presented for women in whom sampling was not attempted (3.2%). For the majority of important clinical outcomes including type of pregnancy loss, 'intention to treat' analysis is not possible because the data were presented only for women with genetically normal pregnancies (91.5%).

Brambati 1991 used telephone randomisation and 'excluded' 38 women after randomisation (3.2%) because of non-viable pregnancies at the time of sampling.

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A full assessment of the trial by Bovicelli 1986 is limited, because the study is reported only as a brief letter to the Lancet. Women were "randomly assigned" to transcervical or transvaginal CVS.

(5) EARLY AMNIOCENTESIS VERSUS CVS

According to our prespecified criteria, Copenhagen l997 and Leiden 1998 used adequate concealment of allocation, i.e. central telephone randomisation and consecutively numbered sealed envelopes, respectively. The randomisation method used in King's 1996 (sealed envelopes that are not numbered sequentially) is known to be a potential source of biased allocation. Sequential numbering aims to prevent manipulation of the schedule of random assignment by those recruiting participants to the trial. In the King's 1996 trial, potentially eligible women were excluded because of increased fetal nuchal translucency thickness (an anatomical marker of chromosomal abnormality). Again, as in the above comparisons adequate blinding of women, investigators and outcome assessors was not possible. Analysis on all randomised women ('intention to treat') was available for all principal measures of outcome. The percentage of women who received the allocated intervention varied significantly ranging from 100% in the King's 1996 trial and 95% (1103/1160) in the Copenhagen l997 trial to 90% (104/115) in the Leiden 1998 trial. Unfortunately, in the Leiden 1998 trial the number of women who did not receive the intervention according to allocation was not evenly distributed between the groups. In the early amniocentesis group, all 55 women had amniocentesis (one was done in the midtrimester). In the other group seven women randomised to transabdominal CVS received early amniocentesis and three transcervical CVS. Two women randomised to CVS, who in fact had early amniocentes, is suffered early pregnancy loss, thus introducing considerable bias in an 'intention-to-treat' analysis.

(6) ULTRASOUND ASSISTED AMNIOCENTESIS

It was not possible to ascertain the method of randomisation in the study by Nolan 1981. Judging from the number of randomised women (112 versus 111) and the placental position, the groups appear to be well balanced. Ultrasound was performed in both groups, but revealed only in the experimental group. A scan report was, however, revealed in 14 cases in the control group (12.6%). The type of ultrasound-assisted amniocentesis used in this trial is nowadays considered obsolete.

One of the common criticisms of Cochrane Reviews with included trials that span over several decades is the lack of relevance of earlier studies on the current clinical practice. One of our peer-reviewers commented that earlier studies like MRC 1991were undertaken when CVS was being developed as a technique, i.e. practitioners were on their learning curve. This is certainly one of the possible sources of heterogeneity. However, in everyday practice women will always be exposed to operators with varying degrees of skills and experience and data from very skilled and experienced operators have also limited external validity (generalisibility).

RESULTS

(1) SECOND TRIMESTER AMNIOCENTESIS VERSUS CONTROL

The study by Tabor 1986 provides the best estimate of an excess pregnancy loss in low-risk women caused by amniocentesis. An increase of 1% in total pregnancy loss (3.2% versus 2.2%) does not reach statistical significance, but an increase in spontaneous miscarriages of 0.8% (2.1% versus 1.3%) is statistically significant (relative risk (RR) 1.6, 95% confidence interval (CI) 1.02 to 2.52). The 95% confidence interval for risk difference ranges from 0% to 2% for both outcomes. There was no difference in vaginal bleeding between the two groups, but amniotic fluid leakage was more common after amniocentesis (1.7% versus 0.4%; RR 3.9, 95% CI 1.9 to 7.8)

(2) EARLY VERSUS SECOND TRIMESTER AMNIOCENTESIS

Compared to an early amniocentesis, mid-trimester procedure is safer and technically less demanding. Total pregnancy loss after early amniocentesis was 7.6% compared with 5.9% after mid-trimester procedure (RR 1.29, 95% CI 1.03 to 1.61). The number of congenital anomalies was also significantly increased in the early amniocentesis group (4.6% versus 2.7%), in particular the number of babies with talipes equinovarus was higher (1.3% versus 0.09%). If one restricts the analysis to women who actually had early amniocentesis ('on treatment' analysis) the risk of talipes is even higher (1.6%). Early amniocentesis required multiple needle insertions in 4.7% of procedures compared with only 1.7% for mid-trimester amniocentesis. Early amniocentesis was also more demanding for cytogeneticists with 1.8% laboratory failures after early procedure and only 0.2% after mid-trimester amniocentesis. There were three known false negative cytogenetic results in the early amniocentesis group and none after mid-trimester amniocentesis. Two reports resulted in the incorrect information with regard to the sex chromosomes, and in one case a very subtle chromosome abnormality at the terminal end of chromosome one was missed and detected postnatally. Interestingly, a false positive rate was reported to be 3.6% for early amniocentesis and 8% for mid-trimester amniocentesis. The actual numbers could not be extracted from the trial reports, so this outcome is not shown in the outcome table. It appears that most of these false positive results were so called 'pseudomosaics' not reported to the physicians.

(3) TRANSABDOMINAL OR TRANSCERVICAL CVS VERSUS SECOND TRIMESTER AMNIOCENTESIS

3.1. Transcervical CVS versus second trimester amniocentesis

Four trials compared transcervical CVS with second trimester amniocentesis (Canada 1992; Denmark 1992; MRC (Finland) 1993; Borrell 1999). Total pregnancy loss was consistently higher after transcervical CVS (14.5% versus 11%). In the transcervical CVS group the total pregnancy loss varied from 9.4% in the MRC (Finland) 1993 trial to 19.5% in the Borrell 1999 trial. Interestingly,

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the statistical test for heterogeneity was significant despite the fact that the results look quite similar in terms of the size and direction of the observed differences in total pregnancy loss. However, overall difference is statistically significant even when more conservative random effect model is used for analysis. The sensitivity analysis suggests that the heterogeneity is caused by the differences between the two largest trials (Canada 1992; Denmark 1992). The increase in pregnancy loss after transcervical CVS in the Denmark 1992 trial was statistically significant (95% CI 1.3 to 2.2), but not in the Canada 1992 trial (95% CI 0.9 to 1.3). Unsurprisingly, spontaneous miscarriages were the main contributor to the pregnancy loss in all four trials.

3.2. TransabdominalCVS versus second trimester amniocentesis

A subgroup of Denmark 1992 compared transabdominal CVS with second trimester amniocentesis and found no significant difference in the total pregnancy loss between the two procedures (6.3% versus 7%).

3.3. CVS by any route versus second trimester amniocentesis

Two trials presented data that allowed the comparison between CVS performed by any route and mid-trimester amniocentesis (MRC 1991; Denmark 1992). Overall loss was higher after CVS (11% versus 8.2%) and this difference was statistically significant (RR 1.43, 95% CI 1.22 to 1.67). Again, an increase in spontaneous miscarriages after CVS was the main contributing factor (RR 1.51, 95% CI 1.23 to 1.85).

Overall, the test had to be repeated more commonly after transcervical CVS compared with second trimester amniocentesis (6.3% versus 0.2%). Also, there were more problems in analysing placental tissue obtained from CVS compared with amniotic fluid analysis. In the transcervical CVS group, laboratory failure occurred in 1.7% cases compared with only 0.07% after amniocentesis, there were more cytogenetic abnormalities confined only to placenta (2.3% versus 0.4%) and more false positive and false negative results (2.2% versus 0.2% and 0.3% versus 0%, respectively). However, cytogenetic results presented here should be interpreted with caution. They probably underestimate the true incidence of inaccurate results in both the CVS and amniocentesis groups because the majority of fetal losses were not karyotyped post-mortem, either because of technical difficulties or concerns about medico-legal implications. The lack of complete cytogenetic follow up in all trials makes unbiased analysis on all randomized women impossible.

Complications were uncommon after both procedures and there were no reports that these were ever life-threatening. Vaginal bleeding following the procedure was much more common after transcervical CVS, although there was no difference in the incidence of vaginal bleeding later in pregnancy. There was no significant difference in the amniotic fluid leakage following the procedure and prelabour spontaneous rupture of membranes before 28 weeks in MRC 1991, but this observation should be interpreted cautiously because data on ruptured membranes are missing for large numbers of women. Interestingly, one participating centre (MRC (Finland) 1993) reported significant increase in ruptured membranes after transcervical CVS (4.1% versus 0.8%). No differential effect was detected on antenatal admission to hospital.

In the sub-project of the Canada 1992 trial, Spencer and Cox (Spencer 1987; Spencer 1988) and Robinson (Robinson 1988) compared the psychological effects of transcervical CVS and amniocentesis. In mid-pregnancy, women allocated to amniocentesis were more anxious, and felt less attachment to their babies, although by 22 weeks these differences seemed to have disappeared. (Data are not available in a form suitable for inclusion in a meta-analysis.) Nevertheless, at 22 weeks there was a suggestion of a persistent differential effect manifested in a decreased desire for another child associated with amniocentesis (7/26 in the CVS group compared with 13/25 after amniocentesis).

Possible link between CVS, amniocentesis and congenital anomalies could not be explored fully because of incomplete reporting and relatively small number of participants. There have been several reports in the past suggesting the presence of congenital anomalies (limb deformities in particular) in infants exposed to CVS in the first trimester. The available data from included randomised trials do not support this observation. However, it must be remembered that the relationship may be gestation-dependent. The majority of procedures were carried out after 9 weeks' gestation and therefore do not address the possibility that CVS carried out very early in pregnancy may increase the risk of congenital abnormalities.

(4) TRANSABDOMINAL VERSUS TRANSCERVICAL CVS

Compared with transabdominal CVS, total pregnancy loss and spontaneous miscarriages were higher after transcervical CVS (9% versus 7.4% and 7.9% versus 4.5%, respectively), but this was due to the excess loss in the transcervical arm of the Denmark 1992 trial (12.4% versus 7.4% and 8.2% versus 3%). Total pregnancy loss and miscarriage rate in four other trials (Bovicelli 1986; Tomassini 1988; Brambati 1991; USNICHD 1992) were almost identical in both groups. Because of these differences the tests for heterogeneity for these two outcomes were statistically significant ($p = 0.006$ and $p = 0.01$). When the fixed effect model is used to summarise the results for these two outcomes, transabdominal CVS is associated with a significant reduction in total pregnancy loss (RR 1.23, 5% CI 1.06 to 1.42) and spontaneous miscarriage (RR 1.75, 95% CI 1.33 to 2.29). However, in the presence of heterogeneity it is prudent to apply a more conservative random effect model. When we applied this statistical model, the differences in pregnancy loss and miscarriage between transabdominal and transcervical CVS were not statistically significant any more.

Congenital anomalies were reported only in two studies (Brambati 1991; Denmark 1992;) but the numbers are too small for meaningful comparisons.

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Transcervical CVS was more likely to 'fail' (2% versus 1.1%) although there was a disproportionate contribution of the data from USNICHD 1992 (weight 91%). Transcervical CVS appears to be more technically demanding requiring more multiple insertions (11.2% versus 4.1%) and causing more vaginal bleeding (10% versus 1.6%). As far as cytogenetic analysis is concerned both procedures are comparable.

(5) EARLY AMNIOCENTESIS (EA) VERSUS TRANSABDOMINAL CVS

Combined total pregnancy loss in the EA group was 6.3% compared with 5% in the CVS group (RR 1.25, 95% CI 0.86 to 1.84). There were more spontaneous miscarriages after EA (4.5% versus 2.3%, RR 1.93, 95% CI 1.15 to 3.24). The increase in spontaneous miscarriages following EA in the subgroup of women who had a procedure remained statistically significant (4% versus 2.1%, RR 1.91, 95% CI 1.11 to 3.31).

There was no difference in the overall incidence of anomalies in the newborn infants (RR 1.21, 95% CI 0.76 to 1.92). Interestingly, inter-study heterogeneity was significant for this outcome with no obvious explanation for the observed differences between Copenhagen l997 and Leiden 1998. The trialists have specifically highlighted two types of anomalies: talipes equinovarus and haemangiomas. The incidence of talipes in the EA group was 1.8% compared with 0.2% in the CVS group (RR 6.43, 95% CI 1.68 to 24.64).

An increased number of haemangiomas after CVS seen in Leiden 1998 has not been seen in the other two studies (RR 0.42, 95% CI 0.13 to 1.36). Only the Leiden Trial reported long-term follow up of randomised infants, and none of them had abnormal results on the Dutch version of the Denver Developmental Screening Test when visited at home between 6 and 9 months of age.

Transabdominal CVS appears to be more technically demanding with more technical difficulties during the procedure, i.e. sampling failure, multiple insertions and need for second test. However, the overall incidence of these complications was low. There were no statistically significant differences in the rate of laboratory failures or number of women with various chromosomal abnormalities. However, in the three trials there were only 33 women with abnormal karyotype (1.8%) that made any meaningful analysis difficult. In the Copenhagen l997, the EA samples required a mean of 9.5 days (range 5 to 19) for culturing compared to 6.1 days (range 4 to 14) for the CVS samples. In the Leiden 1998 trial, the mean culture time in the EA group was 13.8 days for the Amniomax culture and 15.6 for the Chang culture compared to eight days in the CVS group. These results were not pooled because they were not normally distributed.

(6) ULTRASOUND GUIDED AMNIOCENTESIS

The trial by Nolan 1981evaluated the type of ultrasound assisted procedure that is nowadays considered obsolete i.e. this was not an ultrasound-guided procedure in the true meaning of this term. There were no differences in the reported outcomes, but the study was too small to assess the true impact of the placental localisation by ultrasound before the needle insertion.

DISCUSSION

The best estimate of an 'excess' risk after second trimester amniocentesis comes from Tabor 1986. In a low risk population with a background pregnancy loss of around 2%, a mid-trimester amniocentesis will increase this risk by another 1%. Despite relatively large numbers of randomised women (4606) in Tabor 1986, such an increase in total pregnancy loss did not reach statistical difference with confidence interval from almost 0 to 2%. How robust are these figures and should they be used for routine counselling? It is unlikely that a trial of similar size and quality will ever be repeated. In the absence of other randomised data, therefore, any written or oral information for women considering second trimester amniocentesis should include the data from Tabor 1986.

The benefits of earlier diagnosis of fetal genetic abnormalities by chorionic villus sampling (CVS) or early amniocentesis must be set against higher risks of pregnancy loss and diagnostic inaccuracies of these tests when compared with second trimester amniocentesis. The question whether the risks of early procedures disappear in the hands of skilled operators remains one of the main controversies of fetal medicine. In most included trials, the operators were required to perform at least 20 successful early procedures in order to participate and some performed thousands successfully. Undoubtedly, the experience between operators varied. There was, nevertheless, no clear evidence that performance improved over the course of randomised trials (MRC 1991). It is possible that very skilled operators could abolish the observed difference in pregnancy loss between early and later procedures. However, it is difficult to see how such 'experts' can produce local data that would prove to their patients that, in their hands, early procedures are equally safe as second trimester amniocentesis. Such data would have to include thousands of women with complete information on the outcome of pregnancy (not just for several weeks after the procedure) with an adequate 'control' group.

Women who request early diagnostic procedures (e.g. because of religious or personal prohibitions on later pregnancy termination, or because of a very high risk of fetal abnormalities), should be counselled about the relative risks of the various options. Concern about the safety and diagnostic accuracy of the first trimester CVS has led some clinicians to advocate early amniocentesis. Somewhat unexpectedly, the preliminary data from the King's 1996 and from the Leiden 1998 trials suggested an important increase in pregnancy loss following early amniocentesis both before and after fetal viability. However, pooled data from the final reports of these two trials and Copenhagen l997 are not so conclusive. Although the increase in spontaneous miscarriages after early amniocentesis remains statistically significant, the difference in total pregnancy

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loss is not (6.3% versus 5%, relative risk (RR) 1.25, 95% confidence interval (CI) 0.86 to 1.84). In order to test the hypothesis that the total pregnancy loss after early amniocentesis is, indeed, 1.3% higher compared with CVS, around 12,000 women would need to be recruited (power 80%, confidence level 95%).

As far as CVS is concerned, transabdominal CVS appears to be safer than the transcervical route. However, this observation is heavily influenced by the data from Denmark 1992. Increase in pregnancy loss following transcervical procedure has not been replicated in four other direct comparisons between transcervical and transabdominal procedures (Bovicelli 1986; Tomassini 1988; Brambati 1991; USNICHD 1992). Transcervical approach does require multiple insertions more often and causes vaginal bleeding in approximately 10% of cases. The sub-group analysis from Denmark 1992 showed no differential effect on the pregnancy loss between transabdominal CVS and mid-trimester amniocentesis. It would be reassuring if the results achieved by Smidt-Jensen and colleagues could be replicated by other centres (71% of all procedures in the Denmark 1992 trial were performed by Smidt-Jensen himself).

The question about diagnostic accuracy of prenatal testing remains unanswered and our hypothesis that both CVS and amniocentesis are equally accurate remains untested because of incomplete follow-up. Having said that, we do acknowledge the ethical and potential medico-legal problems in trying to obtain adequate cytogenetic follow-up on all randomised women. A higher incidence of abnormal karyotypes is to be expected in the CVS group because of possible spontaneous loss of pregnancies with abnormal karyotype that occur between randomisation and a mid-trimester amniocentesis group. With this proviso, the available data suggest that accurate diagnosis is more likely following second trimester amniocentesis. Abnormalities confined to placenta (placental mosaics) pose particular problem for women who opt for CVS. Although the absolute numbers are small, both false positive and false negative results have such a devastating effect that observed differences should not be ignored.

Another unresolved issue is the possibility of a causal relationship between some fetal abnormalities and invasive procedures in early pregnancy. The difference in the incidence of congenital anomalies observed after early amniocentesis and CVS was not statistically significant (4.4% versus 3.8%). An increased incidence of talipes equinovarus after early amniocentesis has been specifically highlighted (15/836 in the early amniocentesis group compared to 2/851 in the CVS group, RR 6.43, 95% CI 1.68 to 24.64). The 1.8% incidence of talipes following early amniocentesis was remarkably consistent in all three trials despite the fact that aspirated amniotic fluid was re-injected back to the uterus in Copenhagen l997. A detailed analysis of the data from this study suggests that there was an association between the risk of talipes and sampling at the earliest gestational age. Early amniocentesis enthusiasts may argue that the possibility of ascertainment bias needs to be borne in mind when the data from unblinded trials are interpreted. It is virtually impossible to blind women and clinicians to the type of invasive prenatal test actually carried out because the type and handling of the tissue is distinctly different following early amniocentesis compared with CVS. Under those circumstances, it is possible to 'look harder' for certain type of anomalies, i.e. talipes, in babies known to have early amniocentesis and not record them when causation is unlikely (after CVS). In our view the above data are compelling and every effort should be made that amniocentesis is not performed before 15 weeks' gestation.

Observational data have suggested an increased incidence of haemangiomas in infants born following chorionic villus sampling (Burton 1995). Like a risk of oromandibular limb hypogenesis and isolated limb disruption defects following CVS (NICHHD 1993), this association remains controversial. Plausible mechanisms include transient fetal hypoperfusion secondary to bleeding into the sampling site and/or the release of vasoactive substances from the placenta causing vasoconstriction or haemorrhage in the fetus. It is reassuring that there were no reported oromandibular limb hypoplasias in the three trials, which may reflect the fact that all procedures were done after 9 weeks' gestation. Also, a small increase in the haemangiomas after CVS (1% versus 0.4%) was not statistically significant.

AUTHORS' CONCLUSIONS

Implications for practice

Parents considering prenatal diagnosis must be fully informed about the risks and benefits of the alternative procedures before they make a choice. Second trimester amniocentesis is safer than transcervical chorion villus sampling (CVS) or early amniocentesis and benefits of earlier diagnosis must be set against its greater risks. If earlier diagnosis is required, transabdominal CVS is preferable to early amniocentesis or transcervical CVS. In circumstances where transabdominal CVS may be technically difficult, the preferred options are transcervical CVS in the first trimester or second trimester amniocentesis.

Implications for research

New methods of prenatal diagnosis should be rigorously evaluated before deciding whether they should be introduced into clinical practice. Any future trialists, who aim to assess safety and accuracy of new methods, should consider using amniocentesis performed after 15 weeks as a control. Measures of outcome must include total pregnancy loss (antenatal and neonatal), detailed description of anomalies, diagnostic accuracy, and women's views of the alternative procedures. Ascertainment bias should be reduced as much as possible. (Neonatal assessors should be blinded to the allocated procedure.)

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POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Borrell 1999
Methods	Random telephone allocation using a table of random numbers.
Participants	Women requesting fetal karyotyping on the basis of advanced maternal age prior to 12th completed week. Exclusions included: multiple pregnancies, menstrual gestational age greater than 11 plus 6 weeks, or an indication for cytogenetic analysis other than advanced maternal age. 503 randomised to CVS group and 508 to the amniocentesis group.
Interventions	Transcervical CVS performed from 9th to 13th week of pregnancy using round tipped curved steel forceps after initial ultrasound scan. Procedure performed under direct ultrasound guidance. Amniocentesis was performed from the 15th to 18th week of pregnancy using 22 G needle under direct ultrasound guidance.
Outcomes	Diagnostic success and fetal loss rate.

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Characteristics of included studies (*Continued*)

Notes	Trial prematurely discontinued when second trimester serum biochemistry screening was introduced. Lost to follow up was 33.5% (339/1011).
Allocation concealment	A – Adequate

Study	**Bovicelli 1986**
Methods	Randomly assigned - method not described.
Participants	Inclusion criteria: gestational age 9 to 13 weeks, viable embryo with an intact sac.
Interventions	Transcervical performed under direct ultrasound guidance. 16 G cannula passed via the cervix to chorion frondosum and villi aspirated with suction. Transabdominal CVS was performed using continuous ultrasound guidance and an 18 G needle passed to reach the border of the chorion frondosum. A 20 G needle was then passed through this first needle and villi aspirated.
Outcomes	Technical difficulty, fetal loss rate and speed of procedure.
Notes	
Allocation concealment	B – Unclear

Study	**Brambati 1991**
Methods	Randomisation by telephone.
Participants	Women aged between 19 and 48 years attending for first trimester fetal diagnosis of genetic diseases. Indications for fetal diagnosis included chromosomal aberration, sex determination for X linked diseases, metabolic diseases, DNA analysis for haemoglobinopathies and haemophilias. Gestational age between 8 and 12 weeks. Exclusion criteria: multiple pregnancy, vaginal infection, pending cerclage, vaginal bleeding and placenta inaccessible either via cervical canal or via abdominal wall.
Interventions	Transcervical and transabdominal CVS were performed using a 20 G needle and no more than two cannula or needle insertions used in one session.
Outcomes	Technical difficulty and quantity of tissue obtained along with pregnancy outcome.
Notes	
Allocation concealment	A – Adequate

Study	**CEMAT 1998**
Methods	Telephone randomisation. Random allocation list computer generated.
Participants	Participants in 12 centres. Inclusion criteria: prenatal diagnosis due to maternal age, newborn baby with a chromosomal abnormality, viable fetus with a crown rump length of 20-50 mm on ultrasound and consent to enter the trial. Exclusion criteria were: previous open neural tube defect detected by prenatal diagnosis, molecular or biochemical disorders found on prenatal tests, non viable fetus, multiple pregnancy, failed CVS, fetal anomaly or oligohydramnios, active vaginal bleeding, alloimmunised patient, recurrent unexplained miscarriages, intra uterine contraceptive device in utero, previous CEMAT trial randomisation.
Interventions	Both groups underwent detailed fetal anomaly ultrasound examination at 15 and 20 weeks. Early amniocentesis group had amnio performed between 11 and 12 gestational weeks and mid trimester between 15 and 16 weeks. All amniocentesis were performed under direct ultrasound guidance using 22 gauge, 9 cm or 14 cm needles.
Outcomes	Pregnancy outcome, congenital anomalies, abnormal karyotype and technical difficulty.
Notes	
Allocation concealment	A – Adequate

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Characteristics of included studies (*Continued*)

Study	**Canada 1992**
Methods	Central randomisation (?by telephone) and stratified according to age 35-38, >= 39 and centre.
Participants	Participants from 12 centres in Canada. Eligible women - aged 35 years or older at time of delivery or those referred for fetal chromosome analysis. Less than 12 weeks gestation. Viable singleton intrauterine pregnancy confirmed by ultrasound. Women excluded if dead or disorganized embryo, multiple pregnancy, Rh isoimmunisation, untreated cervical infection or gestation greater than 12 weeks. 2787 women randomised. 396 ineligible following randomisation. 1391 randomised to CVS (200 ineligible), 1396 randomised to amniocentesis (196 ineligible).
Interventions	Transcervical versus second trimester amniocentesis.
Outcomes	Technical difficulties, abnormal karyotype, pregnancy complications, perinatal loss, neonatal complications and cytogenetic accuracy.
Notes	
Allocation concealment	A – Adequate

Study	**Copenhagen l997**
Methods	Central telephone randomisation.
Participants	Women aged 35 years or over with risk factors including Down's syndrome in the family, a previous child with chromosomal abnormality, a parent who is a carrier of chromosomal abnormalities, history of a diseased or dead offspring, recurrent miscarriage, environmental exposure during pregnancy or anxiety. All women had a singleton pregnancy and gestational age confirmed by ultrasound. Exclusion criteria: were high risk of genetic disease (25% or more), malformation suspected on ultrasound, intrauterine device, uterine haematomas and malformations. 579 women were assigned to CVS, 581 women to EA and 114/1274 (9%) were excluded.
Interventions	Transabdominal CVS was performed between 10 and 12 weeks with ultrasound guidance and a needle guide. The double needle technique was used (guide needle of 1.2 mm (18 G) and aspiration needle of 0.8 mm (21 G). Amniocentesis was done between 11 and 13 weeks with a needle guide and a 0.9 mm (20 G) standard amniocentesis needle. The filter system was used which allowed circulation of amniotic fluid (25 ml) back to the sac during sampling.
Outcomes	Technical difficulties, abnormal karyotype, pregnancy complications, perinatal loss, neonatal complications.
Notes	Trial was stopped early due to slow recruitment and due to clustering of talipes equinovarus in the EA group.
Allocation concealment	A – Adequate

Study	**Denmark 1992**
Methods	Three way randomisation of low risk women (TA vs TC vs AC). A two way randomisation of high risk women (TA vs TC). Central randomisation (?telephone) with stratification for genetic risk.
Participants	Two centres in Denmark from 1985-1990. Eligible low risk women: age > 34 or father > 49, history of or anxiety about chromosomal abnormality, > 3 spontaneous miscarriages with viable fetus at 9-11 weeks. Eligible high risk women: history of translocation, late termination or fetus at risk of metabolic disorder with a viable fetus at 9-11 weeks. Exclusions: active bleeding, intrauterine device, genital infection, severe mental illness, use of teratogenic drugs, history of neural tube defects and discrepant dating.
Interventions	CVS vs second trimester amniocentesis. Transabdominal CVS vs second trimester amniocentesis.

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Characteristics of included studies (*Continued*)

	Transcervical CVS vs second trimester amniocentesis. Transcervical CVS vs transabdominal CVS.
Outcomes	Pregnancy outcome, antenatal complications and diagnostic accuracy.
Notes	
Allocation concealment	A – Adequate

Study	**King's 1996**
Methods	Sealed opaque envelope containing a card for one of the procedures. Not sequentially numbered envelopes.
Participants	Median age 38 years range (22-46). Inclusion criteria: ultrasonographic evidence of a viable fetus at 10-13 weeks 6 days' gestation (minimum CRL = 38 mm) and maternal request for karyotyping due to advanced maternal age, anxiety or family history of chromosomal abnormality. Exclusions: increased nuchal translucency, missed abortion, multiple pregnancy, major fetal abnormality, intrauterine device, multiple fibroids or large placental haemorrhage. EA was performed in 840 women (278 after randomisation) and CVS in 652 women (277 after randomisation).
Interventions	Early amniocentesis versus CVS. Both procedures being carried out by Professor Nicolaides or under his direct supervision. A free hand technique and a 20 G needle was used for both EA and CVS. No local anaesthesia, prophylactic antibiotics or bed rest. EA: 11 ml of fluid aspirated, first 1 ml discarded. CVS: 6-10 ml of tissue aspirated manually through a 20 ml syringe.
Outcomes	Technical difficulties, abnormal karyotype, pregnancy complications, perinatal loss and maternal complications.
Notes	Aimed to recruit 4400 women. However, by March 1993 recruitment collapsed because of widespread publicity that CVS can cause fetal limb abnormalities and is associated with a high risk of spontaneous abortion and that non invasive screening by ultrasonography and maternal serum biochemistry can provide sufficient reassurance to avoid invasive testing.
Allocation concealment	A – Adequate

Study	**Leiden 1998**
Methods	Early amniocentesis versus transabdominal CVS. Women eligible were given the choice as to randomisation or to decide the method of prenatal diagnosis themselves. Randomisation was performed using sequentially numbered envelopes.
Participants	Women requesting prenatal diagnosis due to age related risk. 212 women were recruited, 115 agreed to be randomised; 70 chose EA and 25 CVS. Two women did not participate because fetal death was diagnosed before any intervention.
Interventions	Transabdominal CVS was performed using a 20 G needle. Amniocentesis was performed using a 22 G needle: 11 ml of amniotic fluid was aspirated, the first ml being discarded.
Outcomes	Technical difficulties, abnormal karyotype, pregnancy complications, perinatal loss, neonatal complications, Dutch version of Denver Developmental Screening Test at 6-9 months.
Notes	Study stopped after 18 months following advice of the institutional ethical committee due to a higher incidence of fetal loss in the EA group.
Allocation concealment	A – Adequate

Study	**MRC (Finland) 1993**
Methods	Consecutively numbered sealed envelopes.

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Characteristics of included studies (*Continued*)

Participants	800 women in early pregnancy requesting prenatal diagnosis.
Interventions	4 operators performed all procedures - transcervical CVS with Portex cannula or amniocentesis at 16 weeks under ultrasound guidance.
Outcomes	Pregnancy outcome, abnormal karyotype, antenatal complications and diagnostic accuracy.
Notes	This study was part of the international MRC trial.
Allocation concealment	A – Adequate

Study	**MRC 1991**
Methods	Central telephone randomisation. Random allocation in balanced blocks and stratified by centre. Finland - consecutively numbered, sealed, opaque envelopes.
Participants	3248 recruited from 31 centres in Europe (21 in the UK, 4 in Italy, 2 in the Netherlands and 1 in Finland, Denmark, Switzerland and Germany). Prenatal diagnosis due to maternal age. Other indications were anxiety and previously affected child with chromosome anomaly. Centres eligible if each participating obstetrician had performed at least 30 procedures with > 10 mg of tissue in 23 out of 25 most recent cases. 1609 randomised to CVS and 1592 to amniocentesis.
Interventions	First trimester CVS transcervical or transabdominal approach versus second trimester amniocentesis.
Outcomes	Pregnancy outcome, abnormal karyotype, antenatal complications and diagnostic accuracy.
Notes	
Allocation concealment	A – Adequate

Study	**Nolan 1981**
Methods	Random allocation (? method).
Participants	223 women randomised.
Interventions	Mid-trimester amniocentesis with or without "the obstetrician having the benefit of ultrasound results". It appears that ultrasound was used to locate the placenta, i.e. the procedure was not performed under direct ultrasound guidance.
Outcomes	Number of taps, bloody taps.
Notes	
Allocation concealment	B – Unclear

Study	**Tabor 1986**
Methods	Random allocation according to a table of random numbers. Randomisation code given out by a medical secretary at Rigshospitalet, Copenhagen (majority). Some women were randomised by envelopes (Fredriksborg county).
Participants	4606 women randomised between ages of 25 and 34. Exclusion criteria: women believed to be at risk of a child with a chromosomal abnormality, neural tube defect or increased risk of spontaneous abortion. Also women with known uterine abnormalities or intrauterine contraceptive devices were excluded along with multiple gestations.
Interventions	Women in the study group were allocated to amniocentesis, all of which were carried out at the centre for prenatal diagnosis. The mean gestational age for amniocentesis was 16.4 +/-1.1 weeks. Amniocentesis was carried out with a 20 G needle under direct ultrasound guidance. Women in the control group were allocated to the routine antenatal programme.
Outcomes	Pregnancy outcome, abnormal karyotype and neonatal complications and congenital abnormalities.
Notes	
Allocation concealment	A – Adequate

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Study	Tomassini 1988
Methods	Random selection (? method).
Participants	44 women between 9 and 12 weeks of gestation.
Interventions	Transcervical CVS with ago-cannula or transabdominal procedure with a spinal needle (?gauge) and a suction pistol.
Outcomes	Sampling failure, vaginal spotting and amniotic fluid leak, pregnancy loss.
Notes	
Allocation concealment	B – Unclear

Study	USNICHD 1992
Methods	Random assignment.
Participants	3998 patients recruited in eight US collaborating centres. Inclusion criteria: favourable placental position allowing both procedures to be performed, gestational age between 49 and 90 days. Exclusion criteria: active genital herpes, active vaginal bleeding or cervical polyps. 1190 randomised to transcervical CVS and 1163 to transabdominal CVS.
Interventions	Transabdominal or transcervical CVS. Transcervical being performed with a plastic catheter and transabdominal with an 18-22 G spinal needle.
Outcomes	Sampling success, pregnancy outcome.
Notes	Initial cohort of 2353 women presented who delivered before July 1 1989.
Allocation concealment	A – Adequate

AC: amniocentesis
CRL: crown rump length
CVS: chorionic villus sampling
EA: early amniocentesis
G: guage
TA: transabdominal
TC: transcervical
vs: versus

Characteristics of excluded studies

Study	Reason for exclusion
Fischer 2000a	This study evaluated the role of local anaesthesia in reducing pain during and immediately after the procedure. This study will be included in the Cochrane review that addresses the issue of pain relief during prenatal diagnostic tests.
Leach 1978	The indication for amniocentesis was a test of fetal lung maturity with only 10.2% of the procedures carried out before 36 weeks' gestation.
Levine 1977	This study evaluated the role of ultrasound immediately before genetic amniocentesis. The patients were "alternately assigned" to the "with ultrasound" and "without ultrasound" groups. According to our protocol quasi-randomised protocols such as alternative allocations are not included.
Pistorius 1998	Amniocentesis was performed later in pregnancy in women with proteinuric hypertension.
Shulman 1990	This study reported comparison between 15 transcervical and 15 transabdominal CVS procedures in terms of the specimen size and change in maternal serum alpha-feto-protein levels. Some women were selected by 'choice' and others took part in the NICH study comparing CVS and amniocentesis (Rhoads GG, Jackson LG, Schlesselman SE, de la Cruz FF, Desnick RJ, Golbus MS et al. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. New England Journal of Medicine 1989;320(10):609-17). This study, therefore, does not fulfill our criteria for randomised study.

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Characteristics of excluded studies (*Continued*)

Van Schoubroeck 2000	This study evaluated the role of therapeutic massage anaesthesia in reducing pain during and immediately after the procedure. This study will be included in the Cochrane review that addresses the issue of pain relief during prenatal diagnostic tests.

CVS: chorionic villus sampling

ANALYSES

Comparison 01. Mid-trimester amniocentesis versus control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Not complied with allocated procedure	1	4606	Relative Risk (Fixed) 95% CI	1.73 [1.03, 2.91]
03 Multiple insertions	1	4606	Relative Risk (Fixed) 95% CI	91.08 [5.61, 1477.53]
04 Second test performed	1	4606	Relative Risk (Fixed) 95% CI	41.04 [2.48, 678.07]
05 Laboratory failure	1	4606	Relative Risk (Fixed) 95% CI	27.02 [1.61, 454.31]
06 All non-mosaic abnormalities	1	4593	Relative Risk (Fixed) 95% CI	30.85 [1.85, 515.31]
13 Vaginal bleeding after test	1	4606	Relative Risk (Fixed) 95% CI	0.95 [0.66, 1.37]
14 Amniotic leakage after test	1	4606	Relative Risk (Fixed) 95% CI	3.90 [1.95, 7.80]
20 All known pregnancy loss (including termination of pregnancy)	1	4606	Relative Risk (Fixed) 95% CI	1.41 [0.99, 2.00]
21 Termination of pregnancy (all)	1	4606	Relative Risk (Fixed) 95% CI	2.50 [0.97, 6.44]
24 Spontaneous miscarriage	1	4606	Relative Risk (Fixed) 95% CI	1.60 [1.02, 2.52]
26 Perinatal deaths	1	4606	Relative Risk (Fixed) 95% CI	0.63 [0.28, 1.38]
27 Stillbirths	1	4606	Relative Risk (Fixed) 95% CI	0.83 [0.36, 1.93]
28 Neonatal deaths	1	4606	Relative Risk (Fixed) 95% CI	0.11 [0.01, 2.06]
29 All recorded deaths after viability	1	4606	Relative Risk (Fixed) 95% CI	0.63 [0.28, 1.38]
30 Anomalies (all recorded)	1	4507	Relative Risk (Fixed) 95% CI	0.93 [0.62, 1.39]
31 Talipes	1	4507	Relative Risk (Fixed) 95% CI	0.68 [0.37, 1.22]
35 Neonatal respiratory distress syndrome	1	4507	Relative Risk (Fixed) 95% CI	2.11 [1.06, 4.19]

Comparison 02. Early versus mid-trimester amniocentesis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Not complied with allocated procedure	1	4368	Relative Risk (Fixed) 95% CI	0.65 [0.57, 0.75]
02 Sampling failure	1	629	Relative Risk (Fixed) 95% CI	4.53 [0.53, 38.56]
03 Multiple insertions	1	4368	Relative Risk (Fixed) 95% CI	2.79 [1.92, 4.04]
04 Second test performed	1	4107	Relative Risk (Fixed) 95% CI	8.72 [3.47, 21.91]
05 Laboratory failure	1	4368	Relative Risk (Fixed) 95% CI	9.76 [3.49, 27.26]
06 All non-mosaic abnormalities	1	4368	Relative Risk (Fixed) 95% CI	1.11 [0.75, 1.66]
07 True mosaics	1	4368	Relative Risk (Fixed) 95% CI	1.00 [0.25, 4.00]
09 Maternal contamination	1	4368	Relative Risk (Fixed) 95% CI	2.00 [0.37, 10.92]
11 False negative chromosomal diagnosis			Relative Risk (Fixed) 95% CI	Subtotals only
12 Reporting time	1	4107	Weighted Mean Difference (Fixed) 95% CI	1.20 [0.89, 1.51]
14 Amniotic leakage after test	1	4368	Relative Risk (Fixed) 95% CI	2.05 [1.43, 2.94]

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20 All known pregnancy loss (including termination of pregnancy)	1	4334	Relative Risk (Fixed) 95% CI	1.29 [1.03, 1.61]
21 Termination of pregnancy (all)	1	4334	Relative Risk (Fixed) 95% CI	1.26 [0.89, 1.77]
24 Spontaneous miscarriage	1	4334	Relative Risk (Fixed) 95% CI	1.41 [1.00, 1.98]
25 Spontaneous miscarriage after test	1	4334	Relative Risk (Fixed) 95% CI	3.22 [1.88, 5.53]
27 Stillbirths	1	4334	Relative Risk (Fixed) 95% CI	0.73 [0.34, 1.59]
28 Neonatal deaths	1	4334	Relative Risk (Fixed) 95% CI	4.98 [0.58, 42.56]
29 All recorded deaths after viability	1	4334	Relative Risk (Fixed) 95% CI	1.00 [0.50, 1.99]
30 Anomalies (all recorded)	1	4334	Relative Risk (Fixed) 95% CI	1.73 [1.26, 2.38]
31 Talipes			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. Chorionic villus sampling versus mid trimester amniocentesis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Not complied with allocated procedure			Relative Risk (Random) 95% CI	Subtotals only
02 Sampling failure			Relative Risk (Fixed) 95% CI	Subtotals only
03 Multiple insertions			Relative Risk (Fixed) 95% CI	Subtotals only
04 Second test performed			Relative Risk (Random) 95% CI	Subtotals only
05 Laboratory failure			Relative Risk (Fixed) 95% CI	Subtotals only
06 All non-mosaic abnormalities			Relative Risk (Fixed) 95% CI	Subtotals only
07 True mosaics			Relative Risk (Fixed) 95% CI	Subtotals only
08 Confined mosaics			Relative Risk (Fixed) 95% CI	Subtotals only
09 Maternal contamination			Relative Risk (Fixed) 95% CI	Subtotals only
10 Known false positive after birth			Relative Risk (Fixed) 95% CI	Subtotals only
11 Known false negative after birth			Relative Risk (Fixed) 95% CI	Subtotals only
13 Vaginal bleeding after test			Relative Risk (Random) 95% CI	Subtotals only
14 Amniotic leakage after test			Relative Risk (Fixed) 95% CI	Subtotals only
15 Vaginal bleeding after 20 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
16 PROM before 28 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
17 Antenatal hospital admission			Relative Risk (Fixed) 95% CI	Subtotals only
18 Delivery before 37 weeks			Relative Risk (Random) 95% CI	Subtotals only
19 Delivery before 33 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
20 All known pregnancy loss (including termination of pregnancy)			Relative Risk (Random) 95% CI	Subtotals only
21 Termination of pregnancy (all)			Relative Risk (Fixed) 95% CI	Subtotals only
24 Spontaneous miscarriage			Relative Risk (Random) 95% CI	Subtotals only
25 Spontaneous miscarriage after test			Relative Risk (Random) 95% CI	Subtotals only
26 Perinatal deaths			Relative Risk (Fixed) 95% CI	Subtotals only
27 Stillbirths			Relative Risk (Random) 95% CI	Subtotals only
28 Neonatal deaths			Relative Risk (Fixed) 95% CI	Subtotals only
29 All recorded deaths after viability			Relative Risk (Fixed) 95% CI	Subtotals only
30 Congenital anomalies (all recorded)			Relative Risk (Fixed) 95% CI	Subtotals only
31 Talipes			Relative Risk (Fixed) 95% CI	Subtotals only
33 Limb reduction defects	1	3201	Relative Risk (Fixed) 95% CI	4.95 [0.24, 102.97]

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38 Result given in less than 7 days (not prespecified)	Relative Risk (Fixed) 95% CI	Subtotals only
39 Result given in less than 14 days (not prespecified)	Relative Risk (Fixed) 95% CI	Subtotals only
40 Result given in less than 21 days (not prespecified)	Relative Risk (Fixed) 95% CI	Subtotals only
41 Result given in more than 21days (not prespecified)	Relative Risk (Fixed) 95% CI	Subtotals only
42 Not wanting another baby at 22 weeks gestation (not prespecified)	Odds Ratio (Fixed) 95% CI	Subtotals only

Comparison 04. Transcervical versus transabdominal CVS

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Not complied with allocated procedure	3	5187	Relative Risk (Random) 95% CI	1.68 [0.59, 4.76]
02 Sampling failure	4	5231	Relative Risk (Fixed) 95% CI	1.82 [1.15, 2.86]
03 Multiple insertions	2	1314	Relative Risk (Fixed) 95% CI	2.73 [1.78, 4.17]
04 Second test performed	1	1194	Relative Risk (Fixed) 95% CI	1.24 [0.65, 2.37]
05 Laboratory failure	1	1194	Relative Risk (Fixed) 95% CI	2.23 [0.69, 7.22]
06 All non-mosaic abnormalities	1	2862	Relative Risk (Fixed) 95% CI	1.23 [0.87, 1.75]
07 True mosaics	1	2862	Relative Risk (Fixed) 95% CI	0.92 [0.39, 2.17]
08 Confined mosaics	1	2862	Relative Risk (Fixed) 95% CI	0.85 [0.26, 2.77]
13 Vaginal bleeding after test	3	1358	Relative Risk (Random) 95% CI	6.93 [0.77, 62.83]
14 Amniotic leakage after test	1	44	Relative Risk (Fixed) 95% CI	0.28 [0.01, 6.52]
20 All known pregnancy loss (including termination of pregnancy)	5	7978	Relative Risk (Random) 95% CI	1.16 [0.81, 1.65]
21 Termination of pregnancy (all)	2	1303	Relative Risk (Fixed) 95% CI	0.83 [0.56, 1.22]
24 Spontaneous miscarriage	4	3384	Relative Risk (Random) 95% CI	1.68 [0.79, 3.58]
25 Spontaneous miscarriage after test	3	1347	Relative Risk (Fixed) 95% CI	1.25 [0.76, 2.06]
26 Perinatal deaths	1	2037	Relative Risk (Fixed) 95% CI	0.44 [0.11, 1.68]
27 Stillbirths	2	1227	Relative Risk (Fixed) 95% CI	1.69 [0.38, 7.62]
28 Neonatal deaths	2	4845	Relative Risk (Fixed) 95% CI	0.60 [0.14, 2.49]
30 Anomalies (all recorded)	2	3622	Relative Risk (Fixed) 95% CI	0.68 [0.41, 1.12]
31 Talipes	1	2624	Relative Risk (Fixed) 95% CI	3.21 [0.33, 30.80]

Comparison 05. Early amniocentesis versus transabdominal CVS

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Not complied with allocated procedure	3	1791	Relative Risk (Fixed) 95% CI	0.11 [0.02, 0.58]
02 Sampling failure	3	1791	Relative Risk (Fixed) 95% CI	0.30 [0.10, 0.84]
03 Multiple insertions	2	670	Relative Risk (Fixed) 95% CI	0.30 [0.15, 0.60]
04 Second test performed	3	1791	Relative Risk (Fixed) 95% CI	0.43 [0.21, 0.88]
05 Laboratory failure	3	1791	Relative Risk (Fixed) 95% CI	0.61 [0.25, 1.48]
06 All non-mosaic abnormalities	3	1791	Relative Risk (Fixed) 95% CI	0.71 [0.33, 1.49]
07 True mosaics	2	1676	Relative Risk (Fixed) 95% CI	0.60 [0.08, 4.53]

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08 Abnormalities confined to non fetal tissues	3	1791	Relative Risk (Fixed) 95% CI	0.56 [0.16, 2.00]
09 Maternal contamination	1	555	Relative Risk (Fixed) 95% CI	0.20 [0.01, 4.13]
10 Known false positive after birth	2	670	Relative Risk (Fixed) 95% CI	0.36 [0.02, 8.73]
11 Known false negative after birth	1	555	Relative Risk (Fixed) 95% CI	Not estimable
13 Vaginal bleeding after test	2	1236	Relative Risk (Fixed) 95% CI	0.64 [0.40, 1.03]
14 Amniotic leakage after test	2	1236	Relative Risk (Random) 95% CI	4.47 [0.03, 709.83]
18 Delivery before 37 weeks	3	1755	Relative Risk (Fixed) 95% CI	1.16 [0.78, 1.74]
19 Delivery before 33 weeks	1	1121	Relative Risk (Fixed) 95% CI	0.50 [0.09, 2.73]
20 All known pregnancy loss (including termination of pregnancy)	3	1793	Relative Risk (Fixed) 95% CI	1.25 [0.86, 1.84]
21 Termination of pregnancy (all)	3	1791	Relative Risk (Fixed) 95% CI	0.65 [0.34, 1.24]
24 Spontaneous miscarriage	3	1793	Relative Risk (Fixed) 95% CI	1.93 [1.15, 3.24]
25 Spontaneous miscarriage after test	3	1791	Relative Risk (Fixed) 95% CI	1.91 [1.11, 3.31]
26 Perinatal deaths	3	1730	Relative Risk (Fixed) 95% CI	1.01 [0.06, 16.07]
27 Stillbirths	3	1730	Relative Risk (Fixed) 95% CI	Not estimable
28 Neonatal deaths	3	1757	Relative Risk (Fixed) 95% CI	1.01 [0.06, 16.03]
29 All recorded deaths after viability	3	1755	Relative Risk (Fixed) 95% CI	1.01 [0.06, 16.03]
30 Anomalies (all recorded)	3	1687	Relative Risk (Random) 95% CI	1.11 [0.35, 3.55]
32 Talipes equinovarus	3	1687	Relative Risk (Fixed) 95% CI	6.43 [1.68, 24.64]
33 Haemangioma	3	1687	Relative Risk (Fixed) 95% CI	0.42 [0.13, 1.36]
35 Neonatal respiratory distress syndrome	3	1328	Relative Risk (Fixed) 95% CI	0.56 [0.20, 1.58]
37 Birthweight below 5th centile	2	629	Relative Risk (Fixed) 95% CI	1.04 [0.43, 2.56]

Comparison 06. Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
02 Sampling failure	1	223	Relative Risk (Fixed) 95% CI	10.90 [0.61, 194.85]
03 Multiple insertions	1	223	Relative Risk (Fixed) 95% CI	0.67 [0.41, 1.09]
20 All known pregnancy loss (including termination of pregnancy)	1	223	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.02]
24 Spontaneous miscarriage	1	223	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.02]
25 Spontaneous miscarriage after test	1	223	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.02]
38 Bloody tap (not prespecified)	1	223	Odds Ratio (Fixed) 95% CI	2.03 [0.86, 4.77]

INDEX TERMS

Medical Subject Headings (MeSH)

Abnormalities [diagnosis]; Amniocentesis [*adverse effects; standards]; Chorionic Villi Sampling [*adverse effects; standards]; Pregnancy Trimester, First; Pregnancy Trimester, Second; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

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COVER SHEET

Title	Amniocentesis and chorionic villus sampling for prenatal diagnosis
Authors	Alfirevic Z, Sundberg K, Brigham S
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Review first published	2003/3
Date of most recent amendment	19 August 2005
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
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Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 01 Not complied with allocated procedure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 01 Not complied with allocated procedure

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	38/2302	22/2304		100.0	1.73 [1.03, 2.91]
Total (95% CI)	2302	2304		100.0	1.73 [1.03, 2.91]
Total events: 38 (Amniocentesis), 22 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.06 p=0.04					

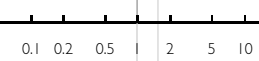
Analysis 01.03. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 03 Multiple insertions

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	45/2302	0/2304		100.0	91.08 [5.61, 1477.53]
Total (95% CI)	2302	2304		100.0	91.08 [5.61, 1477.53]
Total events: 45 (Amniocentesis), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.17 p=0.002					



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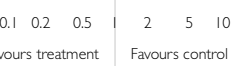
Analysis 01.04. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 04 Second test performed

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 04 Second test performed

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	20/2302	0/2304		100.0	41.04 [2.48, 678.07]
Total (95% CI)	2302	2304		100.0	41.04 [2.48, 678.07]
Total events: 20 (Amniocentesis), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.60 p=0.009					



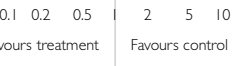
Analysis 01.05. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 05 Laboratory failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 05 Laboratory failure

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	13/2302	0/2304		100.0	27.02 [1.61, 454.31]
Total (95% CI)	2302	2304		100.0	27.02 [1.61, 454.31]
Total events: 13 (Amniocentesis), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.29 p=0.02					



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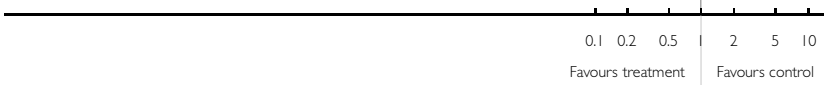
Analysis 01.06. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 06 All non-mosaic abnormalities

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 06 All non-mosaic abnormalities

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	15/2302	0/2291		100.0	30.85 [1.85, 515.31]
Total (95% CI)	2302	2291		100.0	30.85 [1.85, 515.31]
Total events: 15 (Amniocentesis), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.39 p=0.02					



Analysis 01.13. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 13 Vaginal bleeding after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 13 Vaginal bleeding after test

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	55/2302	58/2304		100.0	0.95 [0.66, 1.37]
Total (95% CI)	2302	2304		100.0	0.95 [0.66, 1.37]
Total events: 55 (Amniocentesis), 58 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.28 p=0.8					

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Analysis 01.14. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 14 Amniotic leakage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 14 Amniotic leakage after test

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	39/2302	10/2304		100.0	3.90 [1.95, 7.80]
Total (95% CI)	2302	2304		100.0	3.90 [1.95, 7.80]
Total events: 39 (Amniocentesis), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.86 p=0.0001					

Analysis 01.20. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	73/2302	52/2304		100.0	1.41 [0.99, 2.00]
Total (95% CI)	2302	2304		100.0	1.41 [0.99, 2.00]
Total events: 73 (Amniocentesis), 52 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.90 p=0.06					

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Analysis 01.21. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 21 Termination of pregnancy (all)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 21 Termination of pregnancy (all)

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	15/2302	6/2304		100.0	2.50 [0.97, 6.44]
Total (95% CI)	2302	2304		100.0	2.50 [0.97, 6.44]
Total events: 15 (Amniocentesis), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.90 p=0.06					

Analysis 01.24. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 24 Spontaneous miscarriage

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	48/2302	30/2304		100.0	1.60 [1.02, 2.52]
Total (95% CI)	2302	2304		100.0	1.60 [1.02, 2.52]
Total events: 48 (Amniocentesis), 30 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.04 p=0.04					

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Analysis 01.26. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 26 Perinatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 26 Perinatal deaths

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	10/2302	16/2304		100.0	0.63 [0.28, 1.38]
Total (95% CI)	2302	2304		100.0	0.63 [0.28, 1.38]
Total events: 10 (Amniocentesis), 16 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.17 p=0.2					

Analysis 01.27. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 27 Stillbirths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 27 Stillbirths

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	10/2302	12/2304		100.0	0.83 [0.36, 1.93]
Total (95% CI)	2302	2304		100.0	0.83 [0.36, 1.93]
Total events: 10 (Amniocentesis), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.42 p=0.7					

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Analysis 01.28. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 28 Neonatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 28 Neonatal deaths

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	0/2302	4/2304		100.0	0.11 [0.01, 2.06]
Total (95% CI)	2302	2304		100.0	0.11 [0.01, 2.06]
Total events: 0 (Amniocentesis), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.47 p=0.1					

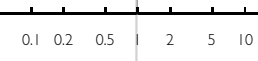
Analysis 01.29. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 29 All recorded deaths after viability

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 29 All recorded deaths after viability

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	10/2302	16/2304		100.0	0.63 [0.28, 1.38]
Total (95% CI)	2302	2304		100.0	0.63 [0.28, 1.38]
Total events: 10 (Amniocentesis), 16 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.17 p=0.2					



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Analysis 01.30. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 30 Anomalies (all recorded)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 30 Anomalies (all recorded)

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	45/2239	49/2268		100.0	0.93 [0.62, 1.39]
Total (95% CI)	2239	2268		100.0	0.93 [0.62, 1.39]
Total events: 45 (Amniocentesis), 49 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					

Analysis 01.31. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 31 Talipes

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 31 Talipes

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	18/2239	27/2268		100.0	0.68 [0.37, 1.22]
Total (95% CI)	2239	2268		100.0	0.68 [0.37, 1.22]
Total events: 18 (Amniocentesis), 27 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.30 p=0.2					

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Analysis 01.35. Comparison 01 Mid-trimester amniocentesis versus control, Outcome 35 Neonatal respiratory distress syndrome

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 01 Mid-trimester amniocentesis versus control

Outcome: 35 Neonatal respiratory distress syndrome

Study	Amniocentesis n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tabor 1986	25/2239	12/2268		100.0	2.11 [1.06, 4.19]
Total (95% CI)	2239	2268		100.0	2.11 [1.06, 4.19]
Total events: 25 (Amniocentesis), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.13 p=0.03					

Analysis 02.01. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 01 Not complied with allocated procedure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 01 Not complied with allocated procedure

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	267/2183	410/2185		100.0	0.65 [0.57, 0.75]
Total (95% CI)	2183	2185		100.0	0.65 [0.57, 0.75]
Total events: 267 (Early amniocentesis), 410 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.90 p<0.00001					

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Analysis 02.02. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 02 Sampling failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 02 Sampling failure

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	5/330	1/299		100.0	4.53 [0.53, 38.56]
Total (95% CI)	330	299		100.0	4.53 [0.53, 38.56]
Total events: 5 (Early amniocentesis), 1 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.38 p=0.2					

Analysis 02.03. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 03 Multiple insertions

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	103/2183	37/2185		100.0	2.79 [1.92, 4.04]
Total (95% CI)	2183	2185		100.0	2.79 [1.92, 4.04]
Total events: 103 (Early amniocentesis), 37 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.41 p<0.00001					

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Analysis 02.04. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 04 Second test performed

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 04 Second test performed

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	46/2108	5/1999		100.0	8.72 [3.47, 21.91]
Total (95% CI)	2108	1999		100.0	8.72 [3.47, 21.91]
Total events: 46 (Early amniocentesis), 5 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.61 p<0.00001					

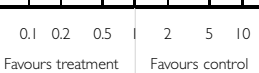
Analysis 02.05. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 05 Laboratory failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 05 Laboratory failure

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	39/2183	4/2185		100.0	9.76 [3.49, 27.26]
Total (95% CI)	2183	2185		100.0	9.76 [3.49, 27.26]
Total events: 39 (Early amniocentesis), 4 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.35 p=0.00001					



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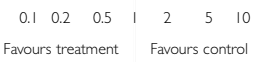
Analysis 02.06. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 06 All non-mosaic abnormalities

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 06 All non-mosaic abnormalities

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	50/2183	45/2185		100.0	1.11 [0.75, 1.66]
Total (95% CI)	2183	2185		100.0	1.11 [0.75, 1.66]
Total events: 50 (Early amniocentesis), 45 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.52 p=0.6					



Analysis 02.07. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 07 True mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 07 True mosaics

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	4/2183	4/2185		100.0	1.00 [0.25, 4.00]
Total (95% CI)	2183	2185		100.0	1.00 [0.25, 4.00]
Total events: 4 (Early amniocentesis), 4 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

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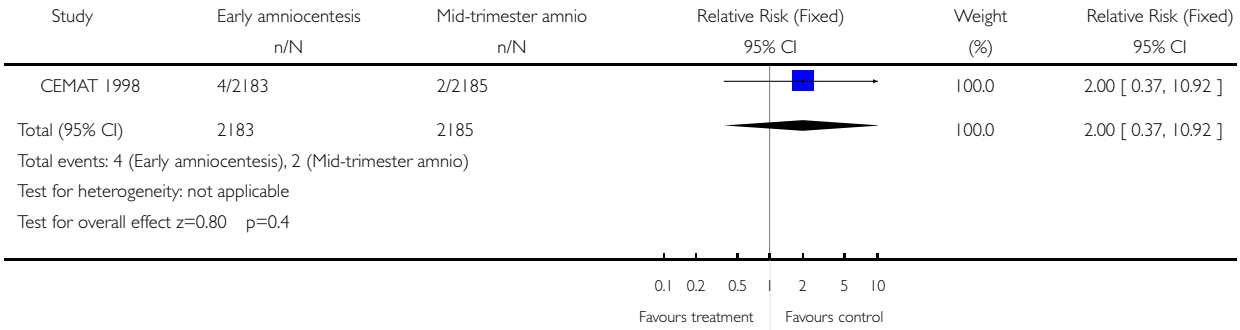
Analysis 02.09. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 09 Maternal contamination

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 09 Maternal contamination

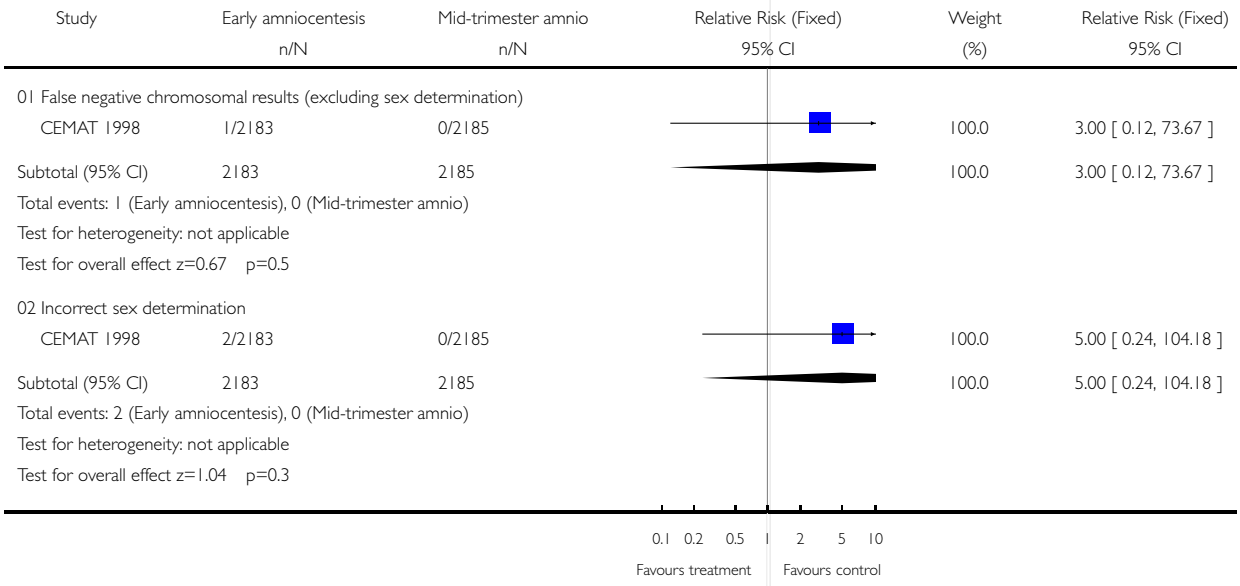


Analysis 02.11. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 11 False negative chromosomal diagnosis

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 11 False negative chromosomal diagnosis



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Analysis 02.12. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 12 Reporting time

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 12 Reporting time

Study	Early amniocentesis N	Early amniocentesis Mean(SD)	Mid-trimester amnio N	Mid-trimester amnio Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
CEMAT 1998	2108	17.70 (4.90)	1999	16.50 (5.30)		100.0	1.20 [0.89, 1.51]
Total (95% CI)	2108		1999			100.0	1.20 [0.89, 1.51]
Test for heterogeneity: not applicable							
Test for overall effect z=7.52 p<0.00001							

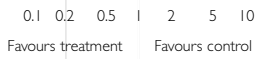
Analysis 02.14. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 14 Amniotic leakage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 14 Amniotic leakage after test

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	88/2183	43/2185		100.0	2.05 [1.43, 2.94]
Total (95% CI)	2183	2185		100.0	2.05 [1.43, 2.94]
Total events: 88 (Early amniocentesis), 43 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.91 p=0.00009					



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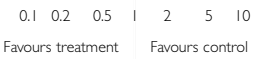
Analysis 02.20. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	166/2172	128/2162		100.0	1.29 [1.03, 1.61]
Total (95% CI)	2172	2162		100.0	1.29 [1.03, 1.61]
Total events: 166 (Early amniocentesis), 128 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.25 p=0.02					



Analysis 02.21. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 21 Termination of pregnancy (all)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 21 Termination of pregnancy (all)

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	72/2172	57/2162		100.0	1.26 [0.89, 1.77]
Total (95% CI)	2172	2162		100.0	1.26 [0.89, 1.77]
Total events: 72 (Early amniocentesis), 57 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.31 p=0.2					

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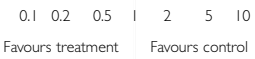
Analysis 02.24. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	78/2172	55/2162		100.0	1.41 [1.00, 1.98]
Total (95% CI)	2172	2162		100.0	1.41 [1.00, 1.98]
Total events: 78 (Early amniocentesis), 55 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.99 p=0.05					



Analysis 02.25. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	55/2172	17/2162		100.0	3.22 [1.88, 5.53]
Total (95% CI)	2172	2162		100.0	3.22 [1.88, 5.53]
Total events: 55 (Early amniocentesis), 17 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.24 p=0.00002					

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Analysis 02.27. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 27 Stillbirths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 27 Stillbirths

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	11/2172	15/2162		100.0	0.73 [0.34, 1.59]
Total (95% CI)	2172	2162		100.0	0.73 [0.34, 1.59]
Total events: 11 (Early amniocentesis), 15 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.80 p=0.4					

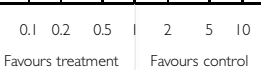
Analysis 02.28. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 28 Neonatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 28 Neonatal deaths

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
CEMAT 1998	5/2172	1/2162		100.0	4.98 [0.58, 42.56]
Total (95% CI)	2172	2162		100.0	4.98 [0.58, 42.56]
Total events: 5 (Early amniocentesis), 1 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.47 p=0.1					



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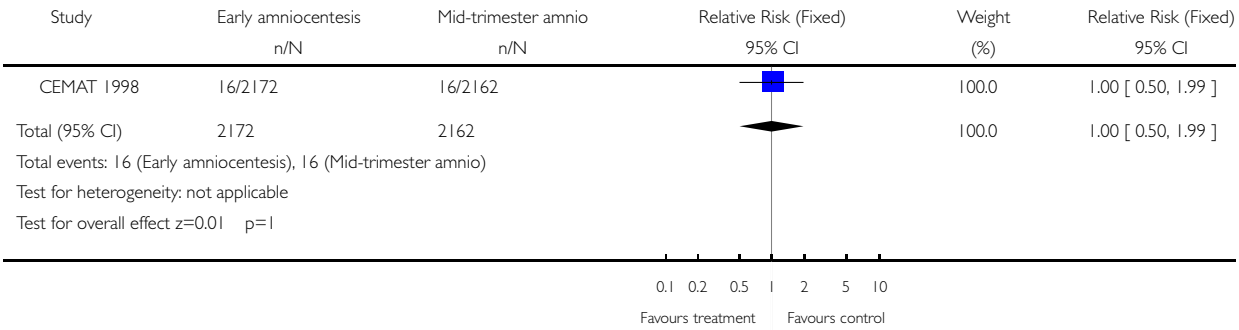
Analysis 02.29. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 29 All recorded deaths after viability

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 29 All recorded deaths after viability

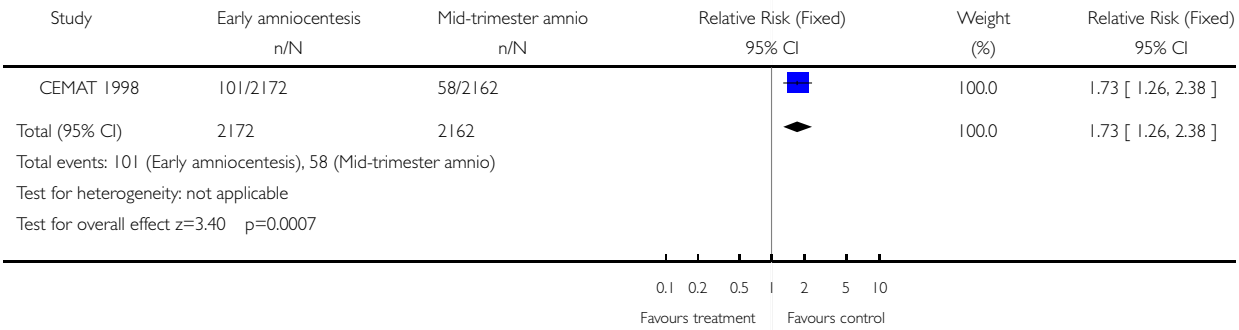


Analysis 02.30. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 30 Anomalies (all recorded)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 30 Anomalies (all recorded)



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Analysis 02.31. Comparison 02 Early versus mid-trimester amniocentesis, Outcome 31 Talipes

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 02 Early versus mid-trimester amniocentesis

Outcome: 31 Talipes

Study	Early amniocentesis n/N	Mid-trimester amnio n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Talipes (all)					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Early amniocentesis), 0 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 Talipes equinovarus					
CEMAT 1998	29/2172	2/2162		100.0	14.43 [3.45, 60.41]
Subtotal (95% CI)	2172	2162		100.0	14.43 [3.45, 60.41]
Total events: 29 (Early amniocentesis), 2 (Mid-trimester amnio)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.65 p=0.0003					

Analysis 03.01. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 01 Not complied with allocated procedure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 01 Not complied with allocated procedure

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Borrell 1999	185/503	145/508		42.1	1.29 [1.08, 1.54]
Canada 1992	200/1391	455/1396		42.3	0.44 [0.38, 0.51]
MRC (Finland) 1993	1/399	18/398		15.6	0.06 [0.01, 0.41]
Subtotal (95% CI)	2293	2302		100.0	0.50 [0.18, 1.36]
Total events: 386 (CVS), 618 (Amniocentesis)					
Test for heterogeneity chi-square=89.14 df=2 p=<0.0001 I^2 =97.8%					
Test for overall effect z=1.36 p=0.2					
03 CVS (any route) versus amniocentesis					
MRC 1991	112/1608	168/1589		100.0	0.66 [0.52, 0.83]
Subtotal (95% CI)	1608	1589		100.0	0.66 [0.52, 0.83]
Total events: 112 (CVS), 168 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.57 p=0.0004					

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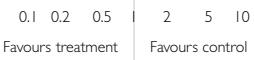
Analysis 03.02. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 02 Sampling failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 02 Sampling failure

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transervical CVS versus amniocentesis					
MRC (Finland) 1993	10/399	18/398		100.0	0.55 [0.26, 1.19]
Subtotal (95% CI)	399	398		100.0	0.55 [0.26, 1.19]
Total events: 10 (CVS), 18 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					
03 CVS (any route) versus amniocentesis					
MRC 1991	78/1609	25/1592		100.0	3.09 [1.98, 4.82]
Subtotal (95% CI)	1609	1592		100.0	3.09 [1.98, 4.82]
Total events: 78 (CVS), 25 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.96 p<0.00001					



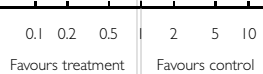
Analysis 03.03. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 03 Multiple insertions

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	123/399	31/395		100.0	3.93 [2.72, 5.68]
Subtotal (95% CI)	399	395		100.0	3.93 [2.72, 5.68]
Total events: 123 (CVS), 31 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=7.28 p<0.00001					
03 CVS (any route) versus amniocentesis					
MRC 1991	460/1496	90/1421		100.0	4.85 [3.92, 6.01]
Subtotal (95% CI)	1496	1421		100.0	4.85 [3.92, 6.01]
Total events: 460 (CVS), 90 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=14.48 p<0.00001					



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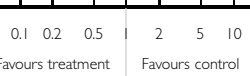
Analysis 03.04. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 04 Second test performed

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 04 Second test performed

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Borrell 1999	13/314	1/358		33.2	14.82 [1.95, 112.66]
Canada 1992	103/1391	0/1396		28.7	207.74 [12.92, 3340.27]
MRC (Finland) 1993	17/399	4/398		38.1	4.24 [1.44, 12.49]
Subtotal (95% CI)	2104	2152		100.0	19.63 [1.24, 309.90]
Total events: 133 (CVS), 5 (Amniocentesis)					
Test for heterogeneity chi-square=12.74 df=2 p=0.002 I^2 =84.3%					
Test for overall effect z=2.11 p=0.03					
03 CVS (any route) versus amniocentesis					
MRC 1991	100/1609	35/1592		100.0	2.83 [1.94, 4.13]
Subtotal (95% CI)	1609	1592		100.0	2.83 [1.94, 4.13]
Total events: 100 (CVS), 35 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.38 p<0.00001					



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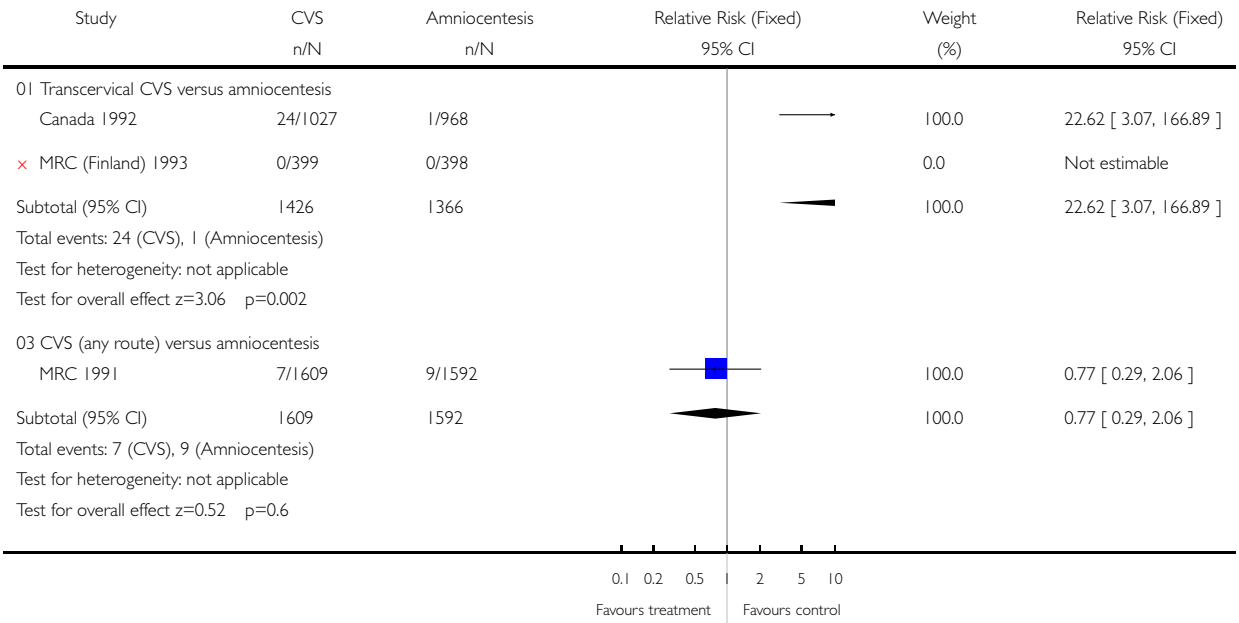
Analysis 03.05. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 05 Laboratory failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 05 Laboratory failure

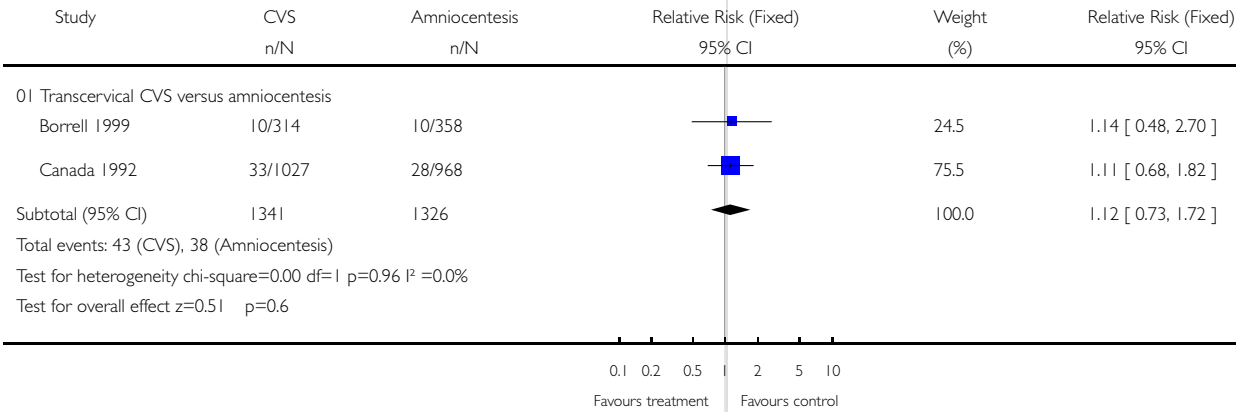


Analysis 03.06. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 06 All non-mosaic abnormalities

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 06 All non-mosaic abnormalities



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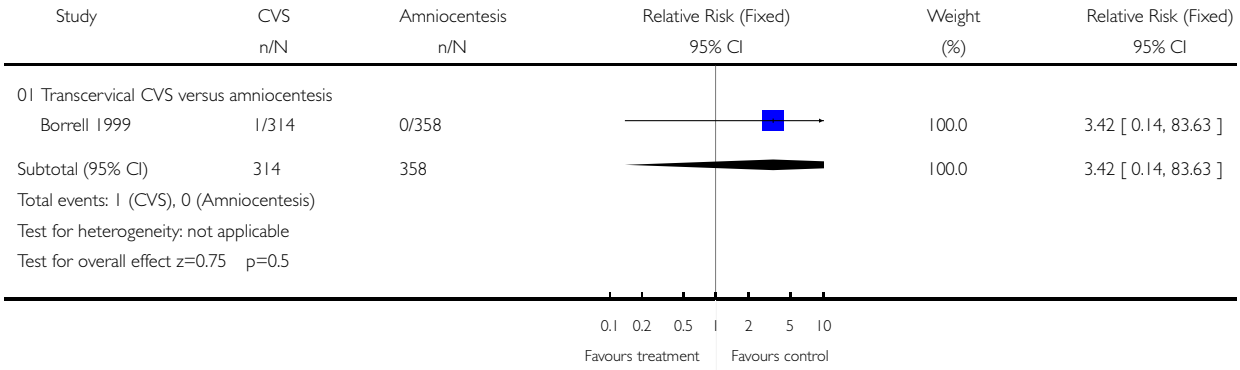
Analysis 03.07. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 07 True mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 07 True mosaics

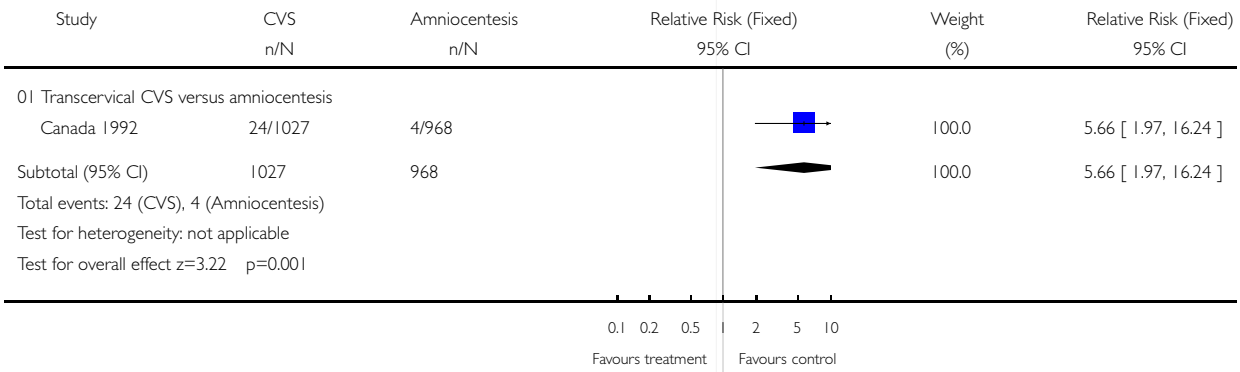


Analysis 03.08. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 08 Confined mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 08 Confined mosaics



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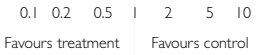
Analysis 03.09. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 09 Maternal contamination

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 09 Maternal contamination

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	39/1023	3/968		100.0	12.30 [3.81, 39.67]
Subtotal (95% CI)	1023	968		100.0	12.30 [3.81, 39.67]
Total events: 39 (CVS), 3 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.20 p=0.00003					
03 CVS (any route) versus amniocentsis					
MRC 1991	4/1609	0/1592		100.0	8.90 [0.48, 165.26]
Subtotal (95% CI)	1609	1592		100.0	8.90 [0.48, 165.26]
Total events: 4 (CVS), 0 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.47 p=0.1					



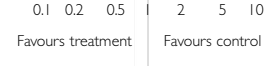
Analysis 03.10. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 10 Known false positive after birth

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 10 Known false positive after birth

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	19/863	2/967		65.3	10.64 [2.49, 45.57]
MRC (Finland) 1993	1/399	1/398		34.7	1.00 [0.06, 15.89]
Subtotal (95% CI)	1262	1365		100.0	7.30 [2.20, 24.25]
Total events: 20 (CVS), 3 (Amniocentesis)					
Test for heterogeneity chi-square=2.24 df=1 p=0.13 I^2 =55.4%					
Test for overall effect z=3.24 p=0.001					
03 CVS (any route) versus amniocentesis					
MRC 1991	1/1609	1/1592		100.0	0.99 [0.06, 15.80]
Subtotal (95% CI)	1609	1592		100.0	0.99 [0.06, 15.80]



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Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 1 (CVS), 1 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					

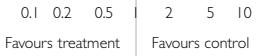
Analysis 03.11. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 11 Known false negative after birth

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 11 Known false negative after birth

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	3/863	0/967		100.0	7.84 [0.41, 151.61]
× MRC (Finland) 1993	0/399	0/398		0.0	Not estimable
Subtotal (95% CI)	1262	1365		100.0	7.84 [0.41, 151.61]
Total events: 3 (CVS), 0 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
03 CVS (any route) versus amniocentesis					
MRC 1991	1/1609	0/1592		100.0	2.97 [0.12, 72.81]
Subtotal (95% CI)	1609	1592		100.0	2.97 [0.12, 72.81]
Total events: 1 (CVS), 0 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					



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Analysis 03.13. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 13 Vaginal bleeding after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 13 Vaginal bleeding after test

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	206/1196	35/1200		54.8	5.91 [4.16, 8.37]
MRC (Finland) 1993	103/399	4/398		45.2	25.69 [9.55, 69.07]
Subtotal (95% CI)	1595	1598		100.0	11.48 [2.58, 51.08]
Total events: 309 (CVS), 39 (Amniocentesis)					
Test for heterogeneity chi-square=8.17 df=1 p=0.004 I^2 =87.8%					
Test for overall effect z=3.21 p=0.001					

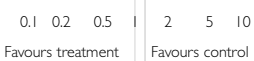
Analysis 03.14. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 14 Amniotic leakage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 14 Amniotic leakage after test

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transabdominal CVS vs amniocentesis					
Canada 1992	11/773	4/712		100.0	2.53 [0.81, 7.92]
Subtotal (95% CI)	773	712		100.0	2.53 [0.81, 7.92]
Total events: 11 (CVS), 4 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.60 p=0.1					
03 CVS (any route) versus amniocentesis					
MRC 1991	5/1609	9/1592		100.0	0.55 [0.18, 1.64]
Subtotal (95% CI)	1609	1592		100.0	0.55 [0.18, 1.64]
Total events: 5 (CVS), 9 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.08 p=0.3					



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Analysis 03.15. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 15 Vaginal bleeding after 20 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 15 Vaginal bleeding after 20 weeks

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	13/399	9/398		100.0	1.44 [0.62, 3.33]
Subtotal (95% CI)	399	398		100.0	1.44 [0.62, 3.33]
Total events: 13 (CVS), 9 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.85 p=0.4					
03 CVS (any route) versus amniocentesis					
MRC 1991	56/1609	56/1592		100.0	0.99 [0.69, 1.42]
Subtotal (95% CI)	1609	1592		100.0	0.99 [0.69, 1.42]
Total events: 56 (CVS), 56 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					

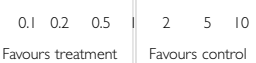
Analysis 03.16. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 16 PROM before 28 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 16 PROM before 28 weeks

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	15/362	3/360		100.0	4.97 [1.45, 17.03]
Subtotal (95% CI)	362	360		100.0	4.97 [1.45, 17.03]
Total events: 15 (CVS), 3 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.55 p=0.01					
03 CVS (any route) versus amniocentesis					
MRC 1991	21/1391	13/1374		100.0	1.60 [0.80, 3.17]
Subtotal (95% CI)	1391	1374		100.0	1.60 [0.80, 3.17]
Total events: 21 (CVS), 13 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.33 p=0.2					



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Analysis 03.17. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 17 Antenatal hospital admission

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 17 Antenatal hospital admission

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	25/390	17/390		100.0	1.47 [0.81, 2.68]
Subtotal (95% CI)	390	390		100.0	1.47 [0.81, 2.68]
Total events: 25 (CVS), 17 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.26 p=0.2					
03 CVS (any route) versus amniocentesis					
MRC 1991	199/1609	219/1592		100.0	0.90 [0.75, 1.08]
Subtotal (95% CI)	1609	1592		100.0	0.90 [0.75, 1.08]
Total events: 199 (CVS), 219 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.16 p=0.2					

Analysis 03.18. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 18 Delivery before 37 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 18 Delivery before 37 weeks

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	56/905	54/833		55.2	0.95 [0.66, 1.37]
MRC (Finland) 1993	33/381	18/387		44.8	1.86 [1.07, 3.25]
Subtotal (95% CI)	1286	1220		100.0	1.29 [0.67, 2.47]
Total events: 89 (CVS), 72 (Amniocentesis)					
Test for heterogeneity chi-square=3.90 df=1 p=0.05 I^2 =74.3%					
Test for overall effect z=0.76 p=0.4					
03 CVS (any route) versus amniocentesis					
MRC 1991	293/1601	218/1588		100.0	1.33 [1.13, 1.57]
Subtotal (95% CI)	1601	1588		100.0	1.33 [1.13, 1.57]

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Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Total events: 293 (CVS), 218 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.50 p=0.0005					

Analysis 03.19. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 19 Delivery before 33 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 19 Delivery before 33 weeks

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	17/381	8/387		100.0	2.16 [0.94, 4.94]
Subtotal (95% CI)	381	387		100.0	2.16 [0.94, 4.94]
Total events: 17 (CVS), 8 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.82 p=0.07					

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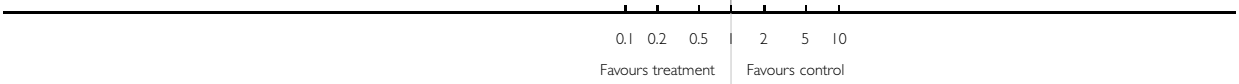
Analysis 03.20. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Borrell 1999	83/425	57/407		25.3	1.39 [1.02, 1.90]
Canada 1992	232/1348	208/1324		34.0	1.10 [0.92, 1.30]
Denmark 1992	127/1068	81/1158		28.0	1.70 [1.30, 2.22]
MRC (Finland) 1993	29/399	16/398		12.7	1.81 [1.00, 3.28]
Subtotal (95% CI)	3240	3287		100.0	1.40 [1.09, 1.81]
Total events: 471 (CVS), 362 (Amniocentesis)					
Test for heterogeneity chi-square=9.15 df=3 p=0.03 I^2 =67.2%					
Test for overall effect z=2.59 p=0.01					
02 Transabdominal CVS versus amniocentesis					
Denmark 1992	68/1076	81/1158		100.0	0.90 [0.66, 1.23]
Subtotal (95% CI)	1076	1158		100.0	0.90 [0.66, 1.23]
Total events: 68 (CVS), 81 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.64 p=0.5					
03 CVS (any route) versus amniocentesis					
Denmark 1992	195/2144	81/1158		38.8	1.30 [1.01, 1.67]
MRC 1991	220/1609	144/1592		61.2	1.51 [1.24, 1.84]
Subtotal (95% CI)	3753	2750		100.0	1.43 [1.22, 1.67]
Total events: 415 (CVS), 225 (Amniocentesis)					
Test for heterogeneity chi-square=0.86 df=1 p=0.35 I^2 =0.0%					
Test for overall effect z=4.48 p<0.00001					



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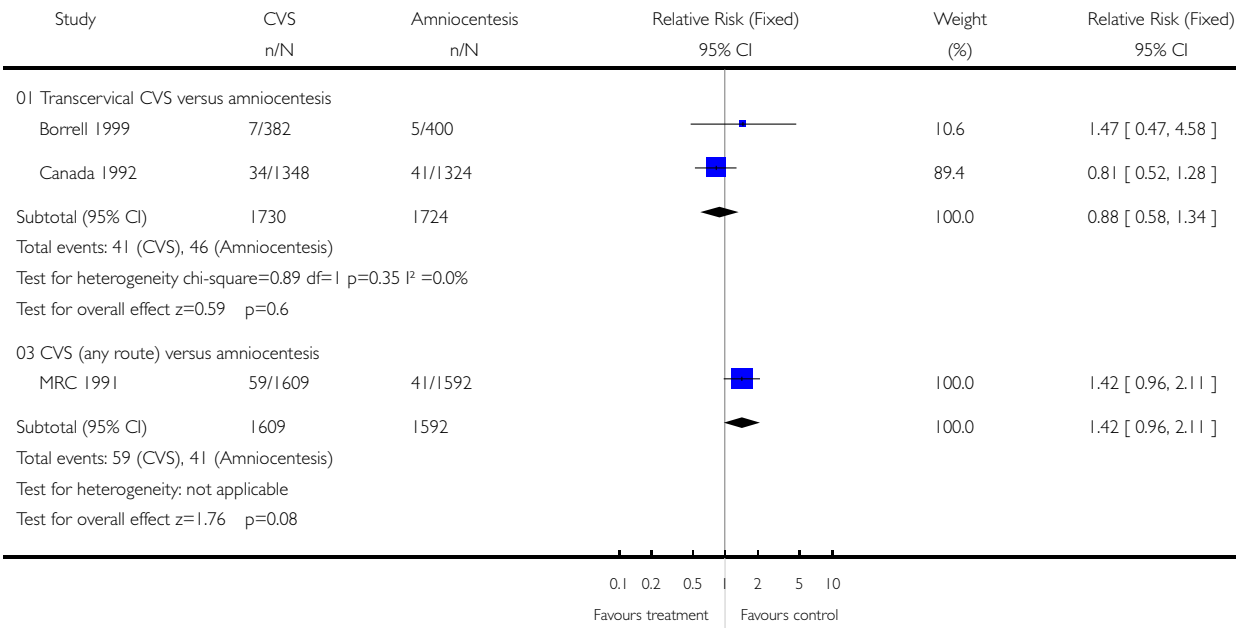
Analysis 03.21. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 21 Termination of pregnancy (all)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 21 Termination of pregnancy (all)



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Analysis 03.24. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Borrell 1999	75/382	52/400		31.7	1.51 [1.09, 2.09]
Canada 1992	196/1348	166/1324		38.8	1.16 [0.96, 1.41]
Denmark 1992	83/1010	41/1042		29.5	2.09 [1.45, 3.01]
Subtotal (95% CI)	2740	2766		100.0	1.50 [1.07, 2.11]
Total events: 354 (CVS), 259 (Amniocentesis)					
Test for heterogeneity chi-square=8.39 df=2 p=0.02 I^2 =76.2%					
Test for overall effect z=2.32 p=0.02					
02 Transabdominal CVS versus amniocentesis					
Denmark 1992	31/1027	41/1042		100.0	0.77 [0.49, 1.21]
Subtotal (95% CI)	1027	1042		100.0	0.77 [0.49, 1.21]
Total events: 31 (CVS), 41 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.13 p=0.3					
03 CVS (any route) versus amniocentesis					
Denmark 1992	114/2037	41/1042		34.2	1.42 [1.00, 2.02]
MRC 1991	145/1609	92/1592		65.8	1.56 [1.21, 2.01]
Subtotal (95% CI)	3646	2634		100.0	1.51 [1.23, 1.85]
Total events: 259 (CVS), 133 (Amniocentesis)					
Test for heterogeneity chi-square=0.18 df=1 p=0.67 I^2 =0.0%					
Test for overall effect z=3.96 p=0.00007					

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Analysis 03.25. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Transcervical CVS versus amniocentesis					
Borrell 1999	7/382	10/400		52.3	0.73 [0.28, 1.91]
MRC (Finland) 1993	14/399	3/398		47.7	4.65 [1.35, 16.07]
Subtotal (95% CI)	781	798		100.0	1.77 [0.28, 11.00]
Total events: 21 (CVS), 13 (Amniocentesis)					
Test for heterogeneity chi-square=5.47 df=1 p=0.02 I^2 =81.7%					
Test for overall effect z=0.61 p=0.5					
03 CVS (any route) versus amniocentesis					
MRC 1991	84/1609	24/1592		100.0	3.46 [2.21, 5.42]
Subtotal (95% CI)	1609	1592		100.0	3.46 [2.21, 5.42]
Total events: 84 (CVS), 24 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.43 p<0.00001					

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Analysis 03.26. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 26 Perinatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 26 Perinatal deaths

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
Canada 1992	8/1348	2/1324		21.2	3.93 [0.84, 18.47]
Denmark 1992	3/1010	6/1042		62.0	0.52 [0.13, 2.06]
MRC (Finland) 1993	4/1609	1/398		16.8	0.99 [0.11, 8.83]
Subtotal (95% CI)	3967	2764		100.0	1.32 [0.57, 3.06]
Total events: 15 (CVS), 9 (Amniocentesis)					
Test for heterogeneity chi-square=3.75 df=2 p=0.15 I^2 =46.6%					
Test for overall effect z=0.64 p=0.5					
02 Transabdominal CVS versus amniocentesis					
Denmark 1992	7/1027	6/1042		100.0	1.18 [0.40, 3.51]
Subtotal (95% CI)	1027	1042		100.0	1.18 [0.40, 3.51]
Total events: 7 (CVS), 6 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.30 p=0.8					
03 CVS (any route) versus amniocentesis					
Denmark 1992	10/2037	6/1042		44.1	0.85 [0.31, 2.34]
MRC 1991	15/1609	10/1592		55.9	1.48 [0.67, 3.29]
Subtotal (95% CI)	3646	2634		100.0	1.21 [0.65, 2.24]
Total events: 25 (CVS), 16 (Amniocentesis)					
Test for heterogeneity chi-square=0.71 df=1 p=0.40 I^2 =0.0%					
Test for overall effect z=0.59 p=0.6					

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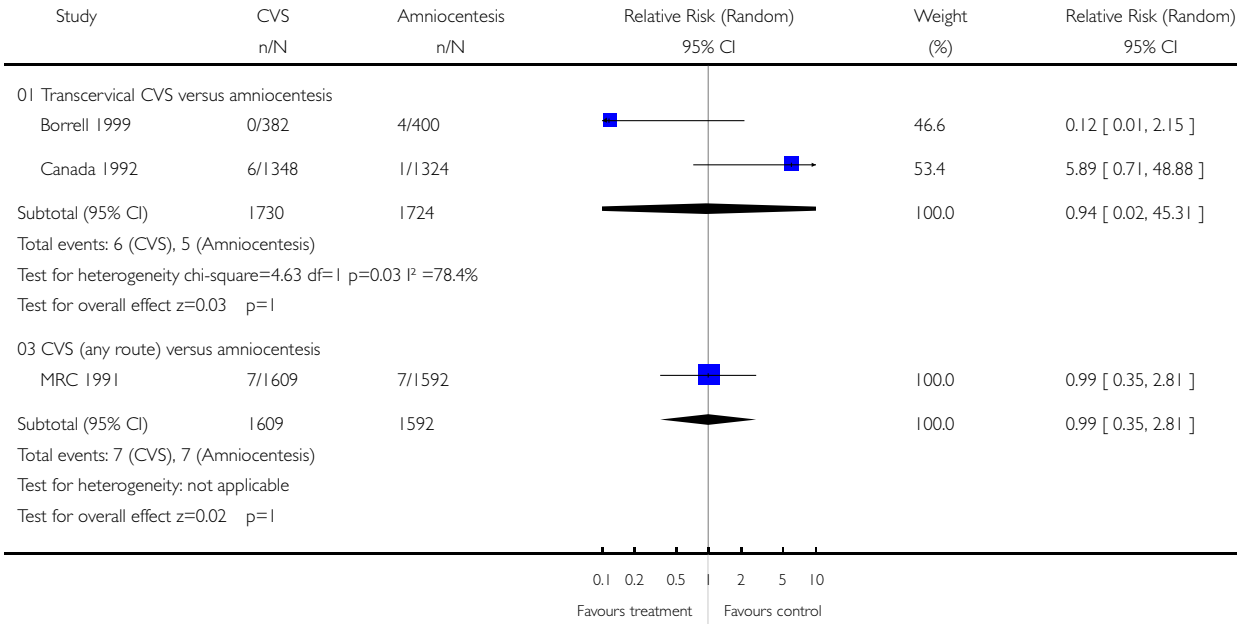
Analysis 03.27. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 27 Stillbirths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 27 Stillbirths



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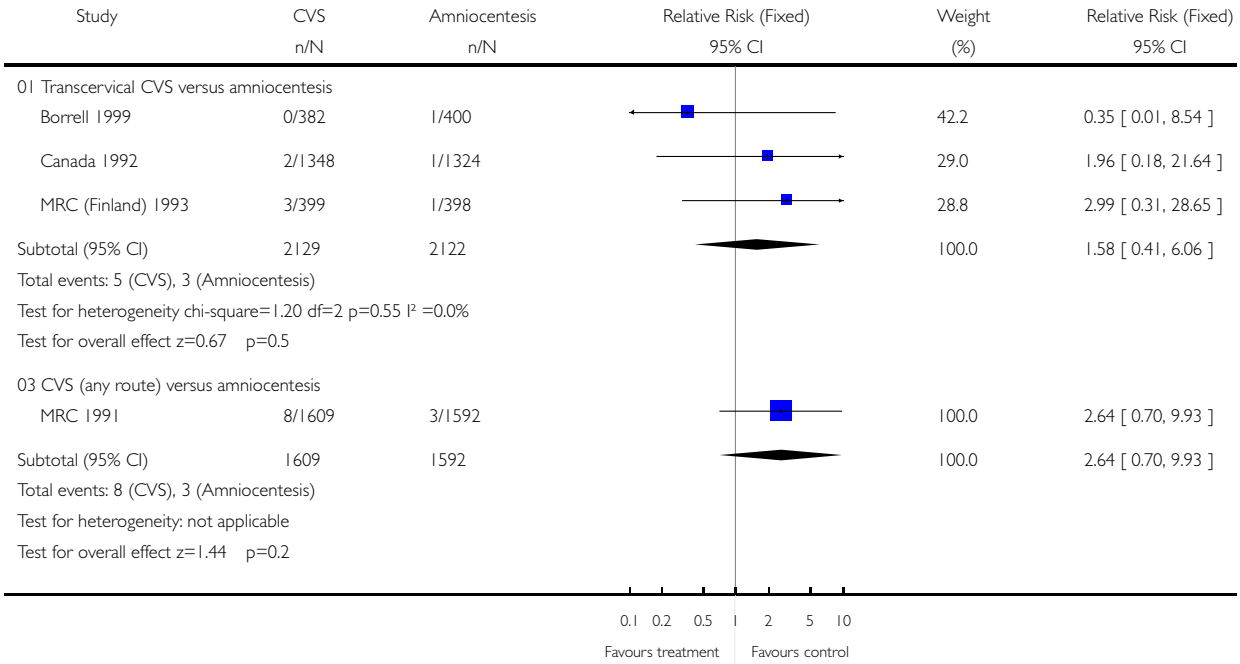
Analysis 03.28. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 28 Neonatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 28 Neonatal deaths



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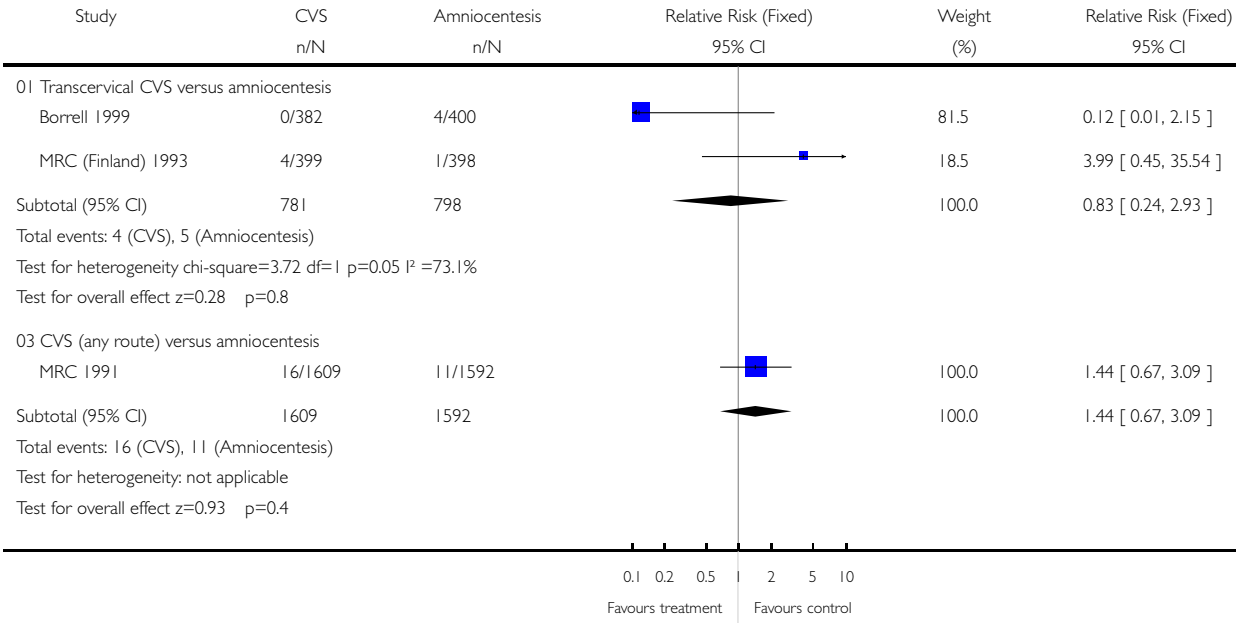
Analysis 03.29. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 29 All recorded deaths after viability

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 29 All recorded deaths after viability

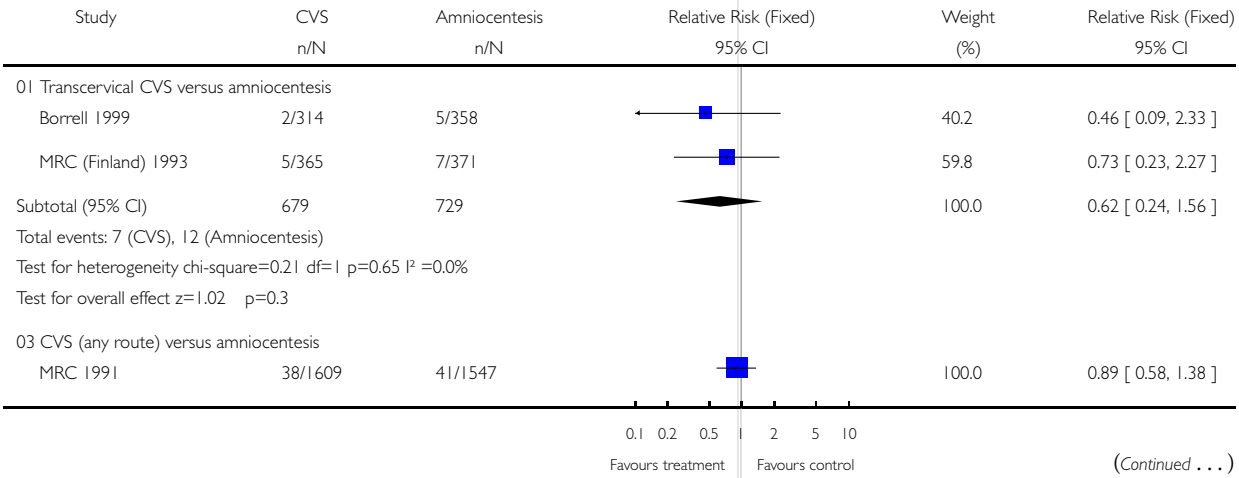


Analysis 03.30. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 30 Congenital anomalies (all recorded)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 30 Congenital anomalies (all recorded)



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Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	1609	1547		100.0	0.89 [0.58, 1.38]
Total events: 38 (CVS), 41 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.52 p=0.6					

Analysis 03.31. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 31 Talipes

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 31 Talipes

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Transcervical CVS versus amniocentesis					
× MRC (Finland) 1993	0/399	0/398		0.0	Not estimable
Subtotal (95% CI)	399	398		0.0	Not estimable
Total events: 0 (CVS), 0 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Analysis 03.33. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 33 Limb reduction defects

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 33 Limb reduction defects

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 CVS (any route) versus amniocentesis					
MRC 1991	2/1609	0/1592		100.0	4.95 [0.24, 102.97]
Total (95% CI)	1609	1592		100.0	4.95 [0.24, 102.97]
Total events: 2 (CVS), 0 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					

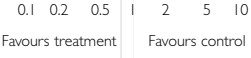
Analysis 03.38. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 38 Result given in less than 7 days (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 38 Result given in less than 7 days (not prespecified)

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 CVS (any route) versus amniocentesis					
MRC 1991	235/1549	10/1550		100.0	23.52 [12.54, 44.10]
Subtotal (95% CI)	1549	1550		100.0	23.52 [12.54, 44.10]
Total events: 235 (CVS), 10 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=9.84 p<0.00001					



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Analysis 03.39. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 39 Result given in less than 14 days (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 39 Result given in less than 14 days (not prespecified)

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 CVS (any route) versus amniocentesis					
MRC (Finland) 1993	348/1549	88/1550		100.0	3.96 [3.17, 4.95]
Subtotal (95% CI)	1549	1550		100.0	3.96 [3.17, 4.95]
Total events: 348 (CVS), 88 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=12.09 p<0.00001					

Analysis 03.40. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 40 Result given in less than 21 days (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 40 Result given in less than 21 days (not prespecified)

Study	CVS n/N	Amniocentesis n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 CVS (any route) versus amniocentesis					
MRC (Finland) 1993	282/1549	392/1550		100.0	0.72 [0.63, 0.82]
Subtotal (95% CI)	1549	1550		100.0	0.72 [0.63, 0.82]
Total events: 282 (CVS), 392 (Amniocentesis)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.74 p<0.00001					

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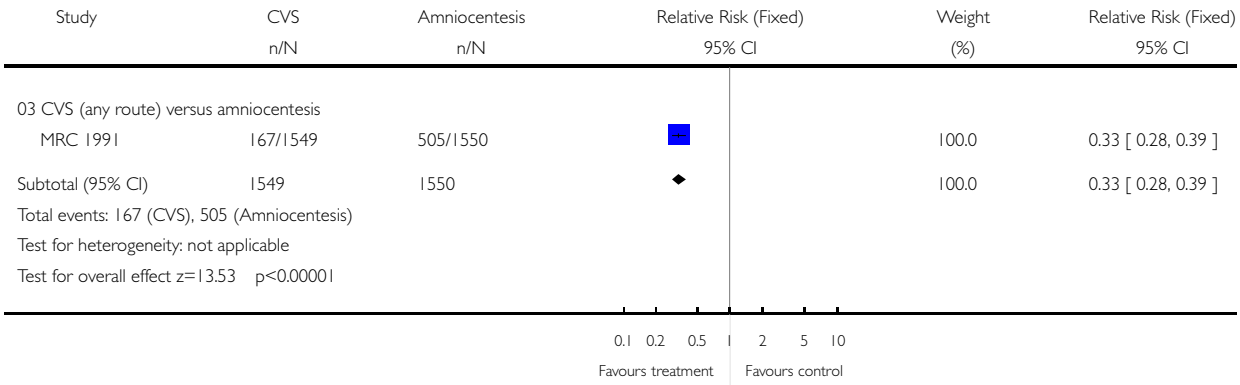
Analysis 03.41. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 41 Result given in more than 21days (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 41 Result given in more than 21days (not prespecified)

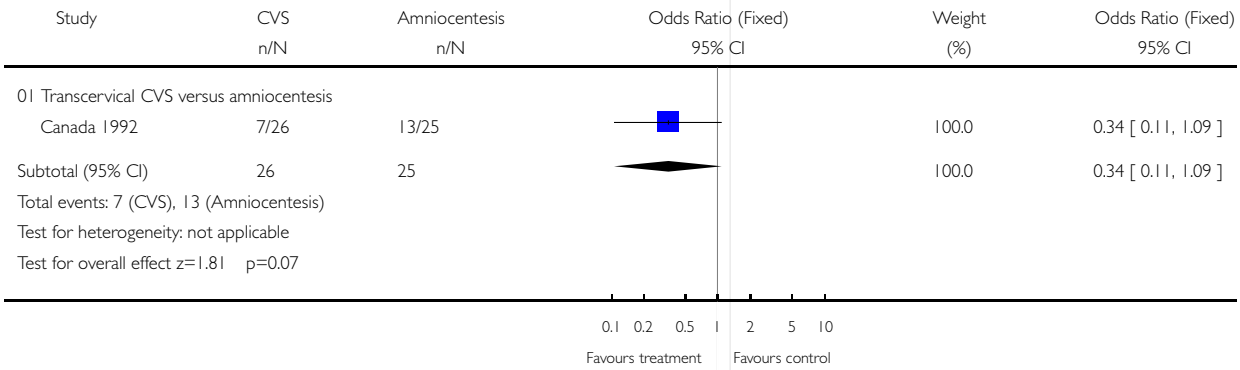


Analysis 03.42. Comparison 03 Chorionic villus sampling versus mid trimester amniocentesis, Outcome 42 Not wanting another baby at 22 weeks gestation (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 03 Chorionic villus sampling versus mid trimester amniocentesis

Outcome: 42 Not wanting another baby at 22 weeks gestation (not prespecified)



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Analysis 04.01. Comparison 04 Transcervical versus transabdominal CVS, Outcome 01 Not complied with allocated procedure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 01 Not complied with allocated procedure

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Bovicelli 1986	0/60	0/60		0.0	Not estimable
Brambati 1991	110/599	38/595		49.2	2.88 [2.02, 4.08]
USNICHD 1992	130/1944	130/1929		50.8	0.99 [0.78, 1.25]
Total (95% CI)	2603	2584		100.0	1.68 [0.59, 4.76]

Total events: 240 (Transcervical CVS), 168 (Transabdominal CVS)

Test for heterogeneity chi-square=24.47 df=1 p=<0.0001 I^2 =95.9%

Test for overall effect z=0.97 p=0.3

Analysis 04.02. Comparison 04 Transcervical versus transabdominal CVS, Outcome 02 Sampling failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 02 Sampling failure

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bovicelli 1986	1/60	1/60		3.5	1.00 [0.06, 15.62]
Brambati 1991	1/599	1/595		3.5	0.99 [0.06, 15.84]
Tomassini 1988	3/24	0/20		1.9	5.88 [0.32, 107.49]
USNICHD 1992	47/1944	26/1929		91.1	1.79 [1.12, 2.88]
Total (95% CI)	2627	2604		100.0	1.82 [1.15, 2.86]

Total events: 52 (Transcervical CVS), 28 (Transabdominal CVS)

Test for heterogeneity chi-square=0.99 df=3 p=0.80 I^2 =0.0%

Test for overall effect z=2.58 p=0.01

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Analysis 04.03. Comparison 04 Transcervical versus transabdominal CVS, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 03 Multiple insertions

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bovicelli 1986	14/60	8/60		29.6	1.75 [0.79, 3.86]
Brambati 1991	60/599	19/595		70.4	3.14 [1.90, 5.19]
Total (95% CI)	659	655		100.0	2.73 [1.78, 4.17]

Total events: 74 (Transcervical CVS), 27 (Transabdominal CVS)

Test for heterogeneity chi-square=1.50 df=1 p=0.22 I^2 =33.5%

Test for overall effect z=4.64 p<0.00001

Analysis 04.04. Comparison 04 Transcervical versus transabdominal CVS, Outcome 04 Second test performed

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 04 Second test performed

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brambati 1991	20/599	16/595		100.0	1.24 [0.65, 2.37]
Total (95% CI)	599	595		100.0	1.24 [0.65, 2.37]

Total events: 20 (Transcervical CVS), 16 (Transabdominal CVS)

Test for heterogeneity: not applicable

Test for overall effect z=0.66 p=0.5

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Analysis 04.05. Comparison 04 Transcervical versus transabdominal CVS, Outcome 05 Laboratory failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 05 Laboratory failure

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brambati 1991	9/599	4/595		100.0	2.23 [0.69, 7.22]
Total (95% CI)	599	595		100.0	2.23 [0.69, 7.22]
Total events: 9 (Transcervical CVS), 4 (Transabdominal CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.34 p=0.2					

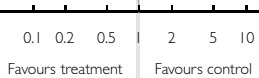
Analysis 04.06. Comparison 04 Transcervical versus transabdominal CVS, Outcome 06 All non-mosaic abnormalities

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 06 All non-mosaic abnormalities

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Denmark 1992	68/1419	56/1443		100.0	1.23 [0.87, 1.75]
Total (95% CI)	1419	1443		100.0	1.23 [0.87, 1.75]
Total events: 68 (Transcervical CVS), 56 (Transabdominal CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.19 p=0.2					



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Analysis 04.07. Comparison 04 Transcervical versus transabdominal CVS, Outcome 07 True mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 07 True mosaics

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Denmark 1992	10/1419	11/1443		100.0	0.92 [0.39, 2.17]
Total (95% CI)	1419	1443		100.0	0.92 [0.39, 2.17]

Total events: 10 (Transcervical CVS), 11 (Transabdominal CVS)

Test for heterogeneity: not applicable

Test for overall effect z=0.18 p=0.9

Analysis 04.08. Comparison 04 Transcervical versus transabdominal CVS, Outcome 08 Confined mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

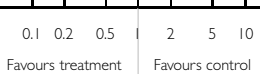
Outcome: 08 Confined mosaics

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Denmark 1992	5/1419	6/1443		100.0	0.85 [0.26, 2.77]
Total (95% CI)	1419	1443		100.0	0.85 [0.26, 2.77]

Total events: 5 (Transcervical CVS), 6 (Transabdominal CVS)

Test for heterogeneity: not applicable

Test for overall effect z=0.27 p=0.8



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Analysis 04.13. Comparison 04 Transcervical versus transabdominal CVS, Outcome 13 Vaginal bleeding after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 13 Vaginal bleeding after test

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Bovicelli 1986	32/60	0/60		27.8	65.00 [4.07, 1037.74]
Brambati 1991	35/599	11/595		47.5	3.16 [1.62, 6.16]
Tomassini 1988	1/24	0/20		24.7	2.52 [0.11, 58.67]
Total (95% CI)	683	675		100.0	6.93 [0.77, 62.83]

Total events: 68 (Transcervical CVS), 11 (Transabdominal CVS)

Test for heterogeneity chi-square=6.21 df=2 p=0.04 I^2 =67.8%

Test for overall effect z=1.72 p=0.09

Analysis 04.14. Comparison 04 Transcervical versus transabdominal CVS, Outcome 14 Amniotic leakage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

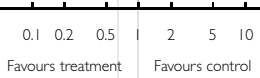
Outcome: 14 Amniotic leakage after test

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tomassini 1988	0/24	1/20		100.0	0.28 [0.01, 6.52]
Total (95% CI)	24	20		100.0	0.28 [0.01, 6.52]

Total events: 0 (Transcervical CVS), 1 (Transabdominal CVS)

Test for heterogeneity: not applicable

Test for overall effect z=0.79 p=0.4



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Analysis 04.20. Comparison 04 Transcervical versus transabdominal CVS, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Bovicelli 1986	5/60	5/60		7.1	1.00 [0.31, 3.28]
Brambati 1991	95/592	102/591		30.6	0.93 [0.72, 1.20]
Denmark 1992	188/1514	113/1527		31.9	1.68 [1.34, 2.10]
Tomassini 1988	2/24	1/20		2.2	1.67 [0.16, 17.06]
USNICHD 1992	74/1846	72/1744		28.2	0.97 [0.71, 1.33]
Total (95% CI)	4036	3942		100.0	1.16 [0.81, 1.65]
Total events: 364 (Transcervical CVS), 293 (Transabdominal CVS)					
Test for heterogeneity chi-square=14.43 df=4 p=0.006 I^2 =72.3%					
Test for overall effect z=0.81 p=0.4					

Analysis 04.21. Comparison 04 Transcervical versus transabdominal CVS, Outcome 21 Termination of pregnancy (all)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 21 Termination of pregnancy (all)

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bovicelli 1986	3/60	3/60		5.8	1.00 [0.21, 4.76]
Brambati 1991	40/591	49/592		94.2	0.82 [0.55, 1.22]
Total (95% CI)	651	652		100.0	0.83 [0.56, 1.22]
Total events: 43 (Transcervical CVS), 52 (Transabdominal CVS)					
Test for heterogeneity chi-square=0.06 df=1 p=0.81 I^2 =0.0%					
Test for overall effect z=0.95 p=0.3					

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Analysis 04.24. Comparison 04 Transcervical versus transabdominal CVS, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 24 Spontaneous miscarriage

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Bovicelli 1986	2/60	2/60		11.5	1.00 [0.15, 6.87]
Brambati 1991	47/592	44/591		41.5	1.07 [0.72, 1.58]
Denmark 1992	83/1010	31/1027		41.3	2.72 [1.82, 4.07]
Tomassini 1988	2/24	0/20		5.6	4.20 [0.21, 82.72]
Total (95% CI)	1686	1698		100.0	1.68 [0.79, 3.58]
Total events: 134 (Transcervical CVS), 77 (Transabdominal CVS)					
Test for heterogeneity chi-square=11.30 df=3 p=0.01 I^2 =73.4%					
Test for overall effect z=1.35 p=0.2					

Analysis 04.25. Comparison 04 Transcervical versus transabdominal CVS, Outcome 25 Spontaneous miscarriage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 25 Spontaneous miscarriage after test

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bovicelli 1986	2/60	2/60		7.5	1.00 [0.15, 6.87]
Brambati 1991	29/592	24/591		90.4	1.21 [0.71, 2.05]
Tomassini 1988	2/24	0/20		2.0	4.20 [0.21, 82.72]
Total (95% CI)	676	671		100.0	1.25 [0.76, 2.06]
Total events: 33 (Transcervical CVS), 26 (Transabdominal CVS)					
Test for heterogeneity chi-square=0.70 df=2 p=0.70 I^2 =0.0%					
Test for overall effect z=0.88 p=0.4					

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Analysis 04.26. Comparison 04 Transcervical versus transabdominal CVS, Outcome 26 Perinatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 26 Perinatal deaths

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Denmark 1992	3/1010	7/1027		100.0	0.44 [0.11, 1.68]
Total (95% CI)	1010	1027		100.0	0.44 [0.11, 1.68]
Total events: 3 (Transcervical CVS), 7 (Transabdominal CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.21 p=0.2					

Analysis 04.27. Comparison 04 Transcervical versus transabdominal CVS, Outcome 27 Stillbirths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 27 Stillbirths

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brambati 1991	4/592	1/591		38.0	3.99 [0.45, 35.62]
Tomassini 1988	0/24	1/20		62.0	0.28 [0.01, 6.52]
Total (95% CI)	616	611		100.0	1.69 [0.38, 7.62]
Total events: 4 (Transcervical CVS), 2 (Transabdominal CVS)					
Test for heterogeneity chi-square=1.85 df=1 p=0.17 I^2 =45.8%					
Test for overall effect z=0.69 p=0.5					

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Analysis 04.28. Comparison 04 Transcervical versus transabdominal CVS, Outcome 28 Neonatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 28 Neonatal deaths

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brambati 1991	2/592	4/591		79.9	0.50 [0.09, 2.71]
USNICHD 1992	1/1846	1/1816		20.1	0.98 [0.06, 15.72]
Total (95% CI)	2438	2407		100.0	0.60 [0.14, 2.49]

Total events: 3 (Transcervical CVS), 5 (Transabdominal CVS)

Test for heterogeneity chi-square=0.17 df=1 p=0.68 I^2 =0.0%

Test for overall effect z=0.71 p=0.5

Analysis 04.30. Comparison 04 Transcervical versus transabdominal CVS, Outcome 30 Anomalies (all recorded)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

Outcome: 30 Anomalies (all recorded)

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Brambati 1991	9/501	13/497		36.0	0.69 [0.30, 1.59]
Denmark 1992	15/1268	24/1356		64.0	0.67 [0.35, 1.27]
Total (95% CI)	1769	1853		100.0	0.68 [0.41, 1.12]

Total events: 24 (Transcervical CVS), 37 (Transabdominal CVS)

Test for heterogeneity chi-square=0.00 df=1 p=0.96 I^2 =0.0%

Test for overall effect z=1.51 p=0.1

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Analysis 04.31. Comparison 04 Transcervical versus transabdominal CVS, Outcome 31 Talipes

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 04 Transcervical versus transabdominal CVS

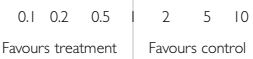
Outcome: 31 Talipes

Study	Transcervical CVS n/N	Transabdominal CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Denmark 1992	3/1268	1/1356		100.0	3.21 [0.33, 30.80]
Total (95% CI)	1268	1356		100.0	3.21 [0.33, 30.80]

Total events: 3 (Transcervical CVS), 1 (Transabdominal CVS)

Test for heterogeneity: not applicable

Test for overall effect z=1.01 p=0.3



Analysis 05.01. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 01 Not complied with allocated procedure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

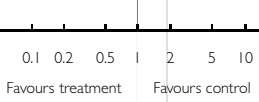
Outcome: 01 Not complied with allocated procedure

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	0/559	4/562		31.9	0.11 [0.01, 2.07]
× King's 1996	0/278	0/277		0.0	Not estimable
Leiden 1998	1/55	10/60		68.1	0.11 [0.01, 0.82]
Total (95% CI)	892	899		100.0	0.11 [0.02, 0.58]

Total events: 1 (Early amniocentesis), 14 (CVS)

Test for heterogeneity chi-square=0.00 df=1 p=0.99 I^2 =0.0%

Test for overall effect z=2.60 p=0.009



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Analysis 05.02. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 02 Sampling failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 02 Sampling failure

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	3/559	11/562		71.3	0.27 [0.08, 0.98]
King's 1996	0/278	2/277		16.3	0.20 [0.01, 4.13]
Leiden 1998	1/55	2/60		12.4	0.55 [0.05, 5.85]
Total (95% CI)	892	899		100.0	0.30 [0.10, 0.84]

Total events: 4 (Early amniocentesis), 15 (CVS)

Test for heterogeneity chi-square=0.33 df=2 p=0.85 I^2 =0.0%

Test for overall effect z=2.29 p=0.02

Analysis 05.03. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 03 Multiple insertions

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
King's 1996	4/278	7/277		22.7	0.57 [0.17, 1.92]
Leiden 1998	5/55	25/60		77.3	0.22 [0.09, 0.53]
Total (95% CI)	333	337		100.0	0.30 [0.15, 0.60]

Total events: 9 (Early amniocentesis), 32 (CVS)

Test for heterogeneity chi-square=1.56 df=1 p=0.21 I^2 =35.9%

Test for overall effect z=3.39 p=0.0007

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Analysis 05.04. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 04 Second test performed

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 04 Second test performed

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/559	13/562		54.5	0.08 [0.01, 0.59]
King's 1996	5/278	7/277		29.5	0.71 [0.23, 2.22]
Leiden 1998	4/55	4/60		16.1	1.09 [0.29, 4.15]
Total (95% CI)	892	899		100.0	0.43 [0.21, 0.88]
Total events: 10 (Early amniocentesis), 24 (CVS)					
Test for heterogeneity chi-square=5.39 df=2 p=0.07 I^2 =62.9%					
Test for overall effect z=2.30 p=0.02					

Analysis 05.05. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 05 Laboratory failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 05 Laboratory failure

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/559	5/562		40.0	0.20 [0.02, 1.72]
King's 1996	5/278	7/277		56.2	0.71 [0.23, 2.22]
Leiden 1998	1/55	0/60		3.8	3.27 [0.14, 78.58]
Total (95% CI)	892	899		100.0	0.61 [0.25, 1.48]
Total events: 7 (Early amniocentesis), 12 (CVS)					
Test for heterogeneity chi-square=2.17 df=2 p=0.34 I^2 =8.0%					
Test for overall effect z=1.10 p=0.3					

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Analysis 05.06. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 06 All non-mosaic abnormalities

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 06 All non-mosaic abnormalities

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	4/559	11/562		66.7	0.37 [0.12, 1.14]
King's 1996	5/278	5/277		30.4	1.00 [0.29, 3.40]
Leiden 1998	2/55	0/60		2.9	5.45 [0.27, 111.01]
Total (95% CI)	892	899		100.0	0.71 [0.33, 1.49]

Total events: 11 (Early amniocentesis), 16 (CVS)

Test for heterogeneity chi-square=3.35 df=2 p=0.19 I^2 =40.3%

Test for overall effect z=0.92 p=0.4

Analysis 05.07. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 07 True mosaics

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

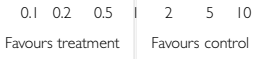
Outcome: 07 True mosaics

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/559	1/562		39.9	1.01 [0.06, 16.03]
King's 1996	0/278	1/277		60.1	0.33 [0.01, 8.12]
Total (95% CI)	837	839		100.0	0.60 [0.08, 4.53]

Total events: 1 (Early amniocentesis), 2 (CVS)

Test for heterogeneity chi-square=0.26 df=1 p=0.61 I^2 =0.0%

Test for overall effect z=0.49 p=0.6



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Analysis 05.08. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 08 Abnormalities confined to non fetal tissues

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 08 Abnormalities confined to non fetal tissues

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	0/559	3/562		53.9	0.14 [0.01, 2.77]
King's 1996	0/278	2/277		38.7	0.20 [0.01, 4.13]
Leiden 1998	2/55	0/60		7.4	5.45 [0.27, 111.01]
Total (95% CI)	892	899		100.0	0.56 [0.16, 2.00]

Total events: 2 (Early amniocentesis), 5 (CVS)

Test for heterogeneity chi-square=3.44 df=2 p=0.18 I^2 =41.9%

Test for overall effect z=0.90 p=0.4

Analysis 05.09. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 09 Maternal contamination

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

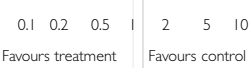
Outcome: 09 Maternal contamination

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
King's 1996	0/278	2/277		100.0	0.20 [0.01, 4.13]
Total (95% CI)	278	277		100.0	0.20 [0.01, 4.13]

Total events: 0 (Early amniocentesis), 2 (CVS)

Test for heterogeneity: not applicable

Test for overall effect z=1.04 p=0.3



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Analysis 05.10. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 10 Known false positive after birth

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 10 Known false positive after birth

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× King's 1996	0/278	0/277		0.0	Not estimable
Leiden 1998	0/55	1/60		100.0	0.36 [0.02, 8.73]
Total (95% CI)	333	337		100.0	0.36 [0.02, 8.73]
Total events: 0 (Early amniocentesis), 1 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.62 p=0.5					

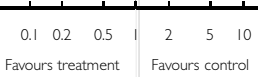
Analysis 05.11. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 11 Known false negative after birth

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 11 Known false negative after birth

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× King's 1996	0/277	0/278		0.0	Not estimable
Total (95% CI)	277	278		0.0	Not estimable
Total events: 0 (Early amniocentesis), 0 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Analysis 05.13. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 13 Vaginal bleeding after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

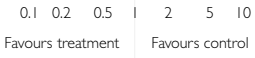
Outcome: 13 Vaginal bleeding after test

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	23/559	40/562		97.7	0.58 [0.35, 0.95]
Leiden 1998	3/55	1/60		2.3	3.27 [0.35, 30.54]
Total (95% CI)	614	622		100.0	0.64 [0.40, 1.03]

Total events: 26 (Early amniocentesis), 41 (CVS)

Test for heterogeneity chi-square=2.21 df=1 p=0.14 I^2 =54.8%

Test for overall effect z=1.82 p=0.07



Analysis 05.14. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 14 Amniotic leakage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

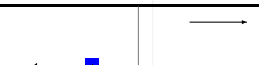
Outcome: 14 Amniotic leakage after test

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Copenhagen 1997	24/559	0/562		51.1	49.26 [3.00, 808.08]
Leiden 1998	0/55	1/60		48.9	0.36 [0.02, 8.73]
Total (95% CI)	614	622		100.0	4.47 [0.03, 709.83]

Total events: 24 (Early amniocentesis), 1 (CVS)

Test for heterogeneity chi-square=5.73 df=1 p=0.02 I^2 =82.6%

Test for overall effect z=0.58 p=0.6



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Analysis 05.18. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 18 Delivery before 37 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 18 Delivery before 37 weeks

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	27/559	24/562		57.5	1.13 [0.66, 1.94]
King's 1996	19/257	15/262		35.7	1.29 [0.67, 2.49]
Leiden 1998	2/55	3/60		6.9	0.73 [0.13, 4.19]
Total (95% CI)	871	884		100.0	1.16 [0.78, 1.74]

Total events: 48 (Early amniocentesis), 42 (CVS)

Test for heterogeneity chi-square=0.38 df=2 p=0.83 I^2 =0.0%

Test for overall effect z=0.72 p=0.5

Analysis 05.19. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 19 Delivery before 33 weeks

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 19 Delivery before 33 weeks

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	2/559	4/562		100.0	0.50 [0.09, 2.73]
Total (95% CI)	559	562		100.0	0.50 [0.09, 2.73]

Total events: 2 (Early amniocentesis), 4 (CVS)

Test for heterogeneity: not applicable

Test for overall effect z=0.80 p=0.4

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Analysis 05.20. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	30/559	27/562		60.1	1.12 [0.67, 1.85]
King's 1996	22/278	15/277		33.5	1.46 [0.77, 2.76]
Leiden 1998	4/56	3/61		6.4	1.45 [0.34, 6.21]
Total (95% CI)	893	900		100.0	1.25 [0.86, 1.84]
Total events: 56 (Early amniocentesis), 45 (CVS)					
Test for heterogeneity chi-square=0.46 df=2 p=0.79 I^2 =0.0%					
Test for overall effect z=1.16 p=0.2					

Analysis 05.21. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 21 Termination of pregnancy (all)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 21 Termination of pregnancy (all)

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	9/559	13/562		56.4	0.70 [0.30, 1.62]
King's 1996	6/278	10/277		43.6	0.60 [0.22, 1.62]
× Leiden 1998	0/55	0/60		0.0	Not estimable
Total (95% CI)	892	899		100.0	0.65 [0.34, 1.24]
Total events: 15 (Early amniocentesis), 23 (CVS)					
Test for heterogeneity chi-square=0.05 df=1 p=0.82 I^2 =0.0%					
Test for overall effect z=1.30 p=0.2					

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Analysis 05.24. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 24 Spontaneous miscarriage

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	20/559	13/562		62.2	1.55 [0.78, 3.08]
King's 1996	16/278	5/277		24.0	3.19 [1.18, 8.58]
Leiden 1998	4/56	3/61		13.8	1.45 [0.34, 6.21]
Total (95% CI)	893	900		100.0	1.93 [1.15, 3.24]
Total events: 40 (Early amniocentesis), 21 (CVS)					
Test for heterogeneity chi-square=1.53 df=2 p=0.47 I^2 =0.0%					
Test for overall effect z=2.47 p=0.01					

Analysis 05.25. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 25 Spontaneous miscarriage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 25 Spontaneous miscarriage after test

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	17/559	12/562		63.4	1.42 [0.69, 2.95]
King's 1996	16/278	5/277		26.5	3.19 [1.18, 8.58]
Leiden 1998	3/55	2/60		10.1	1.64 [0.28, 9.43]
Total (95% CI)	892	899		100.0	1.91 [1.11, 3.31]
Total events: 36 (Early amniocentesis), 19 (CVS)					
Test for heterogeneity chi-square=1.68 df=2 p=0.43 I^2 =0.0%					
Test for overall effect z=2.32 p=0.02					

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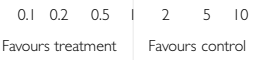
Analysis 05.26. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 26 Perinatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 26 Perinatal deaths

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/527	1/531		100.0	1.01 [0.06, 16.07]
× King's 1996	0/278	0/277		0.0	Not estimable
× Leiden 1998	0/56	0/61		0.0	Not estimable
Total (95% CI)	861	869		100.0	1.01 [0.06, 16.07]
Total events: 1 (Early amniocentesis), 1 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					



Analysis 05.27. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 27 Stillbirths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 27 Stillbirths

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Copenhagen 1997	0/527	0/531		0.0	Not estimable
× King's 1996	0/278	0/277		0.0	Not estimable
× Leiden 1998	0/56	0/61		0.0	Not estimable
Total (95% CI)	861	869		0.0	Not estimable
Total events: 0 (Early amniocentesis), 0 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Analysis 05.28. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 28 Neonatal deaths

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 28 Neonatal deaths

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/559	1/562		100.0	1.01 [0.06, 16.03]
× King's 1996	0/257	0/262		0.0	Not estimable
× Leiden 1998	0/56	0/61		0.0	Not estimable
Total (95% CI)	872	885		100.0	1.01 [0.06, 16.03]
Total events: 1 (Early amniocentesis), 1 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

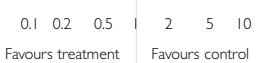
Analysis 05.29. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 29 All recorded deaths after viability

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 29 All recorded deaths after viability

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	1/559	1/562		100.0	1.01 [0.06, 16.03]
× King's 1996	0/257	0/262		0.0	Not estimable
× Leiden 1998	0/55	0/60		0.0	Not estimable
Total (95% CI)	871	884		100.0	1.01 [0.06, 16.03]
Total events: 1 (Early amniocentesis), 1 (CVS)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					



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Analysis 05.30. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 30 Anomalies (all recorded)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 30 Anomalies (all recorded)

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Copenhagen 1997	21/527	8/531		34.4	2.64 [1.18, 5.92]
King's 1996	11/257	8/262		33.1	1.40 [0.57, 3.43]
Leiden 1998	5/52	16/58		32.5	0.35 [0.14, 0.89]
Total (95% CI)	836	851		100.0	1.11 [0.35, 3.55]

Total events: 37 (Early amniocentesis), 32 (CVS)

Test for heterogeneity chi-square=10.58 df=2 p=0.005 I^2 =81.1%

Test for overall effect z=0.17 p=0.9

Analysis 05.32. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 32 Talipes equinovarus

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 32 Talipes equinovarus

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	9/527	0/531		20.5	19.14 [1.12, 328.08]
King's 1996	5/257	1/262		40.7	5.10 [0.60, 43.33]
Leiden 1998	1/52	1/58		38.8	1.12 [0.07, 17.39]
Total (95% CI)	836	851		100.0	6.43 [1.68, 24.64]

Total events: 15 (Early amniocentesis), 2 (CVS)

Test for heterogeneity chi-square=2.17 df=2 p=0.34 I^2 =8.0%

Test for overall effect z=2.71 p=0.007

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Analysis 05.33. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 33 Haemangioma

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

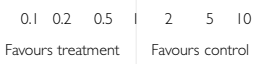
Outcome: 33 Haemangioma

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	3/527	1/531		10.4	3.02 [0.32, 28.97]
King's 1996	0/257	1/262		15.5	0.34 [0.01, 8.30]
Leiden 1998	0/52	7/58		74.1	0.07 [0.00, 1.27]
Total (95% CI)	836	851		100.0	0.42 [0.13, 1.36]

Total events: 3 (Early amniocentesis), 9 (CVS)

Test for heterogeneity chi-square=4.37 df=2 p=0.11 I^2 =54.3%

Test for overall effect z=1.44 p=0.1



Analysis 05.35. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 35 Neonatal respiratory distress syndrome

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 35 Neonatal respiratory distress syndrome

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Copenhagen 1997	5/527	4/531		39.8	1.26 [0.34, 4.66]
King's 1996	0/74	6/86		60.2	0.09 [0.01, 1.56]
× Leiden 1998	0/52	0/58		0.0	Not estimable
Total (95% CI)	653	675		100.0	0.56 [0.20, 1.58]

Total events: 5 (Early amniocentesis), 10 (CVS)

Test for heterogeneity chi-square=3.07 df=1 p=0.08 I^2 =67.5%

Test for overall effect z=1.10 p=0.3

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Analysis 05.37. Comparison 05 Early amniocentesis versus transabdominal CVS, Outcome 37 Birthweight below 5th centile

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 05 Early amniocentesis versus transabdominal CVS

Outcome: 37 Birthweight below 5th centile

Study	Early amniocentesis n/N	CVS n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
King's 1996	9/257	5/262		53.8	1.84 [0.62, 5.40]
Leiden 1998	0/52	4/58		46.2	0.12 [0.01, 2.24]
Total (95% CI)	309	320		100.0	1.04 [0.43, 2.56]

Total events: 9 (Early amniocentesis), 9 (CVS)

Test for heterogeneity chi-square=3.13 df=1 p=0.08 I^2 =68.0%

Test for overall effect z=0.09 p=0.9

Analysis 06.02. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 02 Sampling failure

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 02 Sampling failure

Study	Ultrasound n/N	No ultrasound n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nolan 1981	5/112	0/111		100.0	10.90 [0.61, 194.85]
Total (95% CI)	112	111		100.0	10.90 [0.61, 194.85]

Total events: 5 (Ultrasound), 0 (No ultrasound)

Test for heterogeneity: not applicable

Test for overall effect z=1.62 p=0.1

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Analysis 06.03. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 03 Multiple insertions

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 03 Multiple insertions

Study	Ultrasound n/N	No ultrasound n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nolan 1981	21/112	31/111		100.0	0.67 [0.41, 1.09]
Total (95% CI)	112	111		100.0	0.67 [0.41, 1.09]
Total events: 21 (Ultrasound), 31 (No ultrasound)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.60 p=0.1					

Analysis 06.20. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study	Ultrasound n/N	No ultrasound n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nolan 1981	0/112	1/111		100.0	0.33 [0.01, 8.02]
Total (95% CI)	112	111		100.0	0.33 [0.01, 8.02]
Total events: 0 (Ultrasound), 1 (No ultrasound)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

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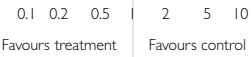
Analysis 06.24. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 24 Spontaneous miscarriage

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

Study	Ultrasound n/N	No ultrasound n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nolan 1981	0/112	1/111		100.0	0.33 [0.01, 8.02]
Total (95% CI)	112	111		100.0	0.33 [0.01, 8.02]
Total events: 0 (Ultrasound), 1 (No ultrasound)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					



Analysis 06.25. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

Study	Ultrasound n/N	No ultrasound n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nolan 1981	0/112	1/111		100.0	0.33 [0.01, 8.02]
Total (95% CI)	112	111		100.0	0.33 [0.01, 8.02]
Total events: 0 (Ultrasound), 1 (No ultrasound)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

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Analysis 06.38. Comparison 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis, Outcome 38 Bloody tap (not prespecified)

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 06 Ultrasound versus no ultrasound before mid-trimester amniocentesis

Outcome: 38 Bloody tap (not prespecified)

Study	Ultrasound n/N	No ultrasound n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Nolan 1981	17/112	9/111		100.0	2.03 [0.86, 4.77]
Total (95% CI)	112	111		100.0	2.03 [0.86, 4.77]
Total events: 17 (Ultrasound), 9 (No ultrasound)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.62 p=0.1					

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