Amniocentesis and chorionic villus sampling for prenatal diagnosis (Review)

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[Intervention Review]

Amniocentesis and chorionic villus sampling for prenatal diagnosis

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ABSTRACT

Background

A major disadvantage of second trimester amniocentesis is that the results are available relatively late in pregnancy (after 16 weeks' gestation). Chorionic villus sampling (CVS) and early amniocentesis can be done in the first trimester of pregnancy and offer an earlier alternative.

Objectives

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's Trials Register (January 2008).

Selection criteria

All randomised trials comparing amniocentesis and CVS by either transabdominal or transcervical route.

Data collection and analysis

Two review authors independently assessed eligibility and trial quality and performed data extraction.

Main results

We included a total of 16 randomised studies.

One study in a low-risk population (N = 4606) with a background pregnancy loss of around 2% found that a second trimester amniocentesis will increase total pregnancy loss by another 1%. This difference did not reach statistical significance and the confidence intervals (CI) around this excess risk were relatively large (risk ratio (RR) 1.41; 95% CI 0.99 to 2.00). In the same study, compared with no intervention, the increase in spontaneous miscarriages following second trimester amniocentesis was statistically significant (2.1% versus 1.3%; RR 1.60; 95% CI 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 (RR 4.61; 95% CI 1.82 to 11.66).

Compared with a second trimester amniocentesis, transcervical CVS carries a significantly higher risk of total pregnancy loss (RR 1.40; 95% CI 1.09 to 1.81) and spontaneous miscarriage (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.

Transcervical CVS is more technically demanding than transabdominal CVS, with more failures to obtain sample and more multiple insertions. However, the results related to comparative pregnancy loss between transabdominal and transcervical CVS are inconclusive, with significant heterogeneity between studies.

Authors' conclusions

Second trimester amniocentesis is safer than early amniocentesis or transcervical CVS, and is the procedure of choice for second trimester testing. Transabdominal CVS should be regarded as the procedure of first choice when testing is done before 15 weeks' gestation. Diagnostic accuracy of different methods could not be assessed adequately because of incomplete karyotype data in most studies.

PLAIN LANGUAGE SUMMARY

Amniocentesis and placental sampling for pre-birth diagnosis

Many women want to be reassured that their unborn baby is healthy. It is important that screening and diagnostic tests used are accurate and safe and can be done early enough in pregnancy to allow them the choice of terminating the pregnancy. Second trimester amniocentesis is most often used, at around 16 weeks' gestation. A needle is inserted through the abdominal wall into the uterus to remove amniotic fluid. Early amniocentesis or chorionic villus sampling (CVS) to withdraw placental tissue can be done before 15 weeks. Either a transabdominal or vaginal (transcervical) approach is used for CVS.

We identified a total of 16 randomised controlled trials for the review. One study of 4606 women in a low-risk population found that a second trimester amniocentesis increased spontaneous miscarriages, 2.1% versus 1.3% with no intervention.

Early amniocentesis was not a safe early alternative to second trimester amniocentesis because of increased pregnancy loss and a higher incidence of deformed or club foot (talipes). It is also technically more demanding and involves a greater number of needle insertions, laboratory failures and false negative results.

Transcervical CVS also increased the risk of total pregnancy compared with a second trimester amniocentesis, mostly because of spontaneous miscarriages. Transabdominal CVS may be safer than the transcervical route, but the data are limited. Transcervical CVS is also more technically demanding than transabdominal CVS, with more failures to obtain sample and more multiple needle insertions required. It is more likely to cause vaginal bleeding immediately after the procedure, in approximately 10% of women.

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 'false positive' screening tests (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 both accurate and safe and can be done early in pregnancy 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, only analysing fetal cells from amniotic fluid, placenta (chorionic villus tissue) or fetal blood can 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 (talipes) and respiratory complications (respiratory distress syndrome).

A major disadvantage of second trimester amniocentesis is that a final result is usually available only after 17 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. Earlier options include chorionic villus sampling (CVS) and early amniocentesis.

CVS was first described in China in the mid-1970s (China 1975) and developed further in the Western world during the 1980s. The procedure 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 six 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 nine 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) was introduced in the late 1980s. It 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 re-injected into the amniotic cavity (Sundberg 1991).

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.

METHODS

Criteria for considering studies for this review

Types of studies

We have included 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. We have excluded quasi-randomised studies (e.g. alternate allocation).

Types of participants

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

Types of interventions

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

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (January 2008).
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. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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 'Specialized Register' section within the editorial information about the CochranePregnancyandChildbirthGroup.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis

We have assessed all trials for methodological quality using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008), with a grade allocated to each trial

on the basis of allocation concealment. We have scored allocation concealment as A (adequate) for telephone randomisation and the use of sealed envelopes; B (unclear) for trials where randomisation is not clearly described or prone to bias (e.g. open cards, toss of a coin). We have excluded inadequate designs (C), such as alternate allocation and the use of record numbers. We have planned no other formal or informal qualitative analysis, as there were no planned exclusions based on quality.

We extracted the data onto hard-copy' data sheets, entered onto the Review Manager computer software (RevMan 2008), checked for accuracy by another co-author, and analysed using the Review Manager software. We extracted the data by allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. We have not included women who were randomised and subsequently either excluded or lost to follow up in the denominator data.

We calculated a weighted estimate of risk ratio for each outcome. Most of the outcomes were uncommon, therefore, odds ratios were similar to risk ratio for most analyses. We tested for heterogeneity between the trials using a I^2 test. In the absence of heterogeneity, we pooled the results using a fixed-effect model. When we found significant (I^2 > 50%) and unexplained heterogeneity, 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.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded 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 performed all procedures; the most experienced operator performed 54%. 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 freehand 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 amniocentesis. 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 procedure 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 comparing transabdominal and transcervical CVS. In total 3999 women were randomised. Transcervical CVS was 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 six to eight 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 was 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

Five 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.

NICHD EATA Group Trial (NICHD EATA 2004) was a large multicentre collaborative study carried out between 1997 and 2001 under the auspices of the US National Institute of Child Health and Human Development and Centre for Evaluation and Health Technology Assessment of the Danish National Board of Health. The trial randomised 3775 women from 3803 eligible women who consented to participation in a total group of 6370 women who were screened for eligibility. Eighty-seven per cent of the women were randomised at Rigshospitalet, Denmark, 7% at 11 U.S. centres, and 6% at two Canadian centres. In the early amniocentesis group, a 22-gauge spinal needle was used and 1 ml of amniotic fluid aspirated for each week of a pregnancy. In the CVS group, a single- (19- to 20-gauge) or double-needle technique (18- to 20-gauge) was used with the larger 'guide' needle introduced to the margin of the chorion, followed by the sample needle passing through the guide needle into the villi. To participate in the trial, operators were required to have completed at least 25 amniocenteses and 25 transabdominal CVS between 77 and 104 days of gestation. Thirty-two operators were certified to perform procedures at the 14 clinical centres. Two sampling passes were allowed. A second procedure, if required, could only be performed seven days after the first attempt.

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 1997 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 1997 compared to King's 1996 and Leiden 1998. In Copenhagen 1997, 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 'freehand' 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 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".

Risk of bias in included studies

(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 (Borrell 1999; Canada 1992; Denmark 1992; MRC 1991), 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. Among women designated as low risk, 3302 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 dropout 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 dropout 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 (generalisability) 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.

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

NICHD EATA 2004 aimed to recruit 6200 cytologically normal pregnancies in order to detect possible 50% increase in pregnancy loss following early amniocentesis. The study failed to reach prespecified sample size within the funding period, in part because of a change in the eligibility criteria. Initally the procedures were to be performed between 11 and 14 weeks (77 to 104 days). However, protocol revisions first eliminated week 11 (before recruitment began), and subsequently week 12 after reports indicated an increased risk of talipes equinovarus after early amniocentesis in those weeks. Thus, more than 90% of the procedures were performed at 13 to 14 weeks (91 to 104 days).
Three other included studies (Copenhagen 1997; King's 1996; Leiden 1998) were also 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 1997 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.
NICHD EATA 2004 used adequate concealment of allocation - telephone randomisation interactive voice response computer-based system. According to our prespecified criteria, Copenhagen 1997 and Leiden 1998 also 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 1997 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 amniocen-

tesis group, all 55 women had amniocentesis (one was done in the mid-trimester). 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 amniocentesis, suffered early pregnancy loss.

(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 1991 were 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).

Effects of interventions

(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 (RR 1.60; 95% CI 1.02 to 2.52). However, it is important to note that 95% CI for absolute 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 3.90; 95% CI 1.95 to 7.80).

(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 significantly higher (RR 1.29; 95% CI 1.03 to 1.61) and the number of congenital anomalies was also significantly increased in the early amniocentesis group. In particular the number of babies with talipes equinovarus was higher in the CEMAT 1998 trial (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.

Early amniocentesis required more multiple needle insertions compared with 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 (Borrell 1999; Canada 1992; Denmark 1992; MRC (Finland) 1993). Total pregnancy loss was consistently higher after transcervical CVS (RR 1.40; 95% CI 1.09 to 1.81). In the transcervical CVS group the total pregnancy loss varied from 7.3% in the MRC (Finland) 1993 trial to 19.5% in the Borrell 1999 trial. Interestingly, 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-effects 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 1.30 to 2.22), but not in the Canada 1992 trial (95% CI 0.92 to 1.30). Unsurprisingly, spontaneous miscarriages were the main contributor to the pregnancy loss in all four trials.

3.2. Transabdominal CVS 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%; RR 0.90; 95% CI 0.66 to 1.23).

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 (Denmark 1992; MRC 1991). Overall loss was higher after CVS 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. 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 also more cytogenetic abnormalities confined only to placenta and more false positive and false negative results. 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 randomised 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. 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 links 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 nine 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) Transbdominal versus transcervical CVS

Compared with transabdominal CVS, total pregnancy loss and spontaneous miscarriages were higher after transcervical CVS, but this was due to the excess loss in the transcervical arm of the Denmark 1992 trial. This trial (Denmark 1992) reported total pregnancy loss after transcervical CVS of 12.4% compared with 7.4% after transabdominal CVS. Corresponding figures for spontaneous pregnancy loss were 8.2% and 3%. However, total pregnancy loss and miscarriage rate in four other trials (Bovicelli 1986; Brambati 1991; Tomassini 1988; USNICHD 1992) were almost identical in both groups. Because of these differences, the tests for heterogeneity for these two outcomes were statistically significant (I^2 = 72.3%). 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; 95% 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-effects 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.

Transcervical CVS was more likely to fail, 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 and causing more vaginal bleeding. As far as cytogenetic analysis is concerned, both procedures are comparable.

(5) Early amniocentesis (EA) versus transabdominal CVS

Although the difference in combined total pregnancy did not reach statistical significance (RR 1.15; 95% CI 0.86 to 1.54), there were more spontaneous miscarriages after early amniocentesis (RR 1.76; 95% CI 1.17 to 2.64).

There was no difference in the overall incidence of anomalies in the newborn infants (RR 1.14; 95% CI 0.57 to 2.30). However, inter-study heterogeneity was significant for this outcome, with no obvious explanation for the observed differences between Copenhagen 1997 and Leiden 1998. Both groups have specifically highlighted two types of anomalies: talipes equinovarus and haemangiomas. The incidence of talipes in the EA group was 0.9% compared with 0.1% in the CVS group (RR 4.61; 95% CI 1.82 to 11.66).

An increased number of haemangiomas after CVS seen in Leiden 1998 has not been seen in the other two studies (RR 0.87; 95% CI 0.69 to 1.10). 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 six and nine 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, the numbers are too small for any meaningful comparison between two methods.

In Copenhagen 1997, 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. In the NICHD EATA 2004 EA, 10.3 days were needed to obtain the result (standard deviation (SD) 2.5), compared with 6.3 days (SD 3). These results were not pooled because they were not normally distributed.

(6) Ultrasound guided amniocentesis

The trial by Nolan 1981 evaluated 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 intervals for an excess pregnancy loss ranging 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. A systematic review of studies published after 1995 revealed lower absolute risks of pregnancy loss (Table 1) (Mujezinovic 2007). It is impossible to say if observed differences are random variations, or true improvement in the safety of the procedure in the last decade.

Table 1. Complications after amniocentesis

Type of fetal loss	Combined Total	Combined %	95% CI
Less than 20 weeks of pregnancy	22/2133	1.1	0.7-1.5
More than 20 weeks of pregnancy	17/1775	0.9	0.5-1.4
Less than 24 weeks of pregnancy	122/14057	0.9	0.6-1.3
More than 24 weeks of pregnancy	57/4195	1.0	0.5-1.8
Less than 28 weeks of pregnancy	283/14915	1.7	1.3-2.2
More than 28 weeks of pregnancy	134/14596	0.9	0.7-1.2

Table 1. Complications after amniocentesis (*Continued*)

Less than 14 days after AC	102/17047	0.6	0.5-0.7
Less than 30 days after AC	85/10727	0.8	0.4-1.2
Less than 60 days after AC	66/9406	0.7	0.5-0.9
Total pregnancy loss	627/49413	1.9	1.4-2.5
Multiple insertions	226/12142	2.0	0.9-3.6

The benefits of earlier diagnosis of fetal genetic abnormalities by chorionic villus sampling (CVS) must be set against possible higher risks of pregnancy loss and diagnostic inaccuracies when compared with second trimester amniocentesis. Unfortunately, the data related to the risk of pregnancy loss following CVS and amniocentesis are inconsistent. Second trimester amniocentesis was consistently safer than transcervical CVS, whilst Denmark 1992 showed no clinically significant difference in the pregnancy loss between transabdominal CVS and second trimester amniocentesis. One would therefore expect a clear benefit of transabdominal CVS in the 'head to head' comparisons with transcervical CVS. Unfortunately, the data are quite heterogeneous; for example, Denmark 1992 showed expected benefits of transabdominal CVS, but other trials did not. It is likely that operator skill and preferences played an important role in these studies. It is unrealistic to expect that any given operator will be equally skilled and experienced in all three methods. The question whether any added risks of early procedures, transcervical CVS in particular, 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. Some performed thousands successfully and therefore, undoubtedly, the experience between operators varied. Interestingly, in the MRC 1991 trial, there was no clear evidence that individual operators' performance improved with more experience over the course of the study.

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 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 1997 are not so conclusive. Although the increase in spontaneous miscarriages after early amniocentesis remains statistically significant, the difference in total pregnancy loss is not (3.5% versus 3.0%, RR 1.15; 95% CI 0.86 to 1.54). In order to test the hypothesis that the total pregnancy loss after early amniocentesis is, indeed, 0.5% higher compared with CVS, around 40,000 women would need to be recruited (power 80%, confidence level 95%). Such a trial is likely to be considered unethical given the causal relationship between early amniocentesis and talipes (*see* below).

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; Brambati 1991; Tomassini 1988; USNICHD 1992). Transcervical approach does require multiple insertions more often and causes vaginal bleeding in approximately 10% of cases. The subgroup 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 results of the systematic review of observational studies (Mujezinovic 2007) are broadly consistent with the randomised data (Table 2).

Table 2. Complications after chorionic villus sampling

Type of fetal loss	Combined total	Combined proportions	95% CI
Less than 20 weeks of pregnancy	8/555	1.5	0.7-2.7
More than 20 weeks of pregnancy	4/555	0.8	0.2-1.7
Less than 22 weeks of pregnancy	11/665	1.7	0.9-2.9
More than 22 weeks of pregnancy	3/665	0.5	0.1-1.2
Less than 24 weeks of pregnancy	44/3402	1.3	1.0-1.7
More than 24 weeks of pregnancy	3/1775	0.2	0.03-0.5
Less than 28 weeks of pregnancy	229/12462	2.0	1.0-3.0
More than 28 weeks of pregnancy	17/10144	0.2	0.1-0.3
Less than 14 days after CVS	5/852	0.7	0.3-1.4
Less than 30 days after CVS	7/607	1.3	0.5-2.3
Less than 60 days after CVS	4/169	2.6	0.8-5.6
Less than 6 weeks after CVS	4/169	2.6	0.8-5.6
Total pregnancy loss	566/24457	2.0	1.4-2.6
Multiple insertions	1324/15693	7.8	3.1-14.2

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 a 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 area of concern 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%). However, an increased incidence of talipes equinovarus after early amniocentesis has been specifically highlighted, with 24/2612 cases in the early amniocentesis group compared to only 5/2693 cases in the CVS group (RR 4.61; 95% CI 1.82 to 11.66). 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. However, it would be virtually impossible to blind women and clinicians to the type of invasive prenatal test actually carried out because the type and handling of the obtained tissue (amniotic fluid or chorionic villi) are distinctly different. Under those circumstances, one may 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 (NICHHD 1993), the association with CVS 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 nine weeks' gestation. Also, a small increase in the haemangiomas after CVS 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 early amniocentesis or transcervical chorion villus sampling (CVS). If earlier diagnosis is required, transabdominal CVS is preferable to early amniocentesis or transcervical CVS.

Although CVS technique is more likely to result in an ambiguous result, the diagnostic accuracy of different methods could not be assessed adequately because of incomplete karyotype data in most studies.

Implications for research

New methods of prenatal diagnosis should be rigorously evaluated before deciding whether they should be introduced into clinical practice. 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, i.e. neonatal assessors should be blinded to the allocated procedure.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Borrell 1999

Methods	Random telephone allocation using a table of random numbers.

Borrell 1999 (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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	TC and TA CVS were performed using a 20 G needle and no more than 2 cannula or needle insertions used in 1 session.
Outcomes	Technical difficulty and quantity of tissue obtained along with pregnancy outcome.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Canada 1992

Methods	Central randomisation (unknown) 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	TC versus second trimester AC.
Outcomes	Technical difficulties, abnormal karyotype, pregnancy complications, perinatal loss, neonatal complications and cytogenetic accuracy.
Notes	

Risk of bias

Item	Authors' judgement	Description

Canada 1992 (*Continued*)

Allocation concealment?	Yes	A - Adequate

CEMAT 1998

Methods	Telephone randomisation. Random allocation list computer generated.
Participants	4368 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, intrauterine 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 second trimester between 15 and 16 weeks. All amniocentesis were performed under direct ultrasound guidance using 22 G, 9 cm or 14 cm needles.
Outcomes	Pregnancy outcome, congenital anomalies, abnormal karyotype and technical difficulty.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Copenhagen 1997

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: 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).

Copenhagen 1997 (*Continued*)

	Amniocentesis was done between 11 and 13 weeks with a needle guide and a 0.9 mm (20 G) standard AC 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Denmark 1992

Methods	3-way randomisation of low-risk women (TA vs TC vs AC). A 2-way randomisation of high-risk women (TA vs TC). Central randomisation (unknown) with stratification for genetic risk.
Participants	2 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 AC. TA CVS vs second trimester AC. TC CVS vs second trimester AC. TC CVS vs TA CVS.
Outcomes	Pregnancy outcome, antenatal complications and diagnostic accuracy.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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	EA versus CVS. Both procedures being carried out by Professor Nicolaides or under his direct supervision. A freehand 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Leiden 1998

Methods	EA versus TA 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. 2 women did not participate because fetal death was diagnosed before any intervention.
Interventions	TA CVS was performed using a 20 G needle. AC 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.

Leiden 1998 (*Continued*)

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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MRC (Finland) 1993

Methods	Consecutively-numbered sealed envelopes.
Participants	800 women in early pregnancy requesting prenatal diagnosis.
Interventions	4 operators performed all procedures - TC CVS with Portex cannula or AC 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 AC.
Interventions	First trimester CVS TC or TA approach versus second trimester AC.
Outcomes	Pregnancy outcome, abnormal karyotype, antenatal complications and diagnostic accuracy.

MRC 1991 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

NICHD EATA 2004

Methods	Telephone randomisation interactive voice response computer-based system.
Participants	14 clinical centres. Inclusion criteria: age of mother more than 34 years, previous affected child, positive screening test. Exclusion criteria: multiple pregnancy, familiar chromosome rearrangements, inherited enzyme disorders, serious maternal illnesses (insulin-dependent diabetes, severe hypertension, HIV), bleeding equal menstruation, IUD in situ, oligohidramnios, recognised fetal abnormalities. Total number of patients = 3775 (CVS group = 1914 and EAC group = 1861).
Interventions	EAC group: 22 G spinal needle, 1 ml for each week. - CVS - single (19 to 20 G) and double needle technique (18 to 20 G). Larger guide needle to the margin of the chorion.
Outcomes	Primary outcome: fetal loss less than 28 weeks. Secondary outcome: all fetal loss, all neonatal death, oligohydramnios, gestational age at the delivery, IUGR, respiratory distress syndrome, limb reduction defects, talipes equinovarus, other congenital anomalies.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nolan 1981

Methods	Random allocation (method unknown).
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.

Nolan 1981 (*Continued*)

Outcomes	Number of taps, bloody taps.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 AC, all of which were carried out at the centre for prenatal diagnosis. The mean gestational age for AC was 16.4 +/-1.1 weeks. AC 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	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Tomassini 1988

Methods	Random selection (method unknown).
Participants	44 women between 9 and 12 weeks of gestation.
Interventions	Transcervical CVS with ago-cannula or transabdominal procedure with a spinal needle (gauge size unknown) and a suction pistol.

Tomassini 1988 (*Continued*)

Outcomes	Sampling failure, vaginal spotting and amniotic fluid leak, pregnancy loss.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

USNICHD 1992

Methods	Random assignment.	
Participants	3998 patients recruited in 8 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 TC CVS and 1163 to TA CVS.	
Interventions	TA or TC CVS. TC being performed with a plastic catheter and TA with an 18 to 22 G spinal needle.	
Outcomes	Sampling success, pregnancy outcome.	
Notes	Initial cohort of 2353 women presented who delivered before July 1 1989.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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

Characteristics of excluded studies *[ordered by study ID]*

ARIA Trial 2006	This study evaluated the impact of providing early results in altering maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued "when available" (i.e. variable date). This study will be included in the Cochrane review that addresses the issue of anxiety reduction during prenatal diagnostic tests.
Chang 1994	This study evaluated the feasibility of midtrimester placental biopsy as an alternative technique of prenatal cytogenetic diagnosis. Midtrimester amniocentesis and placental biopsies were performed simultaneously in 92 cases. According to our protocol this type of study design is not included.
Corrado 2002	This study compared a short prophylactic treatment with progesterone after amniocentesis with untreated controls. It did not compare 2 different methods of invasive testing.
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.
Fischer 2000b	This study evaluated the effect of leg rubbing by the assisting nurse during genetic amniocentesis with regard to pain perception and patient anxiety. 200 women were randomised using sealed envelopes, but the number of women per randomised group was not stated in the abstract. This study will be included in the Cochrane review that addresses the issue of pain relief during prenatal diagnostic tests.
Gordon 2007	This study evaluated the role of local anaesthesia (1% lidocaine) with no anaesthesia before amniocentesis in a diverse population. Immediately after the procedure, subjects were asked to assess their pain using both a Visual Analogue Scale and a 101-point Numerical Rating Scale. This study will be included in the Cochrane review that addresses the issue of pain relief during prenatal diagnostic tests.
Horovitz 1994	This study 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	This study 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.
Leach 1978	In this study amniocentesis was performed to assess fetal lung maturity with only 10.2% of the procedures carried out before 36 weeks' gestation.
Leung 2002	This study evaluated the impact of early reporting of the results obtained from polymerase chain reaction on amniotic fluid cells (amnio-PCR) on anxiety levels in women with positive biochemical screening for Down syndrome. This study will be included in the Cochrane review that addresses the issue of anxiety reduction during prenatal diagnostic tests.

(*Continued*)

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	In this study amniocentesis was performed later in pregnancy in women with proteinuric hypertension.
Shalev 1994	This is an abstract of the study that compared the clinical and laboratory result of first trimester transvaginal amniocentesis with those of CVS and mid-trimester amniocentesis. It had a matched case-control study design. It did not meet inclusion criteria of this review.
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 fulfil our criteria for randomised study.
SIlver 2003	This study was a part of a randomised control study performed by NICHD EATA Trial Group. It evaluated the relationship between placental penetration during amniocentesis or chorionic villus sampling and the development of gestational hypertension/pre-eclampsia. It did not report prespecified outcomes included in this review.
Uppsala 1997	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.
Van Schoubroeck 2000	This study evaluated the role of therapeutic massage 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.
Wax 2005	This study determined whether pain associated with second trimester genetic amniocentesis is decreased by using subfreezing rather than room temperature needles. This study will be included in the Cochrane review that addresses the issue of pain relief during prenatal diagnostic tests.
Zwinger 1994	This study evaluated the efficiency and safety of individual invasive methods of prenatal diagnosis. This study was not a randomised controlled study but based on a population cohort of Institute for Mother and Child Care in Czech Republic. Data were represented in an abstract form for the conference proceeding.

CVS: chorionic villus sampling

DATA AND ANALYSES

Comparison 1. Second trimester amniocentesis versus control

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

Comparison 2. Early versus second trimester amniocentesis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not complied with allocated procedure	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.57, 0.75]
2 Sampling failure	1	629	Risk Ratio (M-H, Fixed, 95% CI)	4.53 [0.53, 38.56]
3 Multiple insertions	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [1.92, 4.04]
4 Second test performed	1	4107	Risk Ratio (M-H, Fixed, 95% CI)	8.72 [3.47, 21.91]
5 Laboratory failure	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	9.76 [3.49, 27.26]
6 All non-mosaic abnormalities	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.75, 1.66]
7 True mosaics	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 4.00]
9 Maternal contamination	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.37, 10.92]
11 False negative chromosomal diagnosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

11.1 False negative chromosomal results (excluding sex determination)	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 73.67]
11.2 Incorrect sex determination	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.24, 104.18]
12 Reporting time	1	4107	Mean Difference (IV, Fixed, 95% CI)	1.20 [0.89, 1.51]
14 Amniotic leakage after test	1	4368	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.43, 2.94]
20 All known pregnancy loss (including termination of pregnancy)	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.03, 1.61]
21 Termination of pregnancy (all)	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.89, 1.77]
24 Spontaneous miscarriage	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.00, 1.98]
25 Spontaneous miscarriage after test	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [1.88, 5.53]
27 Stillbirths	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.59]
28 Neonatal deaths	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	4.98 [0.58, 42.56]
29 All recorded deaths after viability	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 1.99]
30 Anomalies (all recorded)	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.26, 2.38]
31 Talipes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Talipes (all)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
31.2 Talipes equinovarus	1	4334	Risk Ratio (M-H, Fixed, 95% CI)	14.43 [3.45, 60.41]

Comparison 3. Chorionic villus sampling versus second trimester amniocentesis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not complied with allocated procedure	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Transcervical CVS versus amniocentesis	3	4595	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.18, 1.36]
1.3 CVS (any route) versus amniocentesis	1	3197	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.52, 0.83]
2 Sampling failure	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Transervical CVS versus amniocentesis	1	797	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.26, 1.19]
2.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.98, 4.82]
3 Multiple insertions	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Transcervical CVS versus amniocentesis	1	794	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [2.72, 5.68]
3.3 CVS (any route) versus amniocentesis	1	2917	Risk Ratio (M-H, Fixed, 95% CI)	4.85 [3.92, 6.01]
4 Second test performed	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Transcervical CVS versus amniocentesis	3	4256	Risk Ratio (M-H, Random, 95% CI)	19.63 [1.24, 309.90]
4.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.94, 4.13]

5 Laboratory failure	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Transcervical CVS versus amniocentesis	2	2792	Risk Ratio (M-H, Fixed, 95% CI)	22.62 [3.07, 166.89]
5.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.29, 2.06]
6 All non-mosaic abnormalities	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Transcervical CVS versus amniocentesis	2	2667	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
7 True mosaics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Transcervical CVS versus amniocentesis	1	672	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [0.14, 83.63]
8 Confined mosaics	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Transcervical CVS versus amniocentesis	1	1995	Risk Ratio (M-H, Fixed, 95% CI)	5.66 [1.97, 16.24]
9 Maternal contamination	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Transcervical CVS versus amniocentesis	1	1991	Risk Ratio (M-H, Fixed, 95% CI)	12.30 [3.81, 39.67]
9.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	8.90 [0.48, 165.26]
10 Known false positive after birth	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Transcervical CVS versus amniocentesis	2	2627	Risk Ratio (M-H, Fixed, 95% CI)	7.30 [2.20, 24.25]
10.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.80]
11 Known false negative after birth	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Transcervical CVS versus amniocentesis	2	2627	Risk Ratio (M-H, Fixed, 95% CI)	7.84 [0.41, 151.61]
11.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 72.81]
13 Vaginal bleeding after test	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Transcervical CVS versus amniocentesis	2	3193	Risk Ratio (M-H, Random, 95% CI)	11.48 [2.58, 51.08]
14 Amniotic leakage after test	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Transabdominal CVS vs amniocentesis	1	1485	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.81, 7.92]
14.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.18, 1.64]
15 Vaginal bleeding after 20 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Transcervical CVS versus amniocentesis	1	797	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.62, 3.33]
15.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.42]
16 PROM before 28 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Transcervical CVS versus amniocentesis	1	722	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [1.45, 17.03]
16.3 CVS (any route) versus amniocentesis	1	2765	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.80, 3.17]
17 Antenatal hospital admission	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Transcervical CVS versus amniocentesis	1	780	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.81, 2.68]

17.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.08]
18 Delivery before 37 weeks	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Transcervical CVS versus amniocentesis	2	2506	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.67, 2.47]
18.3 CVS (any route) versus amniocentesis	1	3189	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.13, 1.57]
19 Delivery before 33 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Transcervical CVS versus amniocentesis	1	768	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [0.94, 4.94]
20 All known pregnancy loss (including termination of pregnancy)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 Transcervical CVS versus amniocentesis	4	6527	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.09, 1.81]
20.2 Transabdominal CVS versus amniocentesis	1	2234	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.66, 1.23]
20.3 CVS (any route) versus amniocentesis	2	6503	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.22, 1.67]
21 Termination of pregnancy (all)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Transcervical CVS versus amniocentesis	2	3454	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.34]
21.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.96, 2.11]
24 Spontaneous miscarriage	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 Transcervical CVS versus amniocentesis	3	5506	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.07, 2.11]
24.2 Transabdominal CVS versus amniocentesis	1	2069	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.49, 1.21]
24.3 CVS (any route) versus amniocentesis	2	6280	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.23, 1.85]
25 Spontaneous miscarriage after test	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 Transcervical CVS versus amniocentesis	2	1579	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.28, 11.00]
25.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Random, 95% CI)	3.46 [2.21, 5.42]
26 Perinatal deaths	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Transcervical CVS versus amniocentesis	3	5521	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.73, 3.84]
26.2 Transabdominal CVS versus amniocentesis	1	2069	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.40, 3.51]
26.3 CVS (any route) versus amniocentesis	2	6280	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.65, 2.24]
27 Stillbirths	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 Transcervical CVS versus amniocentesis	2	3454	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.02, 45.31]
27.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.35, 2.81]
28 Neonatal deaths	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

28.1 Transcervical CVS versus amniocentesis	3	4251	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.41, 6.06]
28.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [0.70, 9.93]
29 All recorded deaths after viability	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Transcervical CVS versus amniocentesis	2	1579	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.24, 2.93]
29.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.67, 3.09]
30 Congenital anomalies (all recorded)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Transcervical CVS versus amniocentesis	2	1408	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.24, 1.56]
30.3 CVS (any route) versus amniocentesis	2	3338	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.96]
31 Talipes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Transcervical CVS versus amniocentesis	1	797	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
32 Hemangiomas (localised vascular lesions of the skin and subcutaneous tissue)	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.81, 2.24]
33 Limb reduction defects	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	4.95 [0.24, 102.97]
33.3 CVS (any route) versus amniocentesis	1	3201	Risk Ratio (M-H, Fixed, 95% CI)	4.95 [0.24, 102.97]
38 Result given in less than 7 days (not prespecified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.3 CVS (any route) versus amniocentesis	1	3099	Risk Ratio (M-H, Fixed, 95% CI)	23.52 [12.54, 44.10]
39 Result given in less than 14 days (not prespecified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.3 CVS (any route) versus amniocentesis	1	3099	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [3.17, 4.95]
40 Result given in less than 21 days (not prespecified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.3 CVS (any route) versus amniocentesis	1	3099	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
41 Result given in more than 21 days (not prespecified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.3 CVS (any route) versus amniocentesis	1	3099	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.28, 0.39]
42 Not wanting another baby at 22 weeks' gestation (not prespecified)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 Transcervical CVS versus amniocentesis	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.11, 1.09]

Comparison 4. Transcervical versus transabdominal CVS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not complied with allocated procedure	3	5187	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.59, 4.76]
2 Sampling failure	4	5231	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.15, 2.86]
3 Multiple insertions	2	1314	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.78, 4.17]
4 Second test performed	1	1194	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.65, 2.37]
5 Laboratory failure	1	1194	Risk Ratio (M-H, Fixed, 95% CI)	2.23 [0.69, 7.22]
6 All non-mosaic abnormalities	1	2862	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.87, 1.75]
7 True mosaics	1	2862	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.39, 2.17]
8 Confined mosaics	1	2862	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.26, 2.77]
13 Vaginal bleeding after test	3	1358	Risk Ratio (M-H, Random, 95% CI)	6.93 [0.77, 62.83]
14 Amniotic leakage after test	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.52]
20 All known pregnancy loss (including termination of pregnancy)	5	7978	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.81, 1.65]
21 Termination of pregnancy (all)	2	1303	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.56, 1.22]
24 Spontaneous miscarriage	4	3384	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.79, 3.58]
25 Spontaneous miscarriage after test	3	1347	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.76, 2.06]
26 Perinatal deaths	1	2037	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.11, 1.68]
27 Stillbirths	2	1227	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.38, 7.62]
28 Neonatal deaths	2	4845	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.49]
30 Anomalies (all recorded)	2	3622	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.41, 1.12]
31 Talipes	1	2624	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.33, 30.80]

Comparison 5. Early amniocentesis versus transabdominal CVS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not complied with allocated procedure	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.60]
2 Sampling failure	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.14]
3 Multiple insertions	3	4445	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.29, 0.74]
4 Second test performed	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.98]
5 Laboratory failure	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.49]
6 All non-mosaic abnormalities	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.70, 1.55]
7 True mosaics	3	5451	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.10, 2.06]
8 Abnormalities confined to non-fetal tissues	4	5566	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.56, 1.55]
9 Maternal contamination	2	4330	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.83, 11.14]
10 Known false positive after birth	2	670	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.73]
11 Known false negative after birth	1	555	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Reporting time	1	3775	Mean Difference (IV, Fixed, 95% CI)	4.00 [3.82, 4.18]
13 Vaginal bleeding after test	3	4934	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 1.01]

14 Amniotic leakage after test	3	4934	Risk Ratio (M-H, Random, 95% CI)	3.35 [0.37, 30.09]
15 Vaginal bleeding after 20 weeks	1	3698	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.43]
16 Prelabour ruptured membranes less than 28 weeks	1	3698	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.27, 0.92]
18 Delivery before 37 weeks	3	1755	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.78, 1.74]
19 Delivery before 33 weeks	1	1121	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.09, 2.73]
20 All known pregnancy loss (including termination of pregnancy)	4	5491	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.86, 1.54]
21 Termination of pregnancy (all)	4	5489	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.24]
24 Spontaneous miscarriage	4	5491	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.17, 2.64]
25 Spontaneous miscarriage after test	4	5489	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.14, 2.64]
26 Perinatal deaths	4	5428	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.53, 2.28]
27 Stillbirths	4	5428	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.52, 2.36]
28 Neonatal deaths	4	5455	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.17]
29 All recorded deaths after viability	4	5453	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.43, 3.23]
30 Anomalies (all recorded)	4	5305	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.57, 2.30]
32 Talipes equinovarus	4	5305	Risk Ratio (M-H, Fixed, 95% CI)	4.61 [1.82, 11.66]
33 Haemangioma	4	5305	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.10]
35 Neonatal respiratory distress syndrome	4	4725	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.34, 1.89]
36 Birthweight below 10th centile	1	3618	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.06]
37 Birthweight below 5th centile	2	629	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.43, 2.56]

Comparison 6. Ultrasound versus no ultrasound before second trimester amniocentesis

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

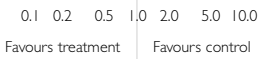
Analysis 1.1. Comparison 1 Second trimester amniocentesis versus control, Outcome 1 Not complied with allocated procedure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 1 Not complied with allocated procedure

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.040)					



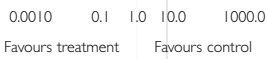
Analysis 1.3. Comparison 1 Second trimester amniocentesis versus control, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 3 Multiple insertions

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.17 (P = 0.0015)					



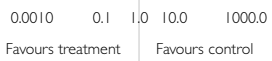
Analysis 1.4. Comparison 1 Second trimester amniocentesis versus control, Outcome 4 Second test performed.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 4 Second test performed

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.60 (P = 0.0094)					



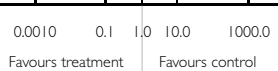
Analysis 1.5. Comparison 1 Second trimester amniocentesis versus control, Outcome 5 Laboratory failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 5 Laboratory failure

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					



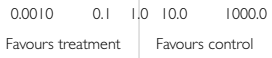
Analysis 1.6. Comparison 1 Second trimester amniocentesis versus control, Outcome 6 All non-mosaic abnormalities.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 6 All non-mosaic abnormalities

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.39 (P = 0.017)					



Analysis 1.13. Comparison 1 Second trimester amniocentesis versus control, Outcome 13 Vaginal bleeding after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 13 Vaginal bleeding after test

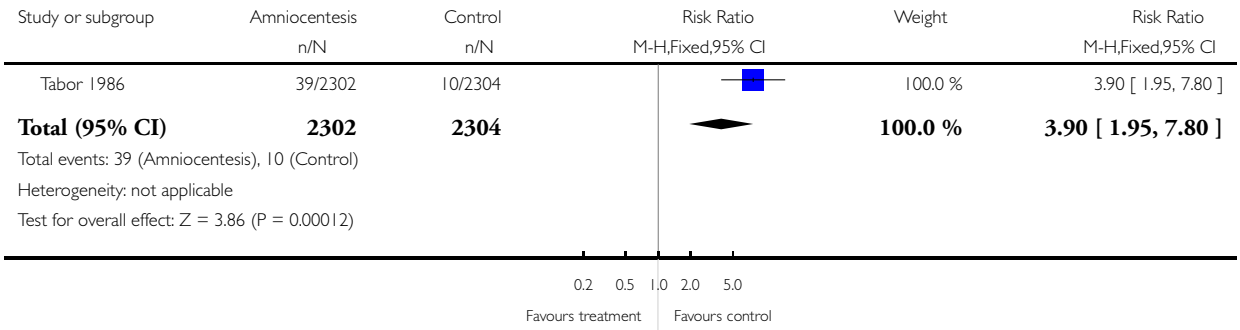
Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tabor 1986	55/2302	58/2304		100.0 %	0.95 [0.66, 1.37]
Total (95% CI)	**2302**	**2304**		**100.0 %**	**0.95 [0.66, 1.37]**
Total events: 55 (Amniocentesis), 58 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					

Analysis 1.14. Comparison 1 Second trimester amniocentesis versus control, Outcome 14 Amniotic leakage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 14 Amniotic leakage after test

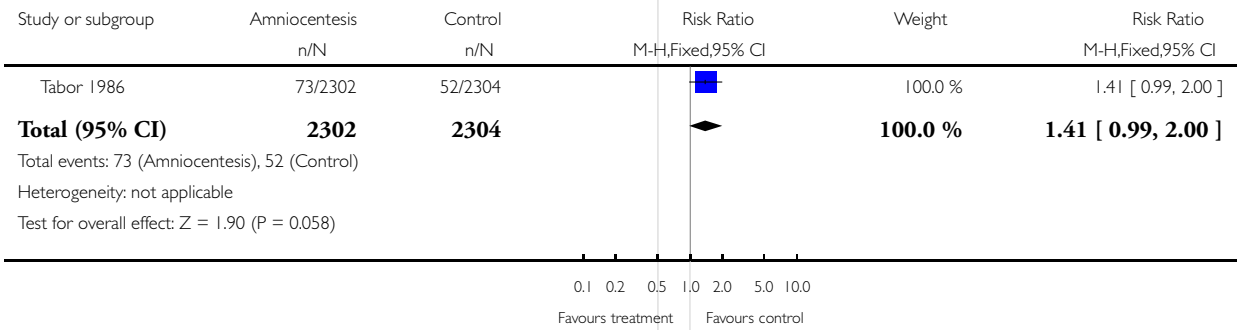


Analysis 1.20. Comparison 1 Second trimester amniocentesis versus control, Outcome 20 All known pregnancy loss (including termination of pregnancy).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

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

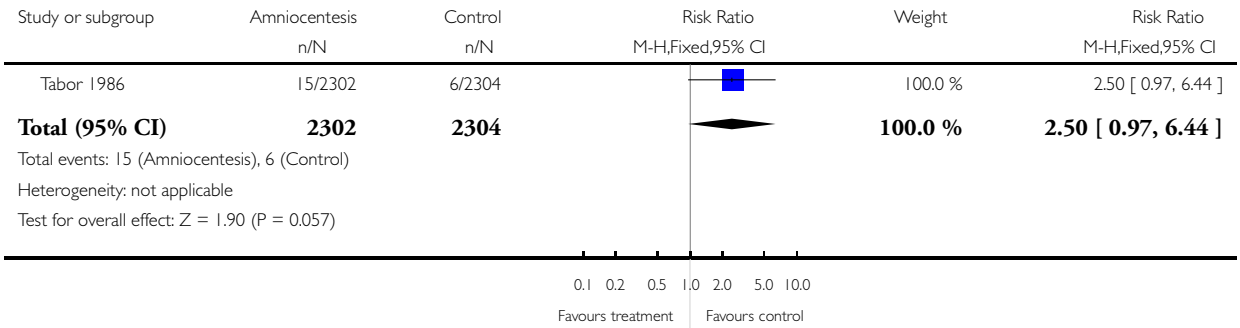


Analysis 1.21. Comparison 1 Second trimester amniocentesis versus control, Outcome 21 Termination of pregnancy (all).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 21 Termination of pregnancy (all)

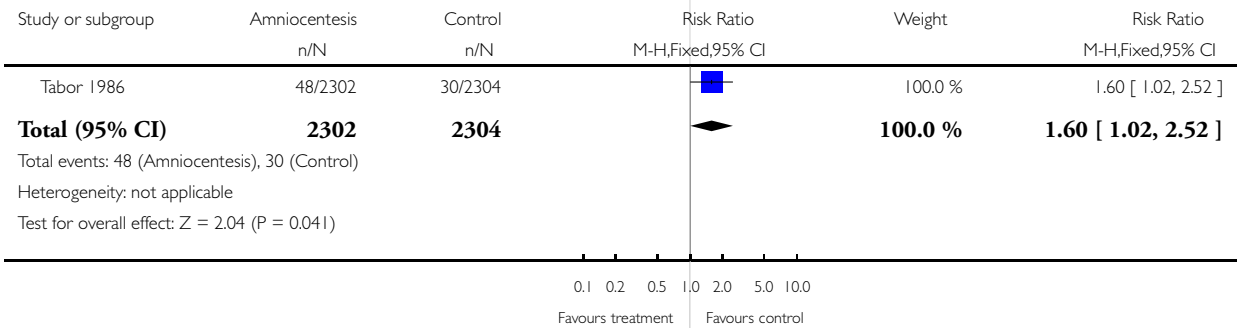


Analysis 1.24. Comparison 1 Second trimester amniocentesis versus control, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 24 Spontaneous miscarriage

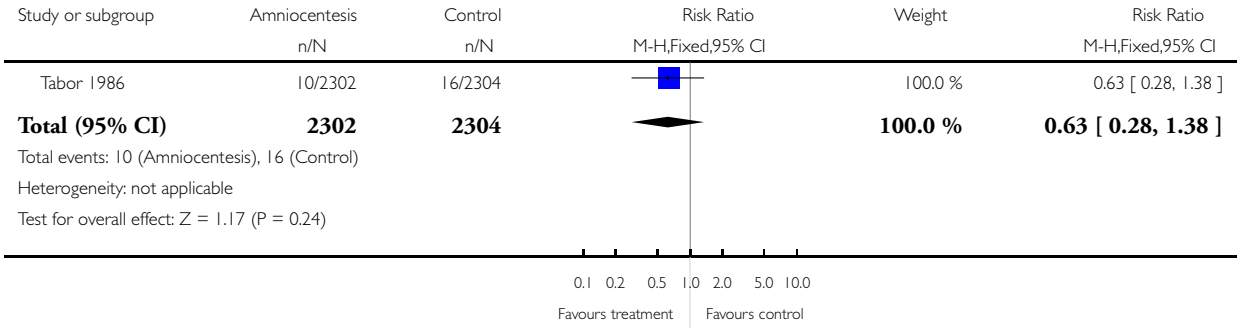


Analysis 1.26. Comparison 1 Second trimester amniocentesis versus control, Outcome 26 Perinatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 26 Perinatal deaths

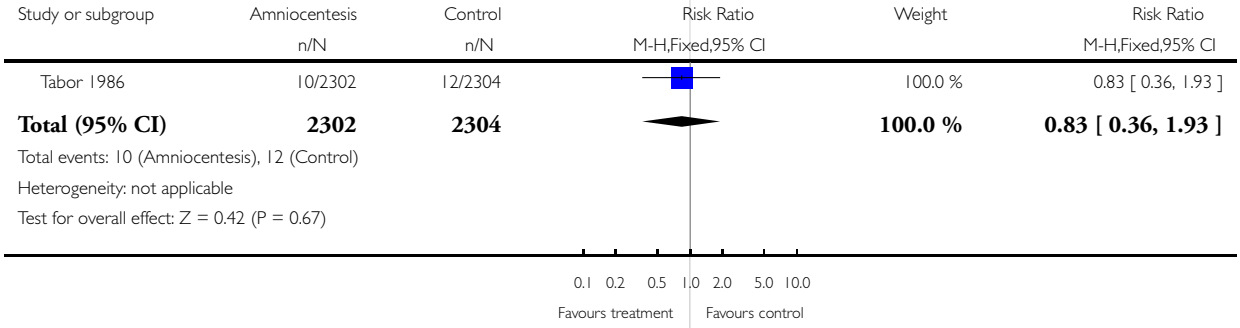


Analysis 1.27. Comparison 1 Second trimester amniocentesis versus control, Outcome 27 Stillbirths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 27 Stillbirths



Analysis 1.28. Comparison 1 Second trimester amniocentesis versus control, Outcome 28 Neonatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 28 Neonatal deaths

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					

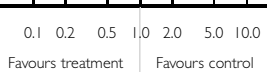
Analysis 1.29. Comparison 1 Second trimester amniocentesis versus control, Outcome 29 All recorded deaths after viability.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 29 All recorded deaths after viability

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.17 (P = 0.24)					

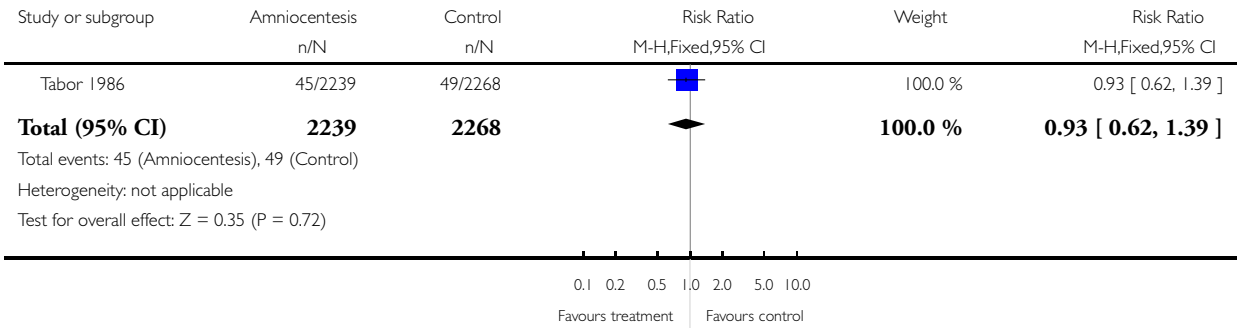


Analysis 1.30. Comparison 1 Second trimester amniocentesis versus control, Outcome 30 Anomalies (all recorded).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 30 Anomalies (all recorded)

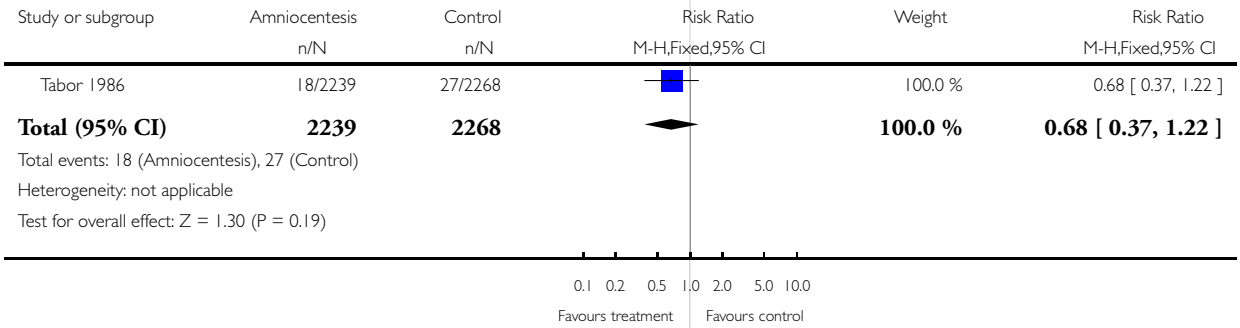


Analysis 1.31. Comparison 1 Second trimester amniocentesis versus control, Outcome 31 Talipes.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 31 Talipes



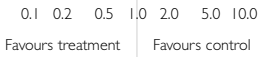
Analysis 1.35. Comparison 1 Second trimester amniocentesis versus control, Outcome 35 Neonatal respiratory distress syndrome.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 1 Second trimester amniocentesis versus control

Outcome: 35 Neonatal respiratory distress syndrome

Study or subgroup	Amniocentesis n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.13 (P = 0.033)					



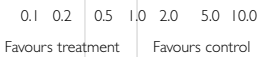
Analysis 2.1. Comparison 2 Early versus second trimester amniocentesis, Outcome 1 Not complied with allocated procedure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 1 Not complied with allocated procedure

Study or subgroup	Early amniocentesis n/N	Mid-trimester amnio n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.90 (P < 0.00001)					

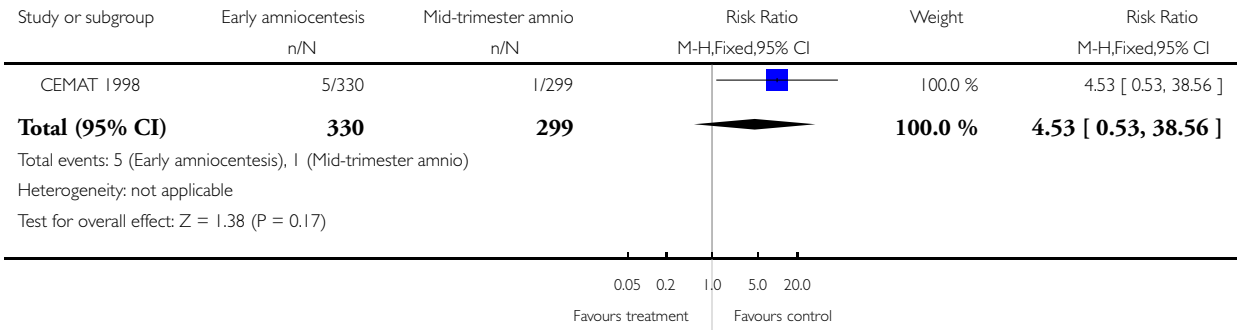


Analysis 2.2. Comparison 2 Early versus second trimester amniocentesis, Outcome 2 Sampling failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 2 Sampling failure

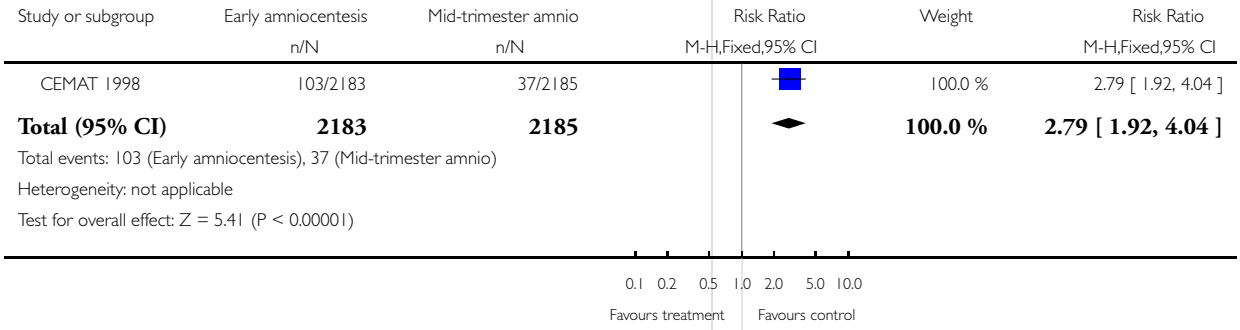


Analysis 2.3. Comparison 2 Early versus second trimester amniocentesis, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 3 Multiple insertions

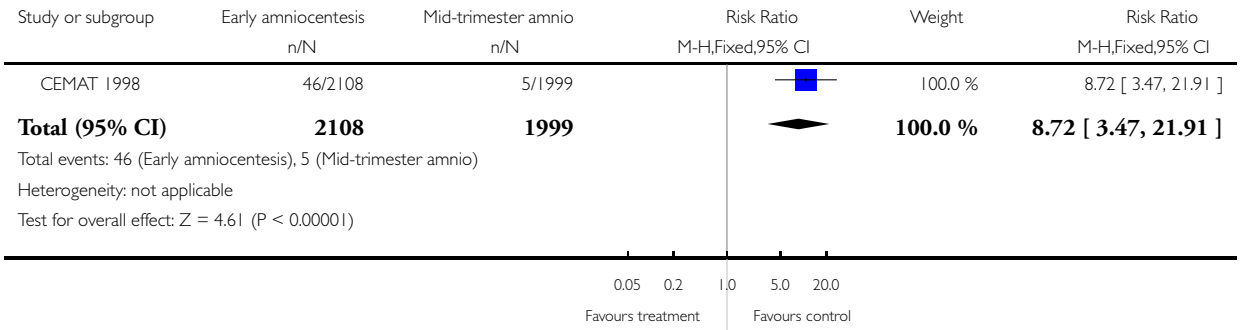


Analysis 2.4. Comparison 2 Early versus second trimester amniocentesis, Outcome 4 Second test performed.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 4 Second test performed

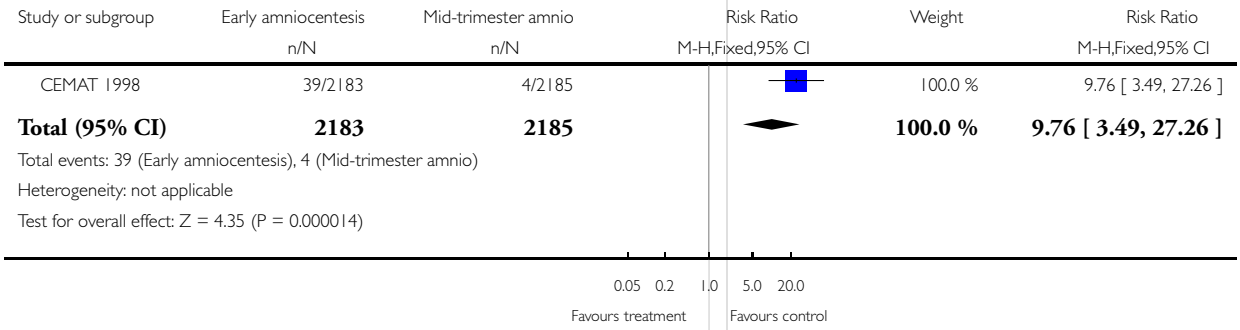


Analysis 2.5. Comparison 2 Early versus second trimester amniocentesis, Outcome 5 Laboratory failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 5 Laboratory failure



Analysis 2.6. Comparison 2 Early versus second trimester amniocentesis, Outcome 6 All non-mosaic abnormalities.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

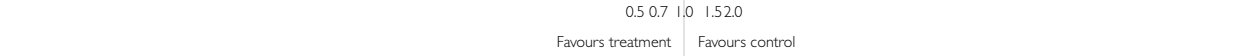
Outcome: 6 All non-mosaic abnormalities

Study or subgroup	Early amniocentesis n/N	Mid-trimester amnio n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: not applicable

Test for overall effect: Z = 0.52 (P = 0.60)



Analysis 2.7. Comparison 2 Early versus second trimester amniocentesis, Outcome 7 True mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 7 True mosaics

Study or subgroup	Early amniocentesis n/N	Mid-trimester amnio n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: not applicable

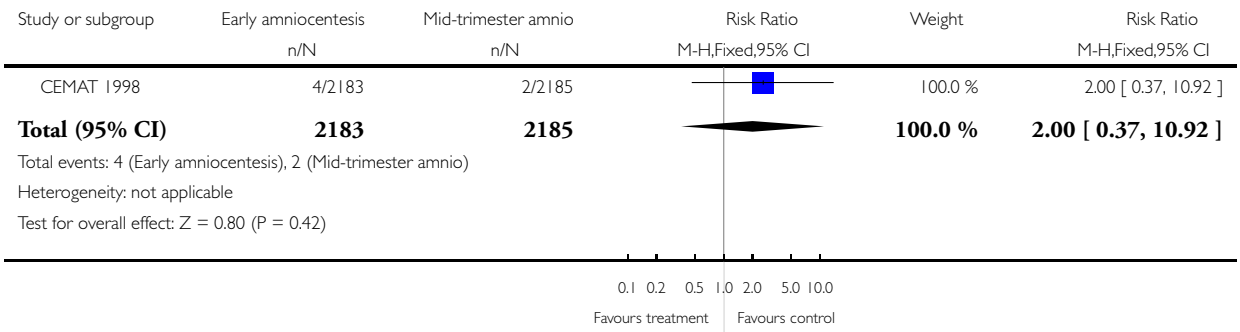
Test for overall effect: Z = 0.00 (P = 1.0)

Analysis 2.9. Comparison 2 Early versus second trimester amniocentesis, Outcome 9 Maternal contamination.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 9 Maternal contamination

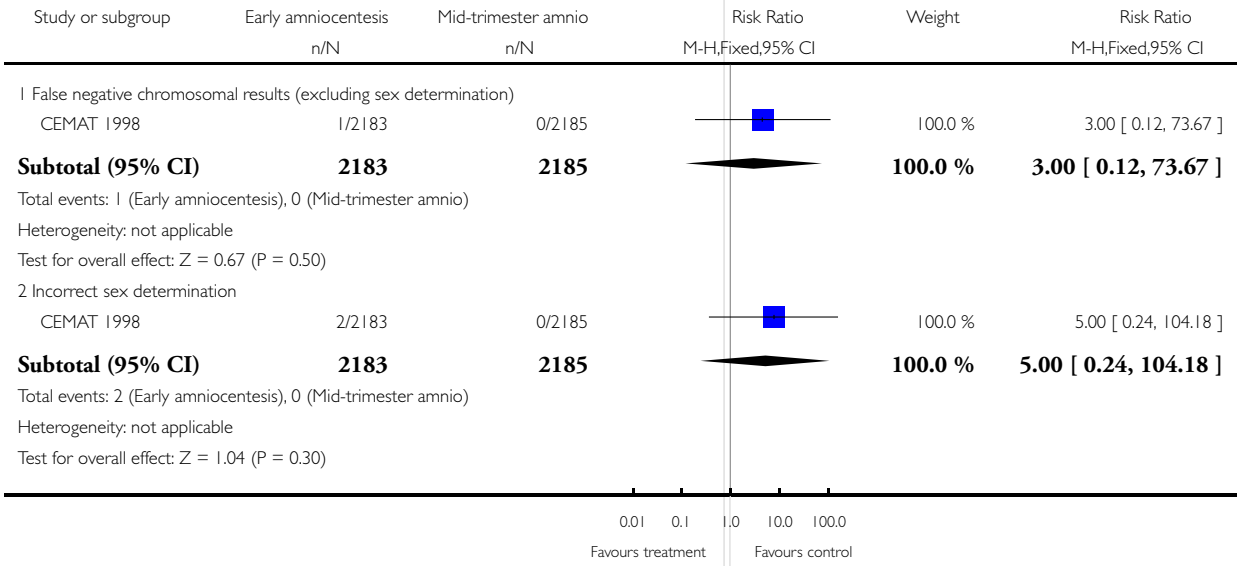


Analysis 2.11. Comparison 2 Early versus second trimester amniocentesis, Outcome 11 False negative chromosomal diagnosis.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

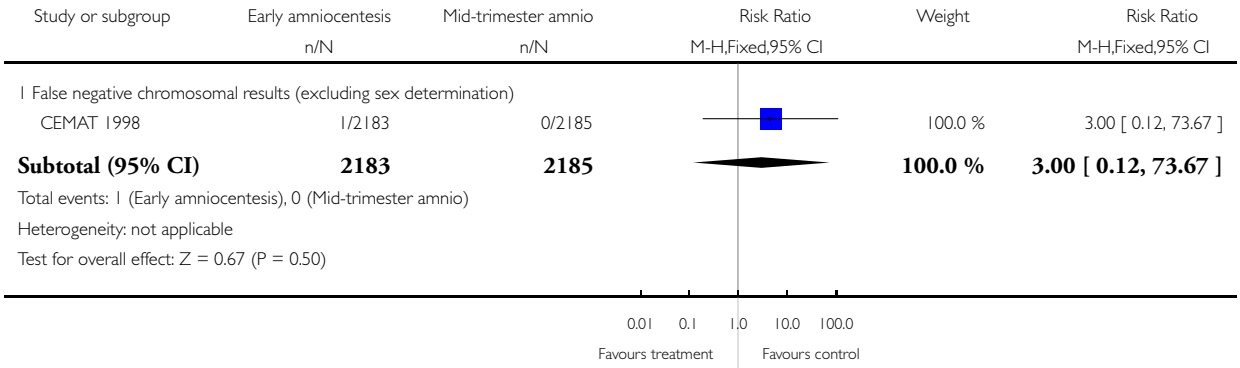
Outcome: 11 False negative chromosomal diagnosis



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

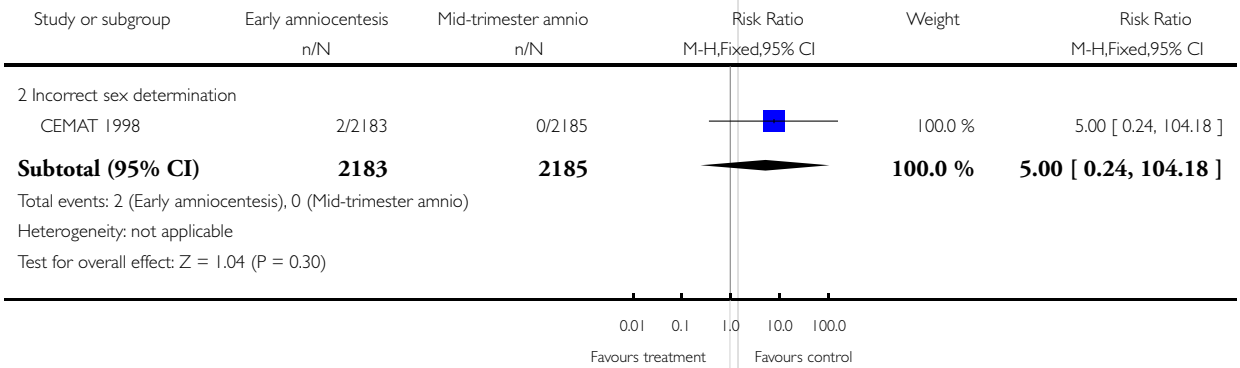
Outcome: 11 False negative chromosomal diagnosis



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 11 False negative chromosomal diagnosis

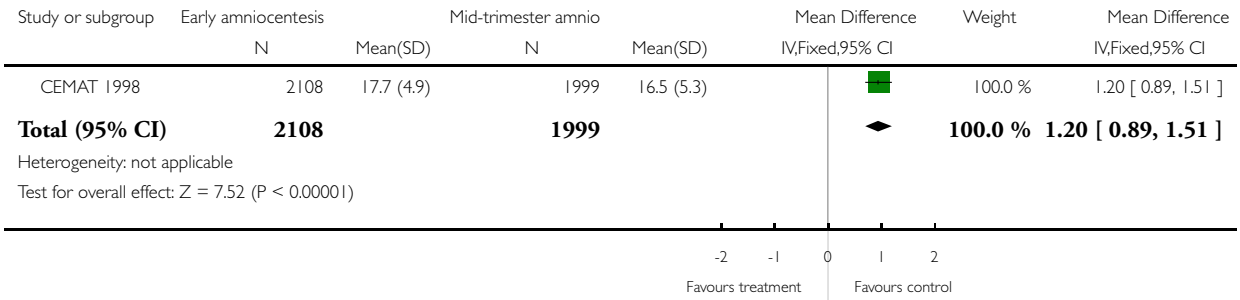


Analysis 2.12. Comparison 2 Early versus second trimester amniocentesis, Outcome 12 Reporting time.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 12 Reporting time

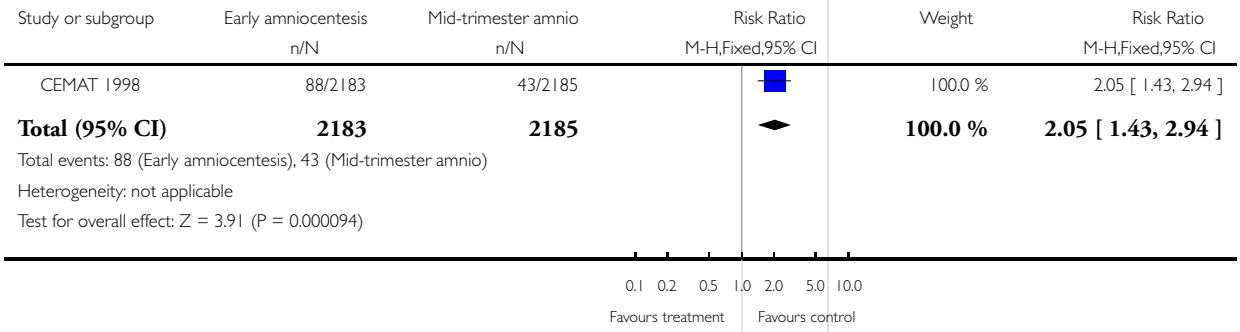


Analysis 2.14. Comparison 2 Early versus second trimester amniocentesis, Outcome 14 Amniotic leakage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 14 Amniotic leakage after test

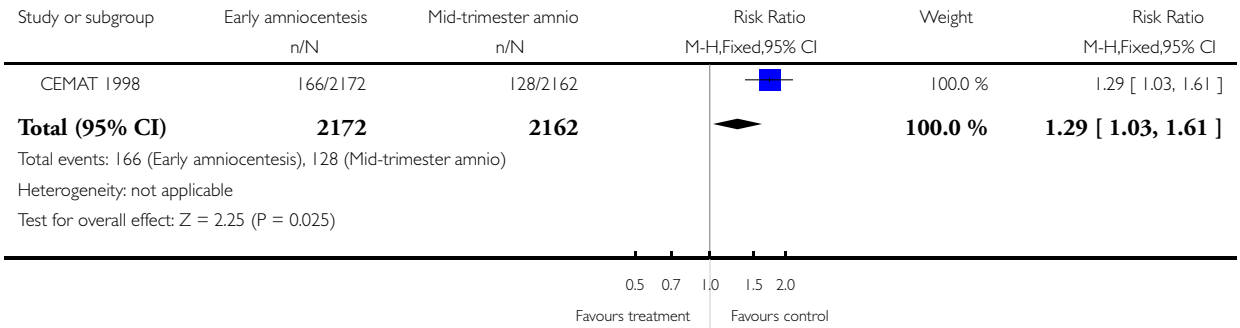


Analysis 2.20. Comparison 2 Early versus second trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

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

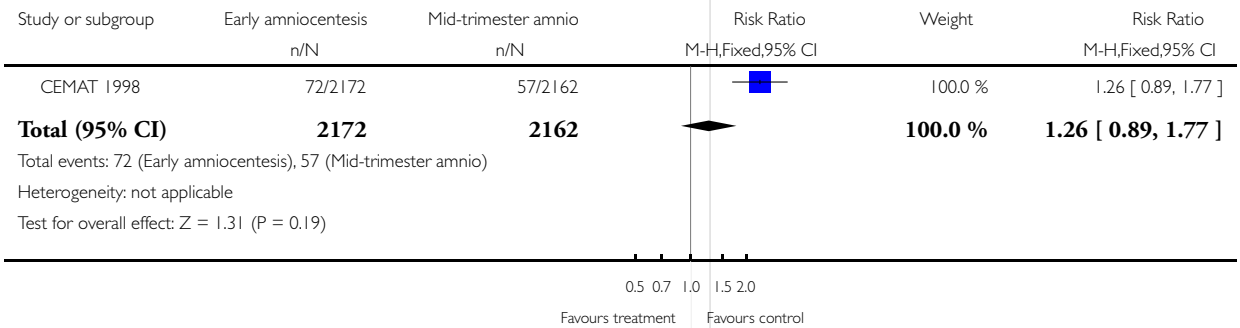


Analysis 2.21. Comparison 2 Early versus second trimester amniocentesis, Outcome 21 Termination of pregnancy (all).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 21 Termination of pregnancy (all)

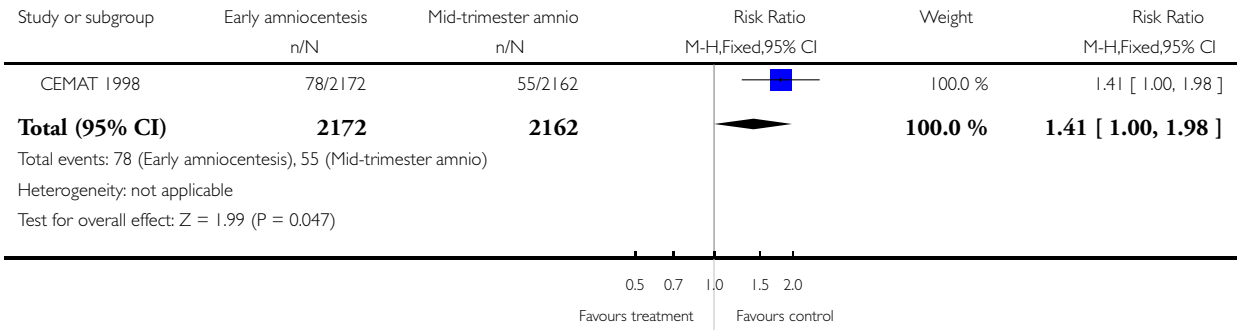


Analysis 2.24. Comparison 2 Early versus second trimester amniocentesis, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

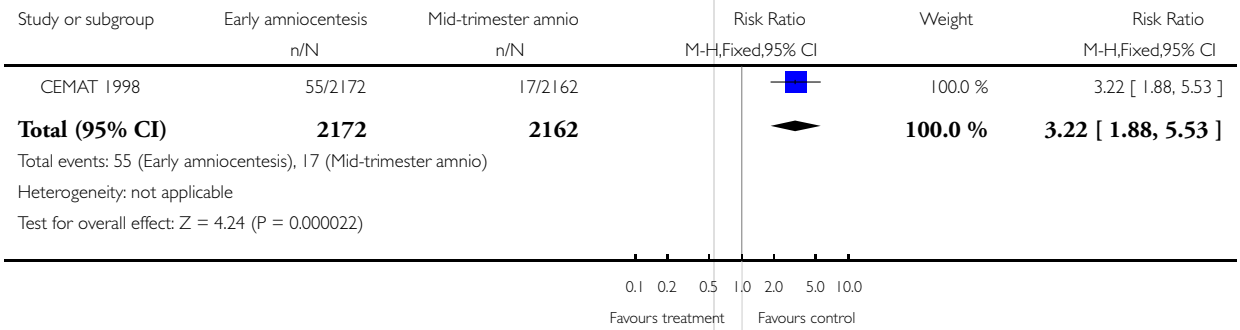


Analysis 2.25. Comparison 2 Early versus second trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

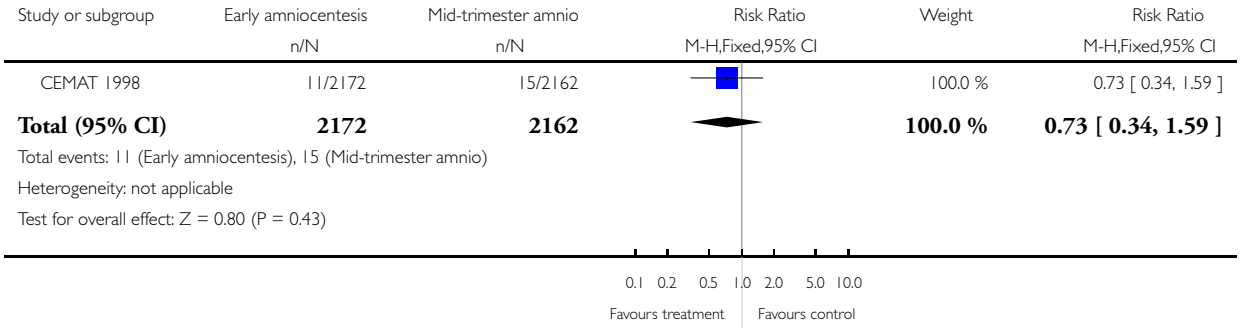


Analysis 2.27. Comparison 2 Early versus second trimester amniocentesis, Outcome 27 Stillbirths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 27 Stillbirths

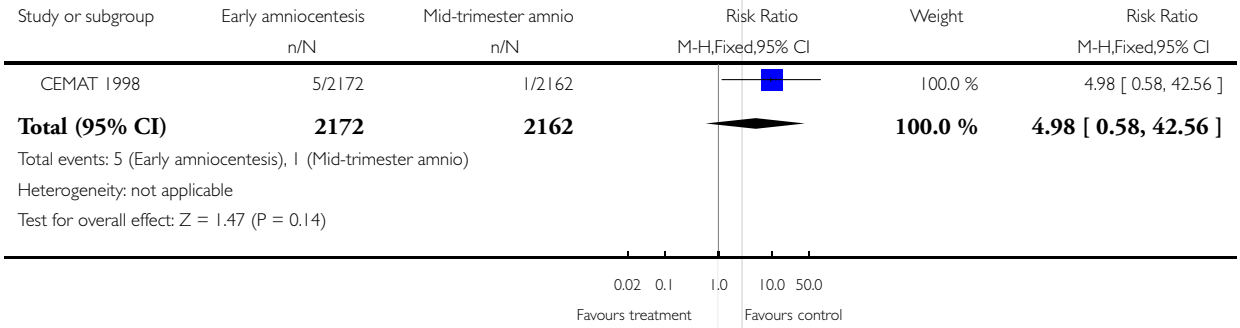


Analysis 2.28. Comparison 2 Early versus second trimester amniocentesis, Outcome 28 Neonatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 28 Neonatal deaths

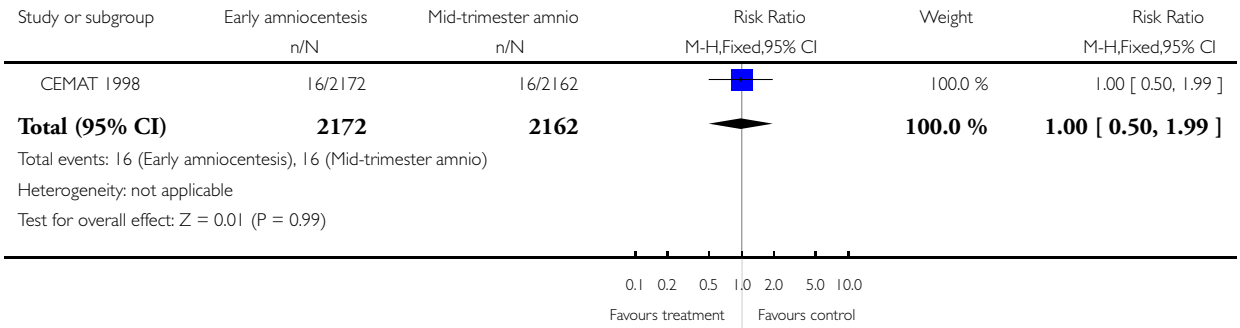


Analysis 2.29. Comparison 2 Early versus second trimester amniocentesis, Outcome 29 All recorded deaths after viability.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 29 All recorded deaths after viability

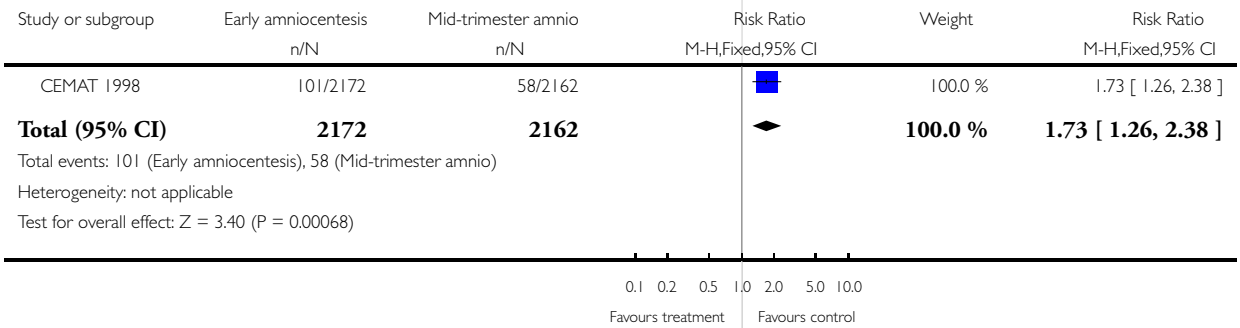


Analysis 2.30. Comparison 2 Early versus second trimester amniocentesis, Outcome 30 Anomalies (all recorded).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 30 Anomalies (all recorded)

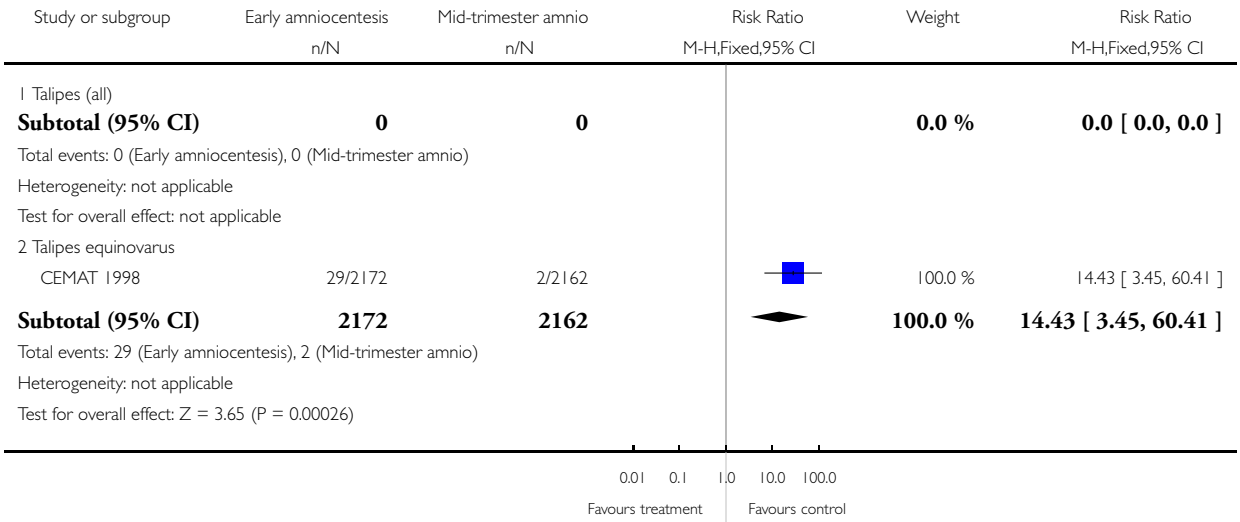


Analysis 2.31. Comparison 2 Early versus second trimester amniocentesis, Outcome 31 Talipes.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

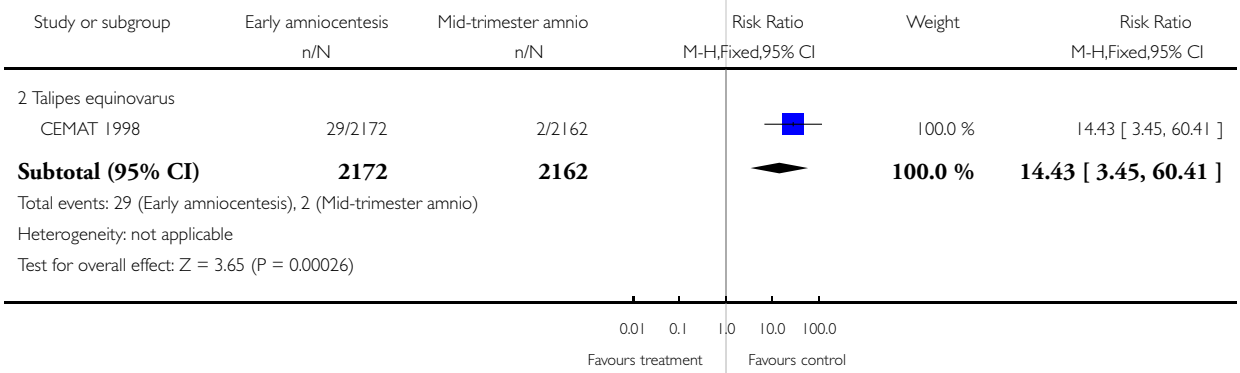
Outcome: 31 Talipes



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 2 Early versus second trimester amniocentesis

Outcome: 31 Talipes

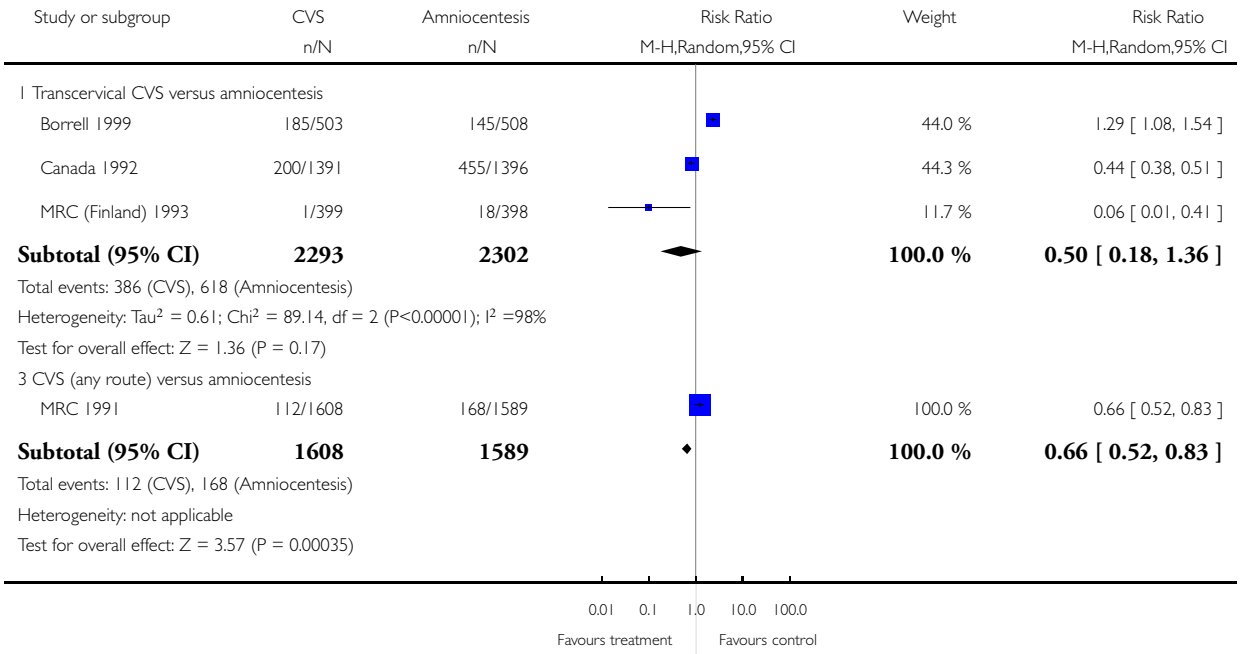


Analysis 3.1. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 1 Not complied with allocated procedure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

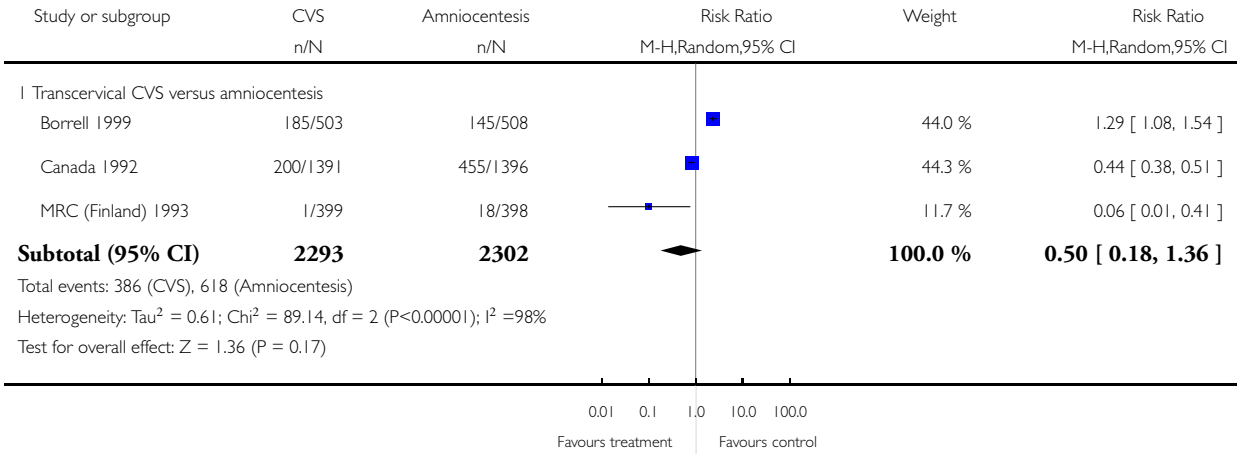
Outcome: 1 Not complied with allocated procedure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

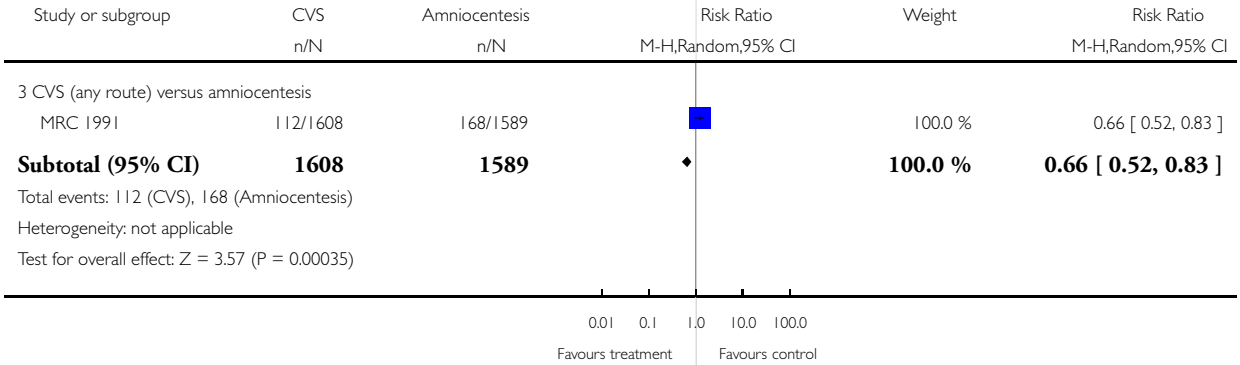
Outcome: 1 Not complied with allocated procedure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 1 Not complied with allocated procedure

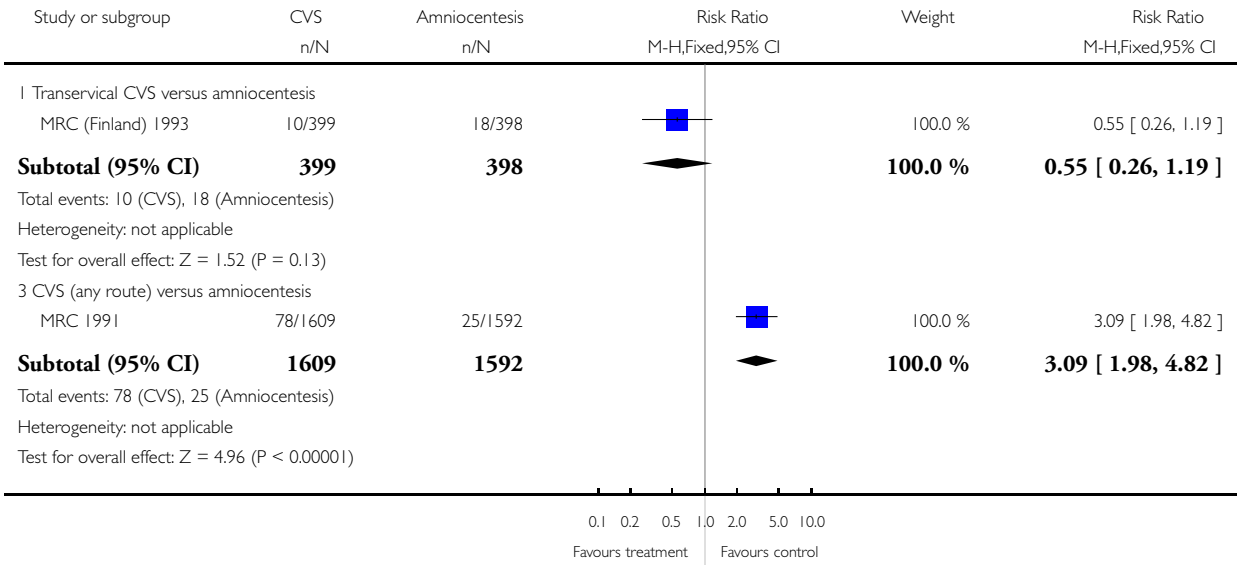


Analysis 3.2. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 2 Sampling failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

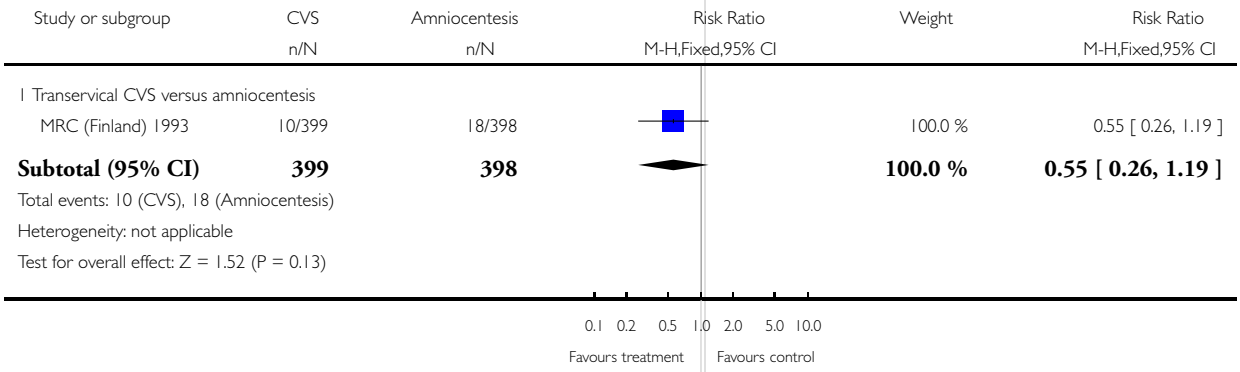
Outcome: 2 Sampling failure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

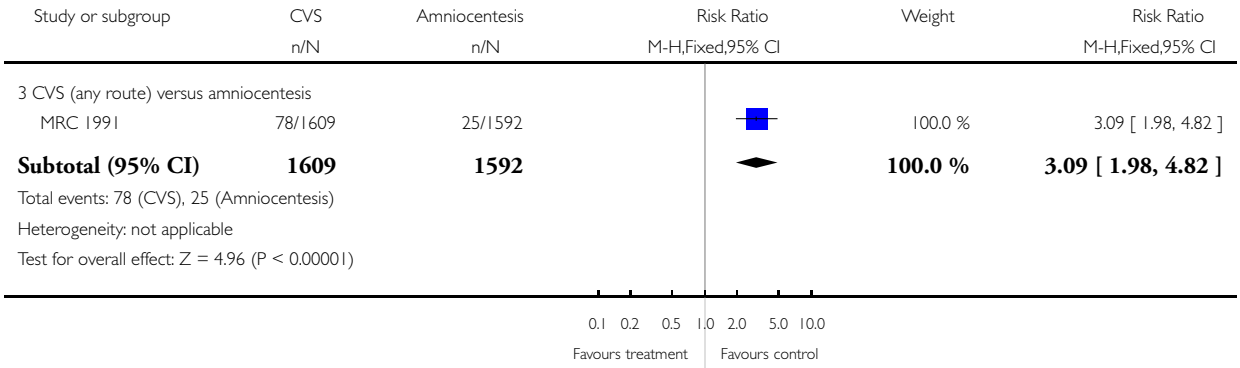
Outcome: 2 Sampling failure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 2 Sampling failure

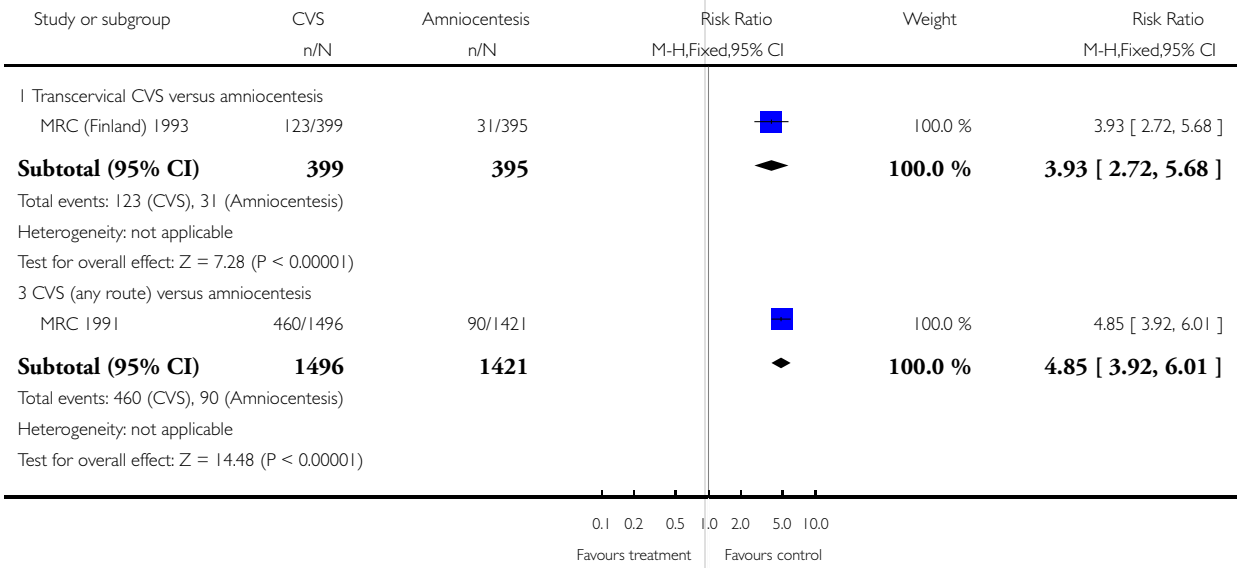


Analysis 3.3. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 3 Multiple insertions

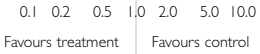


Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 3 Multiple insertions

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.28 (P < 0.00001)					



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 3 Multiple insertions

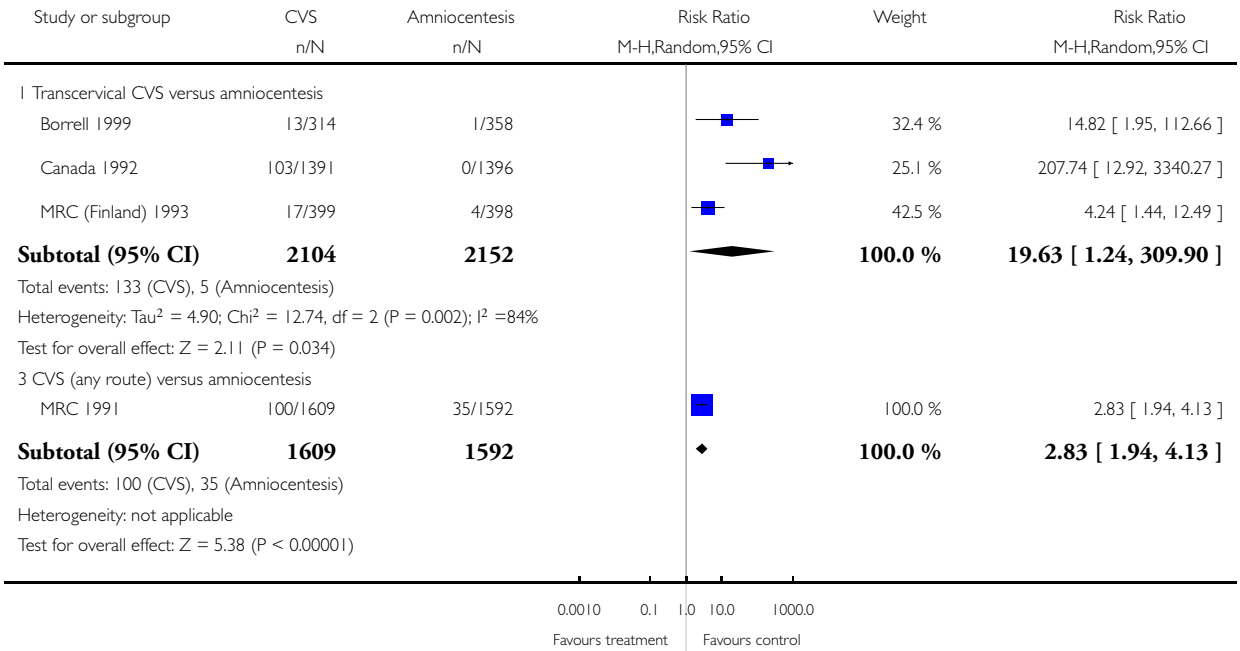
Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 CVS (any route) versus amniocentesis					
MRC 1991	460/1496	90/1421		100.0 %	4.85 [3.92, 6.01]
Subtotal (95% CI)	**1496**	**1421**		**100.0 %**	**4.85 [3.92, 6.01]**
Total events: 460 (CVS), 90 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 14.48 (P < 0.00001)					

Analysis 3.4. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 4 Second test performed.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 4 Second test performed



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 4 Second test performed

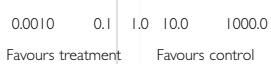
Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transcervical CVS versus amniocentesis					
Borrell 1999	13/314	1/358		32.4 %	14.82 [1.95, 112.66]
Canada 1992	103/1391	0/1396		25.1 %	207.74 [12.92, 3340.27]
MRC (Finland) 1993	17/399	4/398		42.5 %	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)					
Heterogeneity: Tau^2 = 4.90; Chi^2 = 12.74, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 2.11 (P = 0.034)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 4 Second test performed

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.38 (P < 0.00001)					

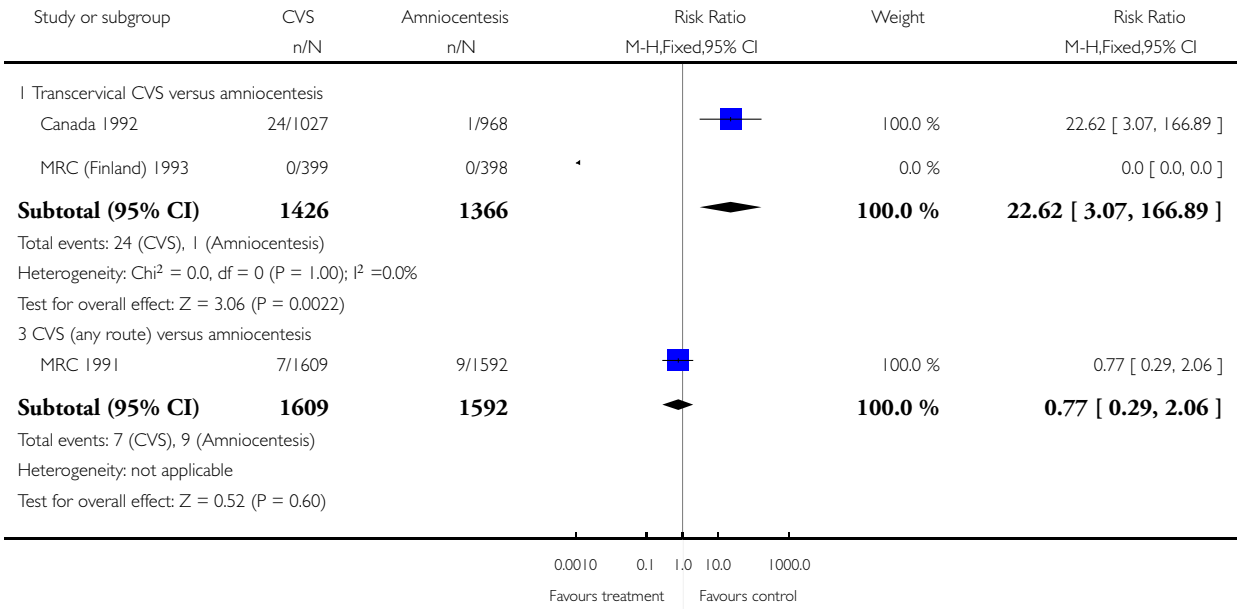


Analysis 3.5. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 5 Laboratory failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

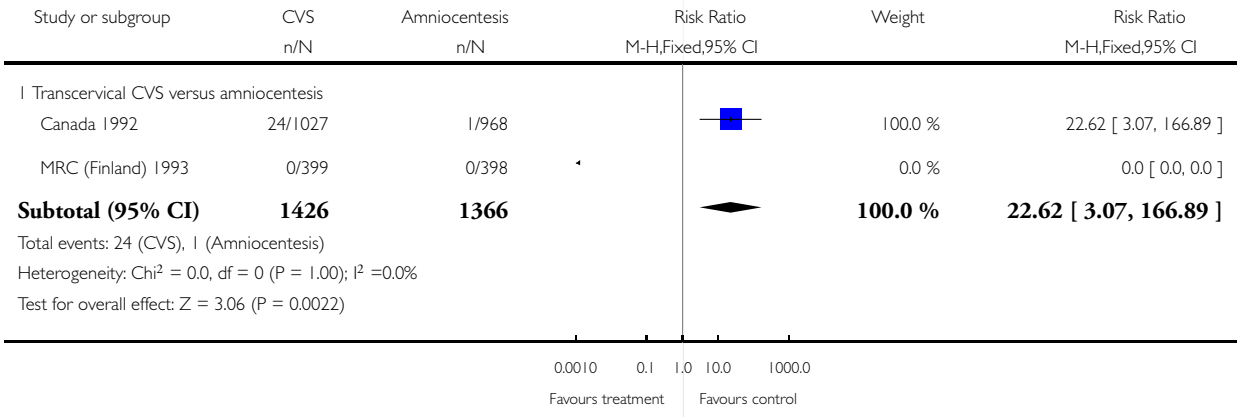
Outcome: 5 Laboratory failure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

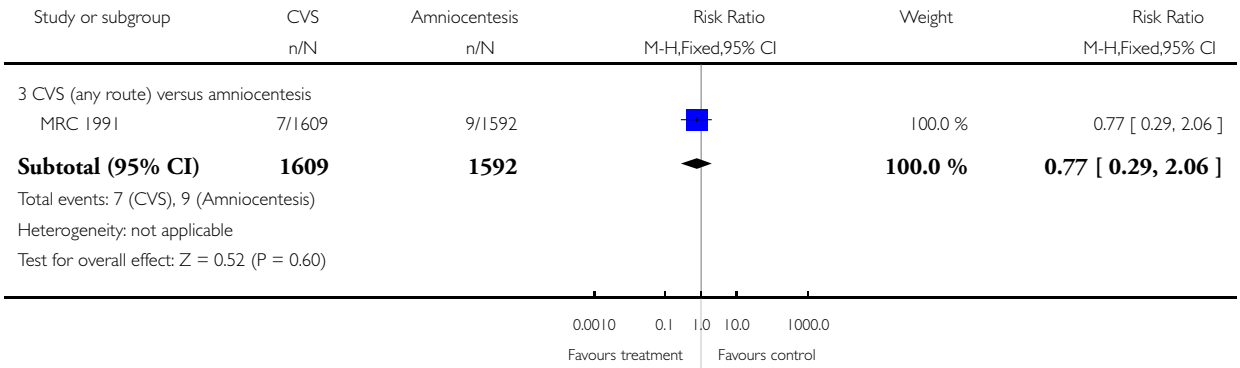
Outcome: 5 Laboratory failure



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 5 Laboratory failure

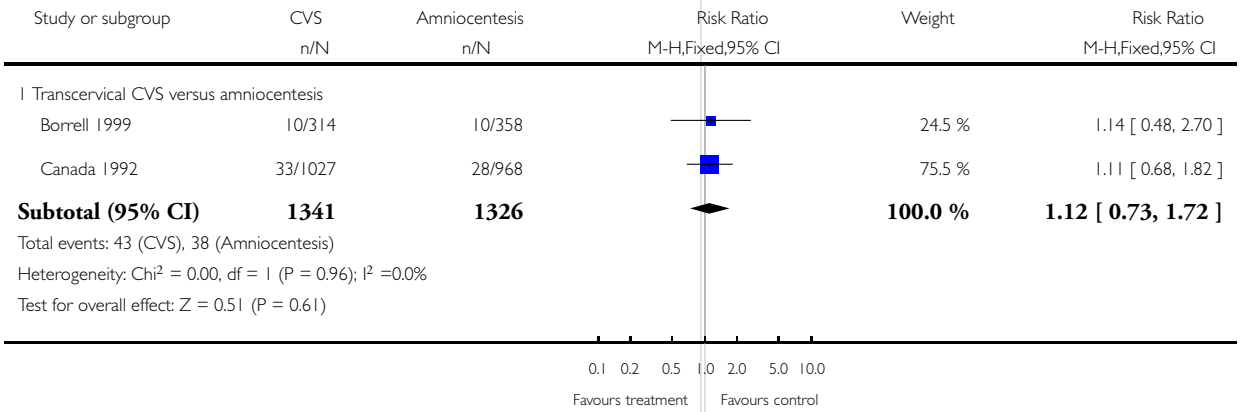


Analysis 3.6. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 6 All non-mosaic abnormalities.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

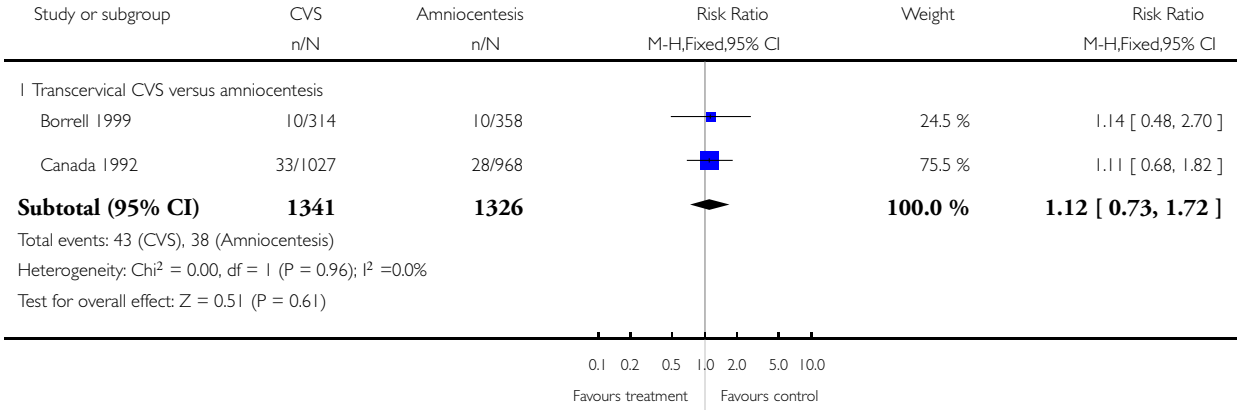
Outcome: 6 All non-mosaic abnormalities



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 6 All non-mosaic abnormalities

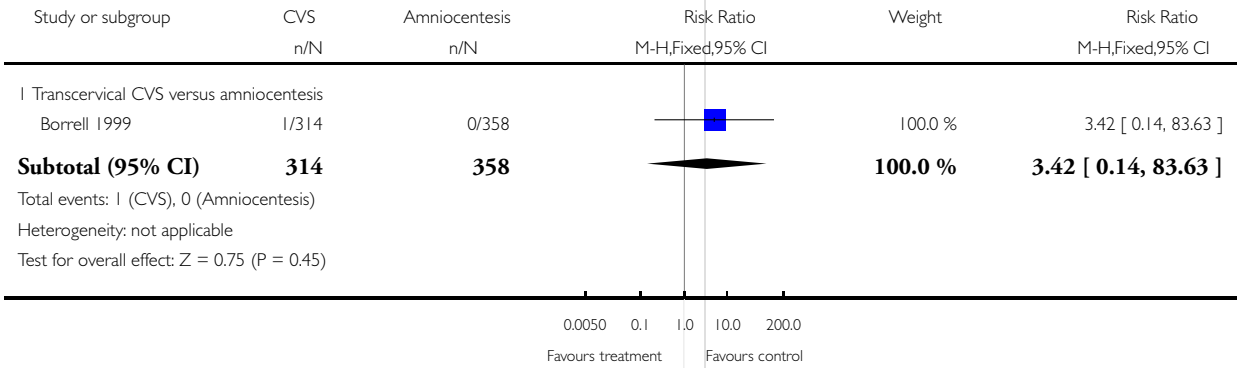


Analysis 3.7. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 7 True mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

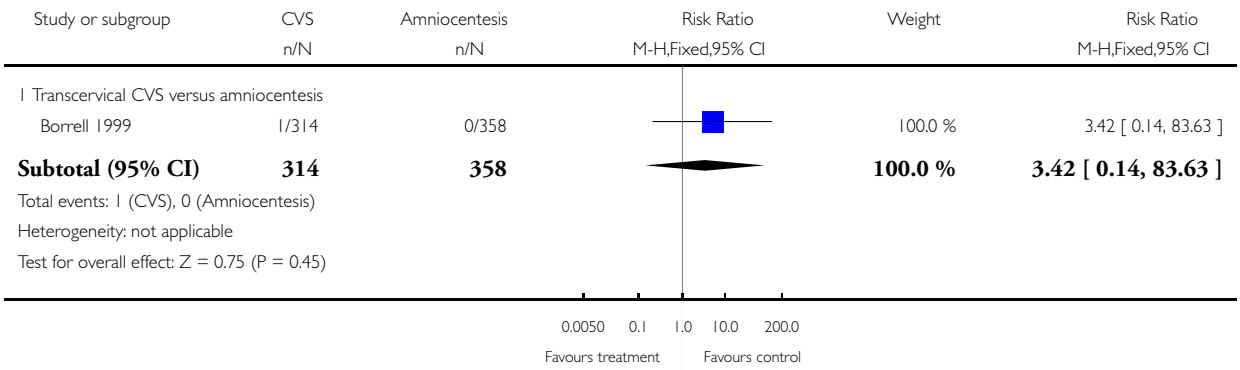
Outcome: 7 True mosaics



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 7 True mosaics

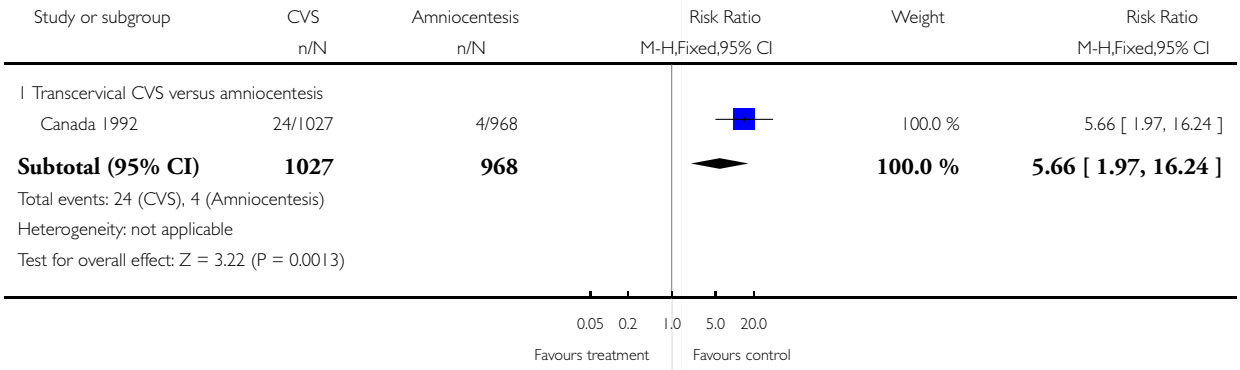


Analysis 3.8. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 8 Confined mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

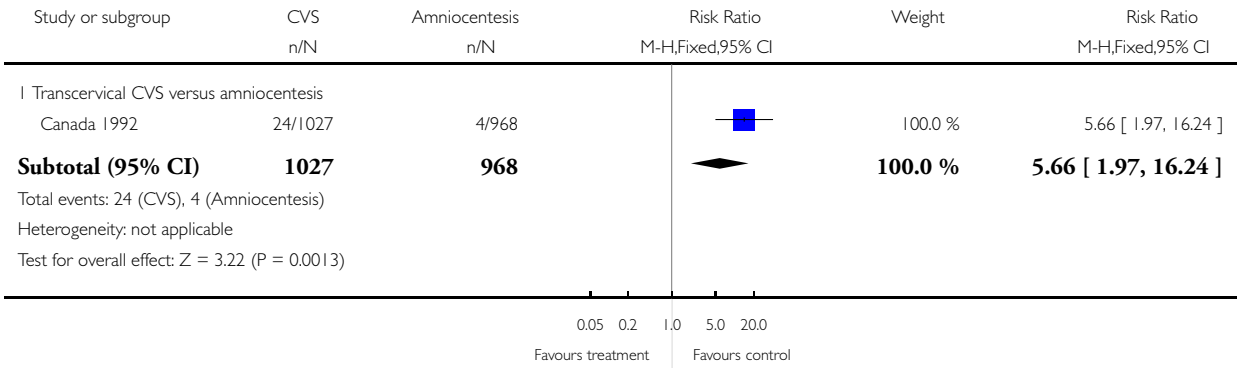
Outcome: 8 Confined mosaics



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 8 Confined mosaics

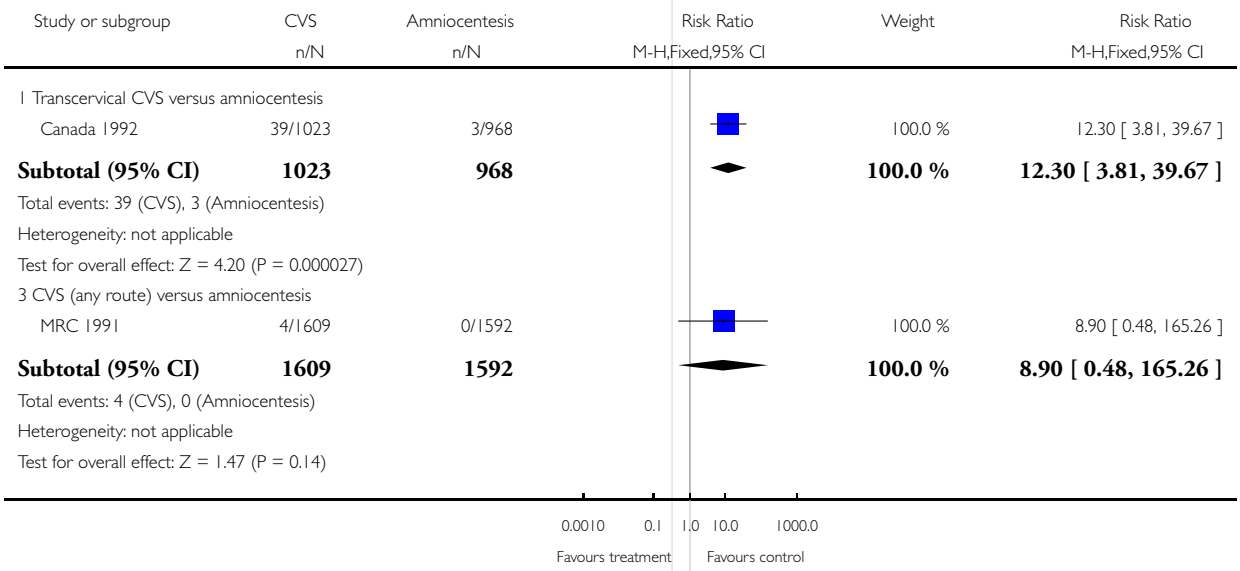


Analysis 3.9. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 9 Maternal contamination.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

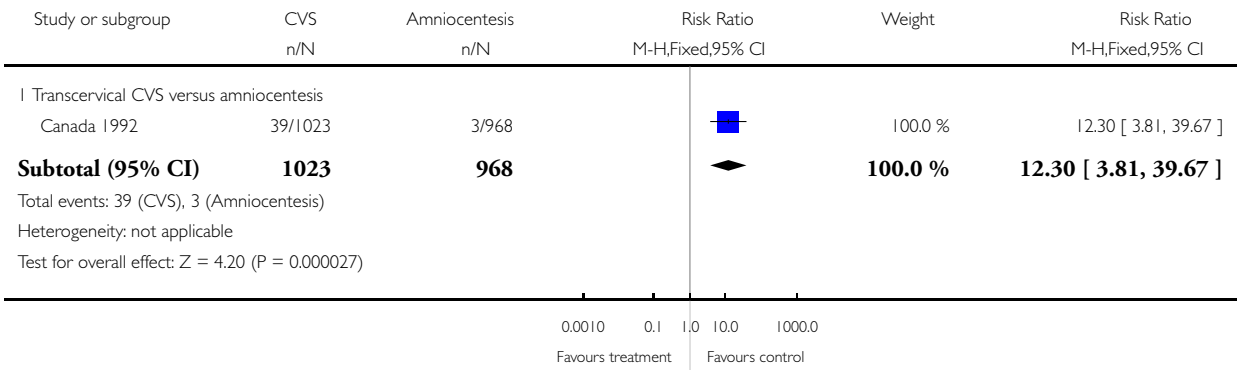
Outcome: 9 Maternal contamination



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

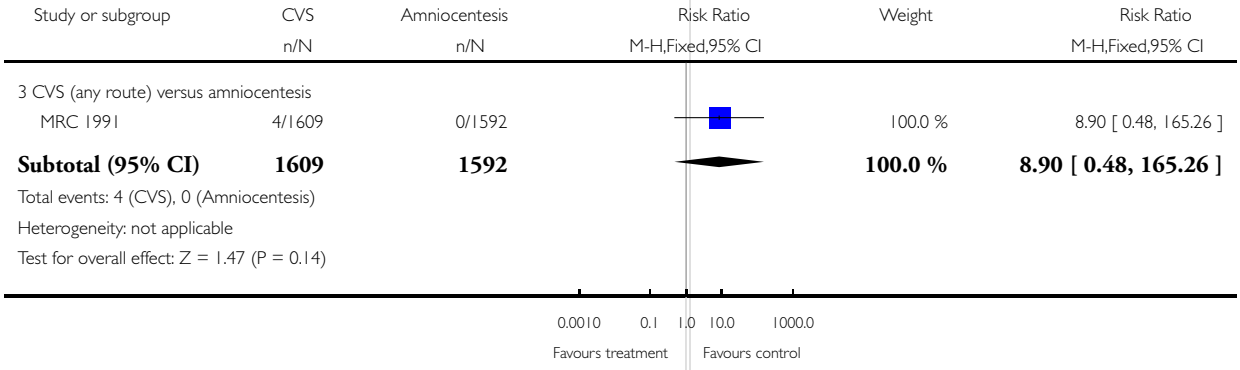
Outcome: 9 Maternal contamination



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 9 Maternal contamination

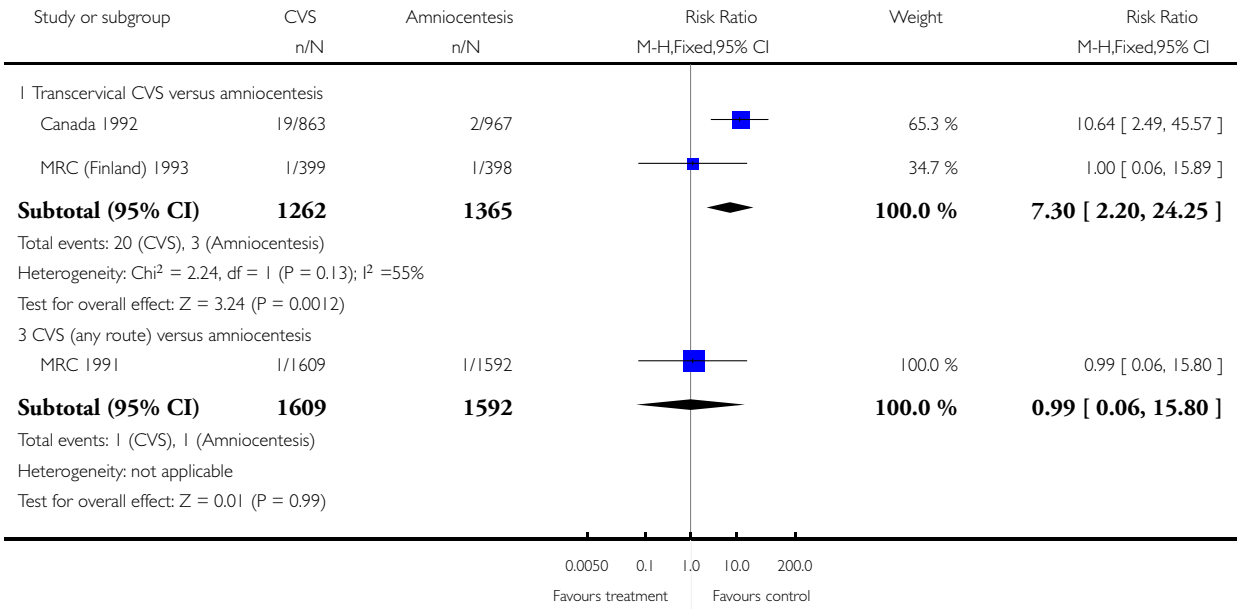


Analysis 3.10. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 10 Known false positive after birth.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

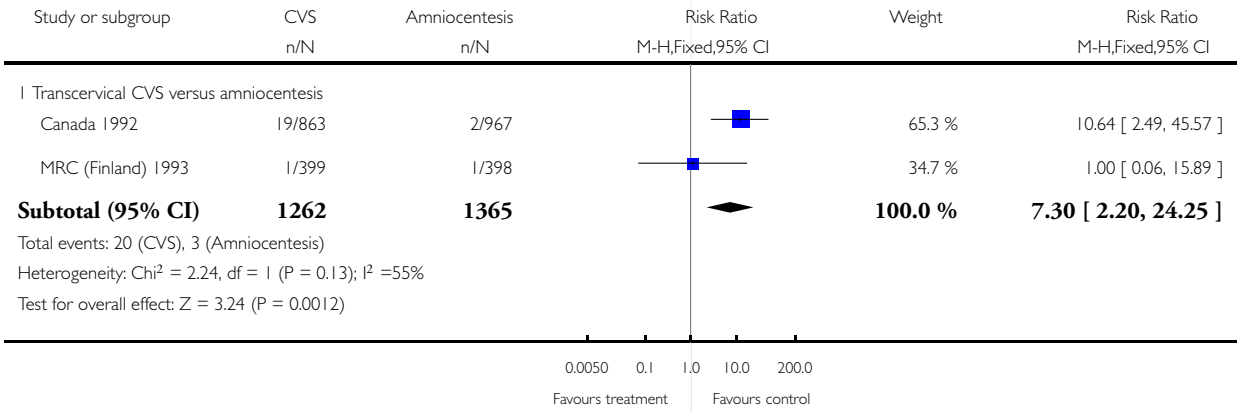
Outcome: 10 Known false positive after birth



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

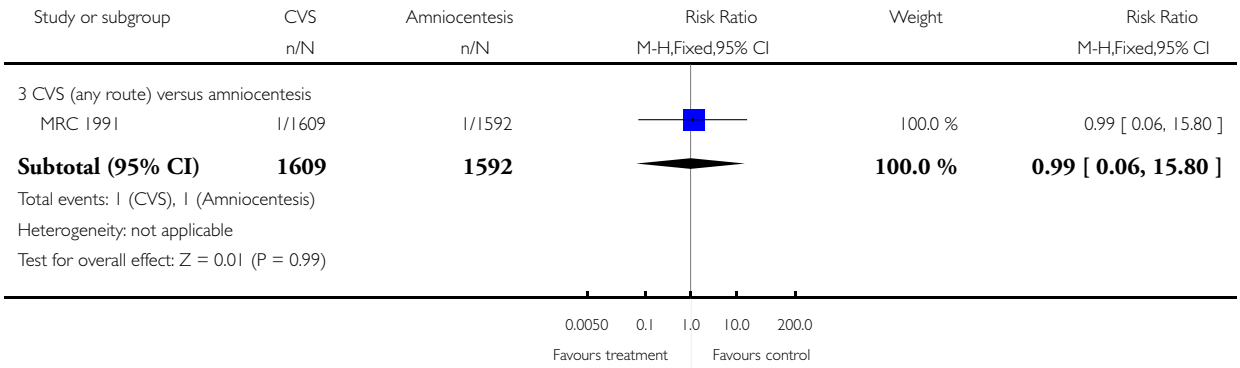
Outcome: 10 Known false positive after birth



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 10 Known false positive after birth

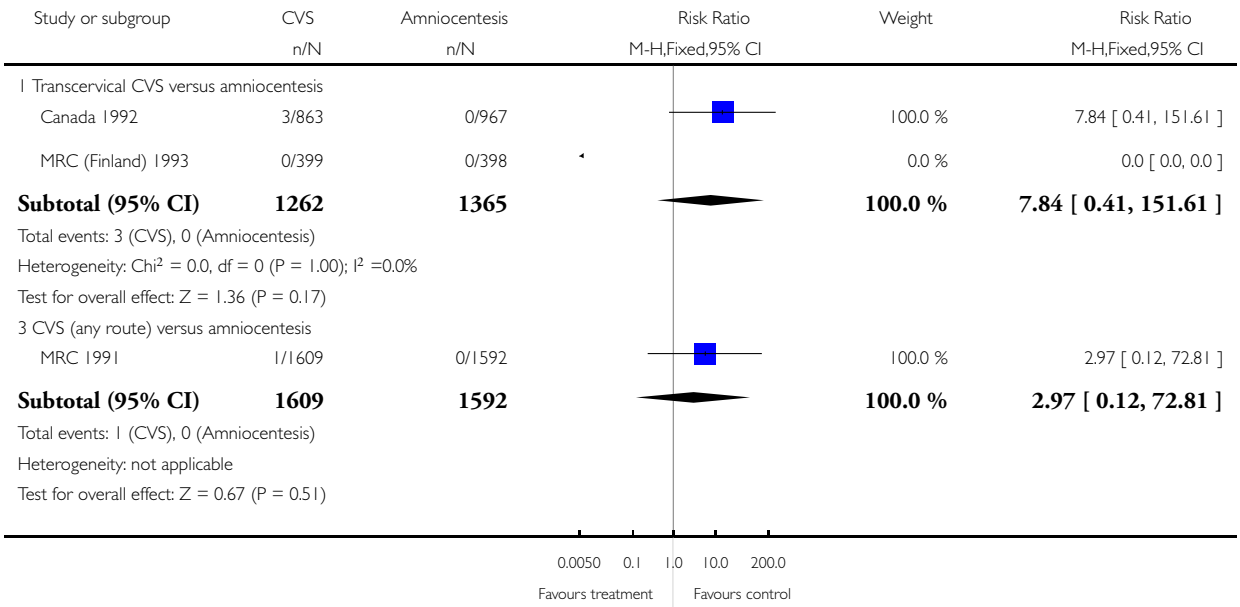


Analysis 3.11. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 11 Known false negative after birth.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

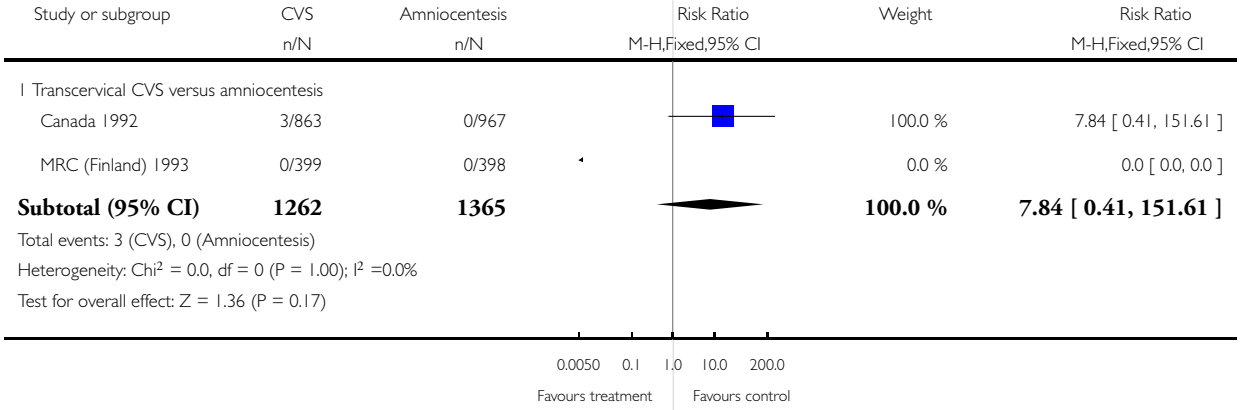
Outcome: 11 Known false negative after birth



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

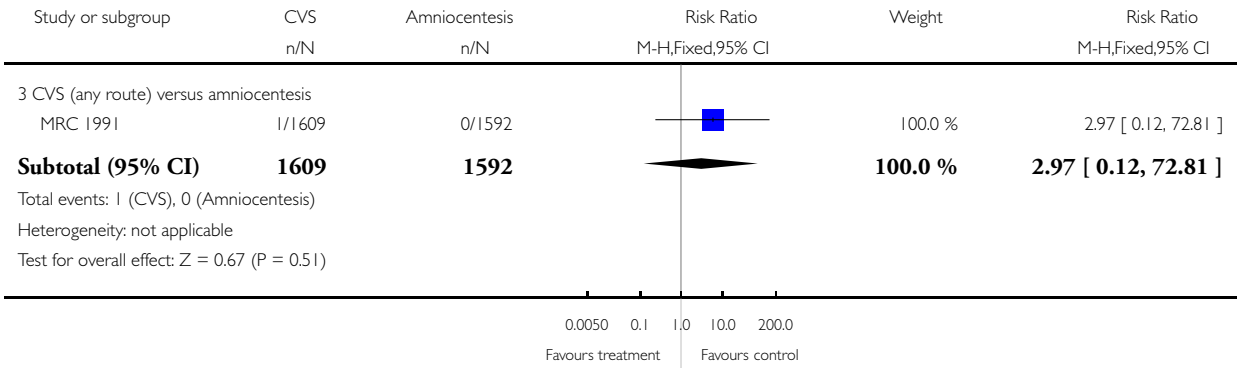
Outcome: 11 Known false negative after birth



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 11 Known false negative after birth

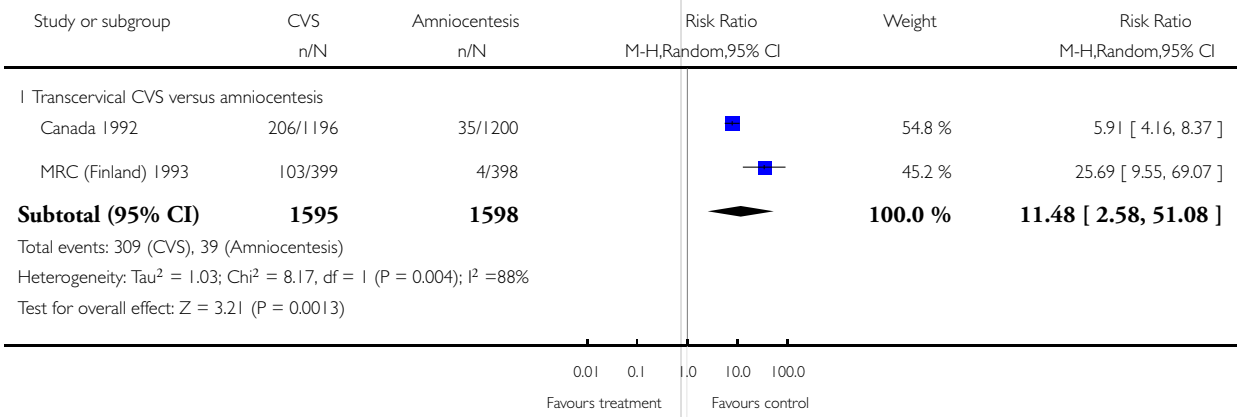


Analysis 3.13. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 13 Vaginal bleeding after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

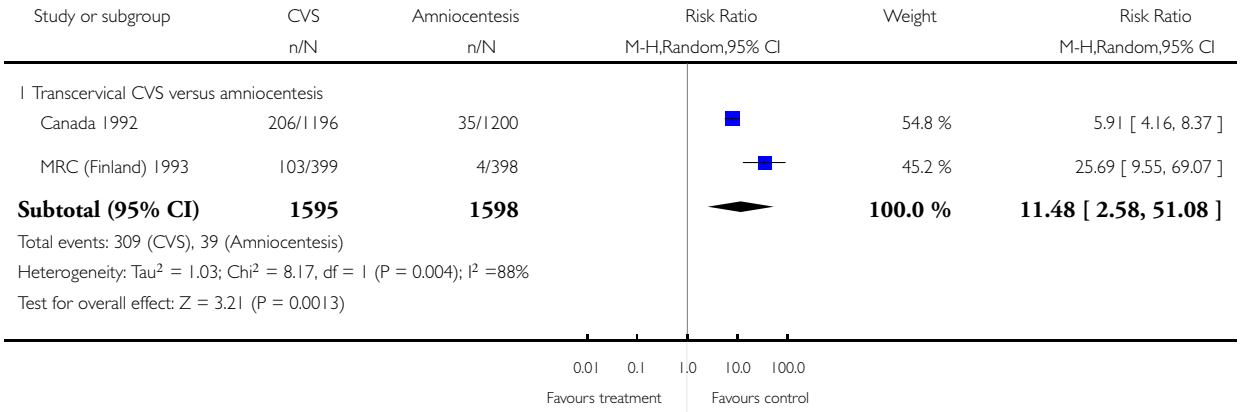
Outcome: 13 Vaginal bleeding after test



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 13 Vaginal bleeding after test

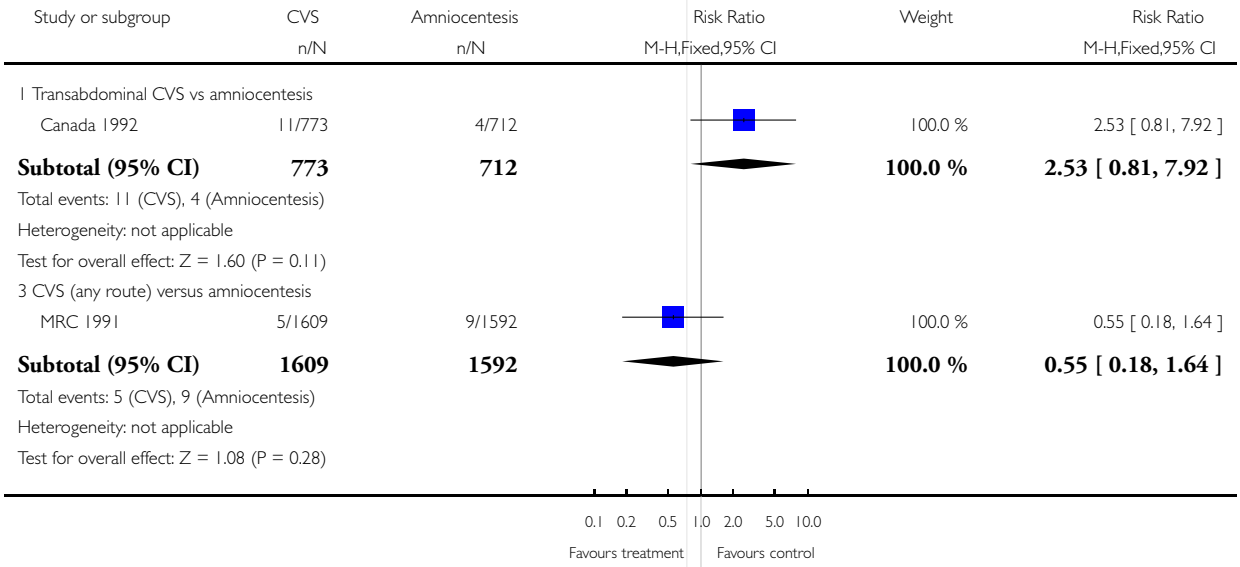


Analysis 3.14. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 14 Amniotic leakage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

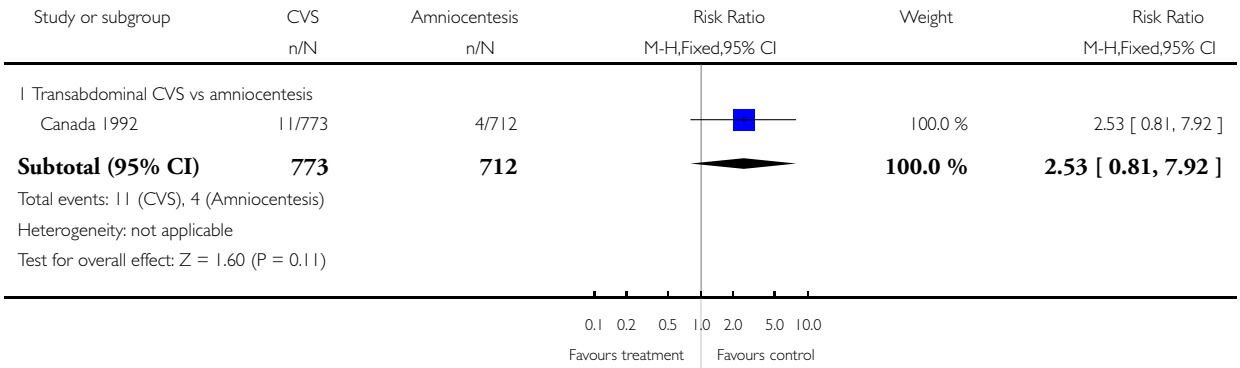
Outcome: 14 Amniotic leakage after test



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

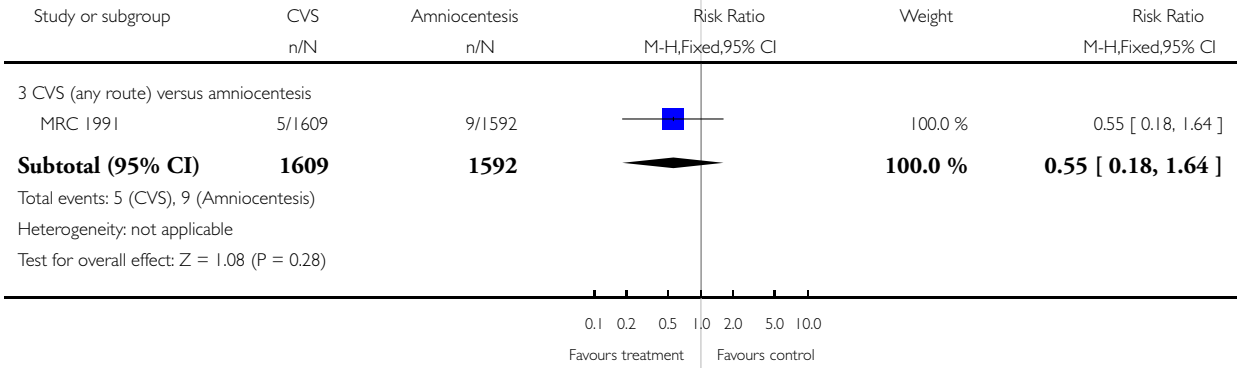
Outcome: 14 Amniotic leakage after test



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 14 Amniotic leakage after test

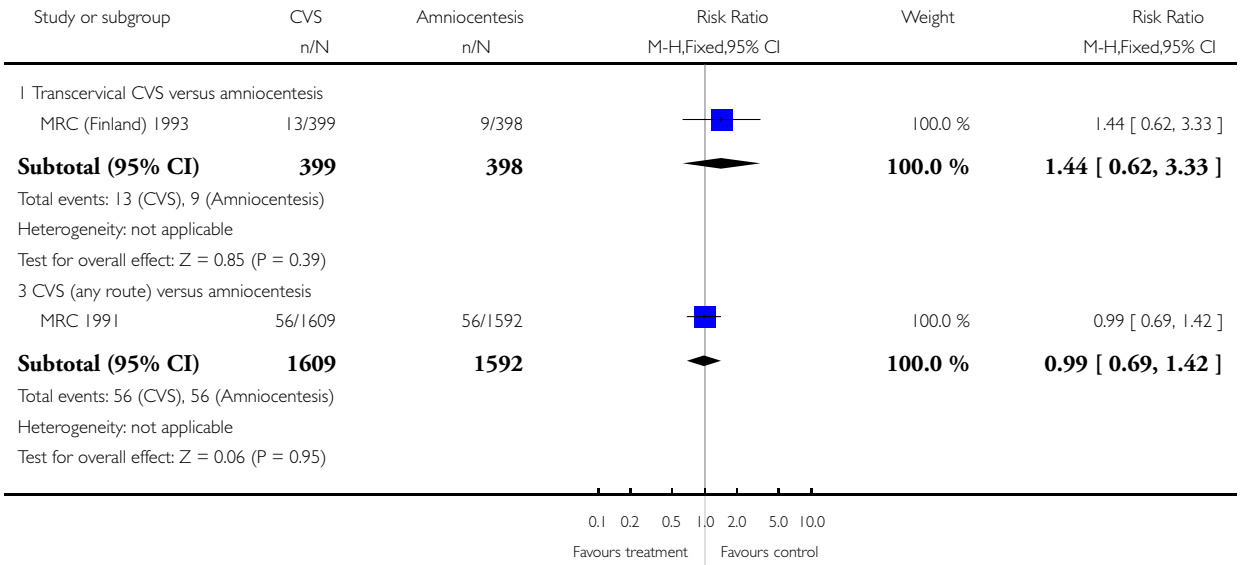


Analysis 3.15. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 15 Vaginal bleeding after 20 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

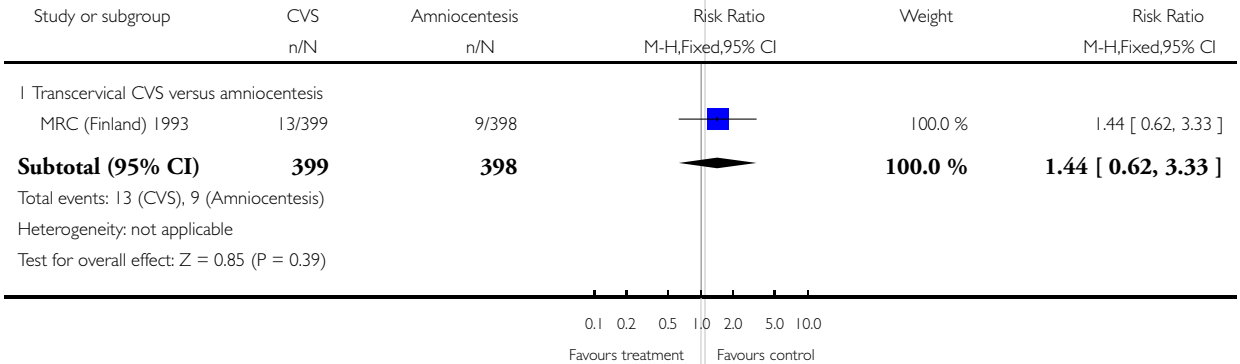
Outcome: 15 Vaginal bleeding after 20 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

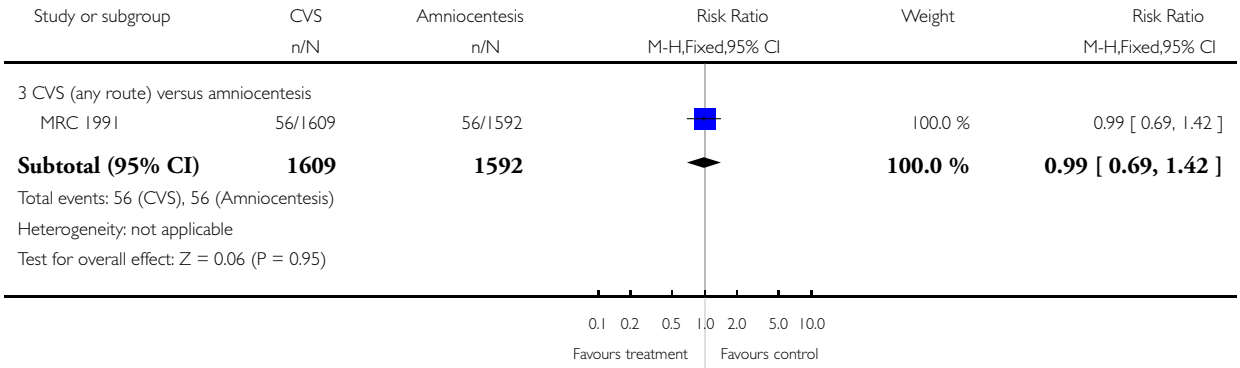
Outcome: 15 Vaginal bleeding after 20 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 15 Vaginal bleeding after 20 weeks

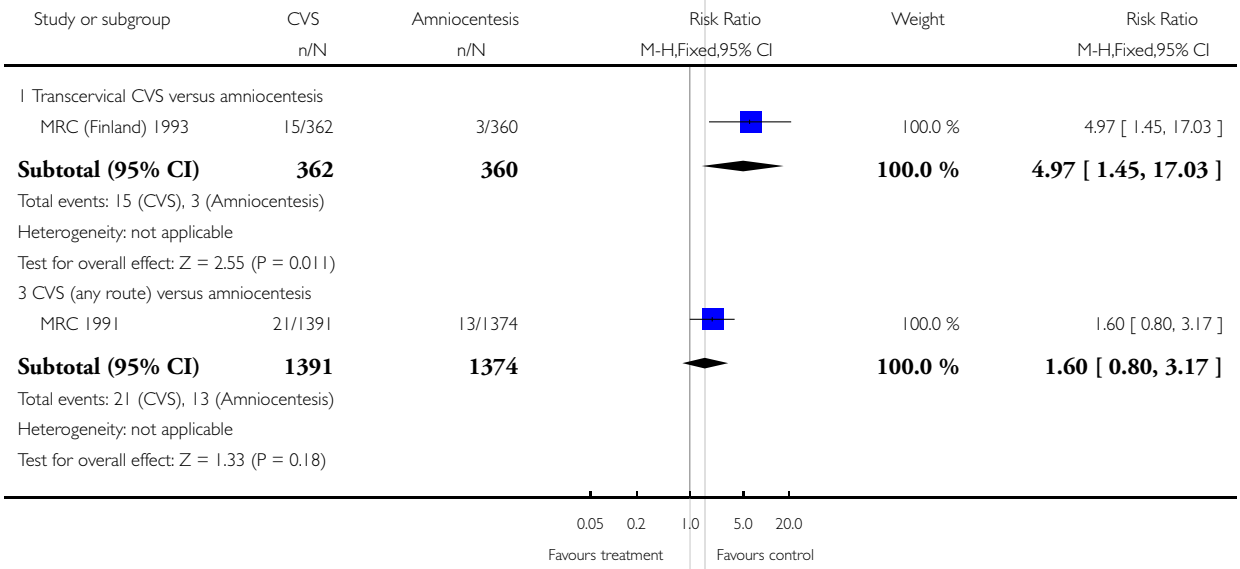


Analysis 3.16. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 16 PROM before 28 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

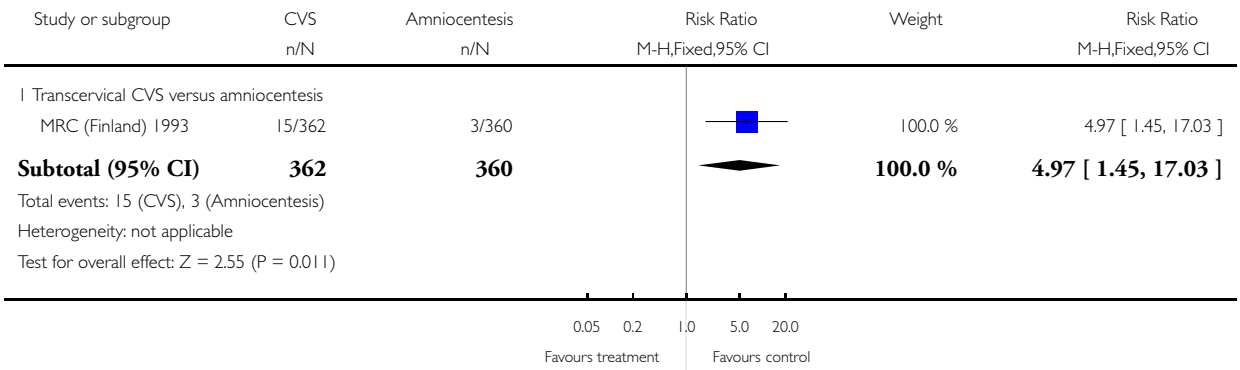
Outcome: 16 PROM before 28 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

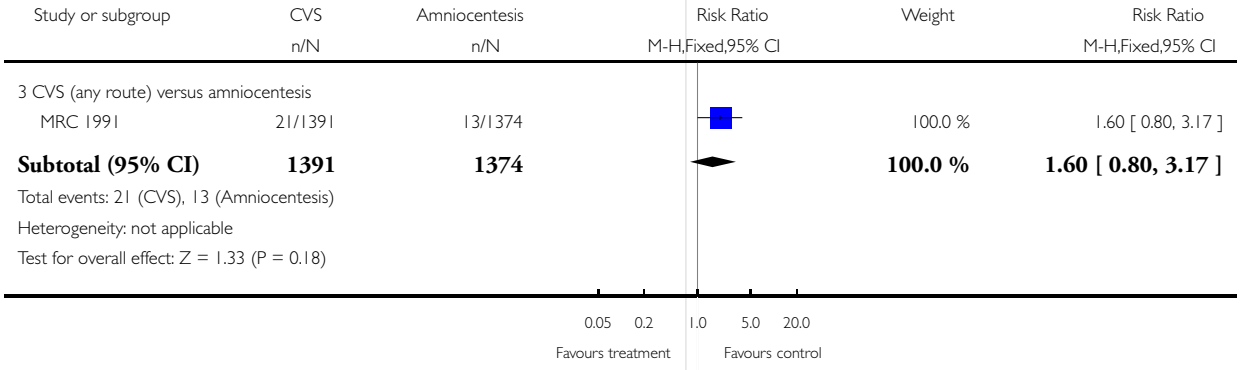
Outcome: 16 PROM before 28 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 16 PROM before 28 weeks

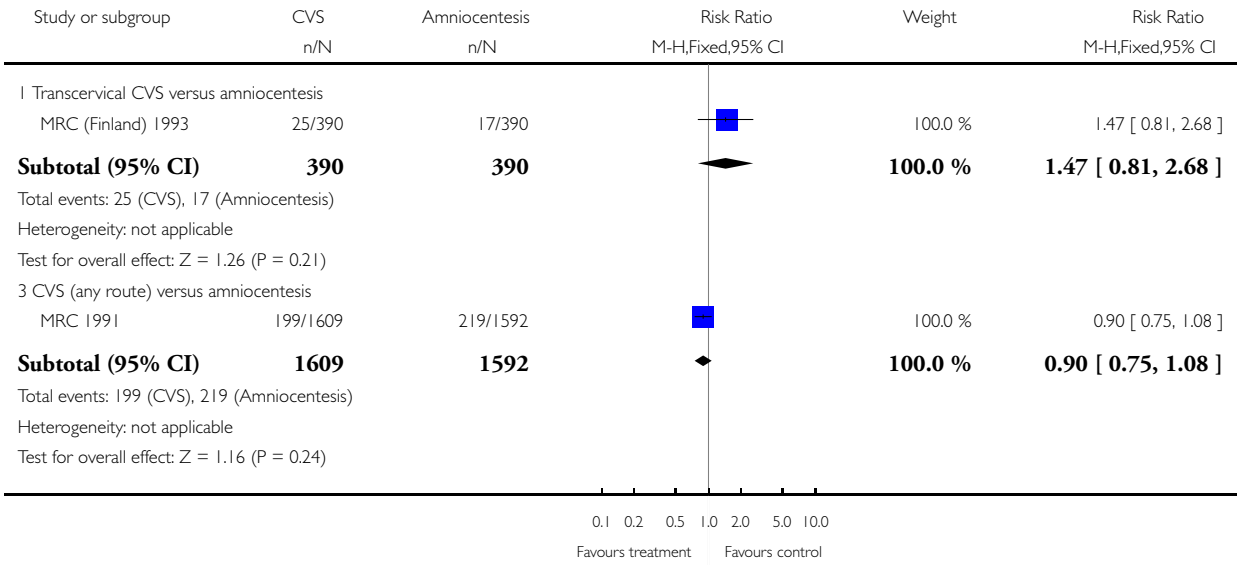


Analysis 3.17. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 17 Antenatal hospital admission.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

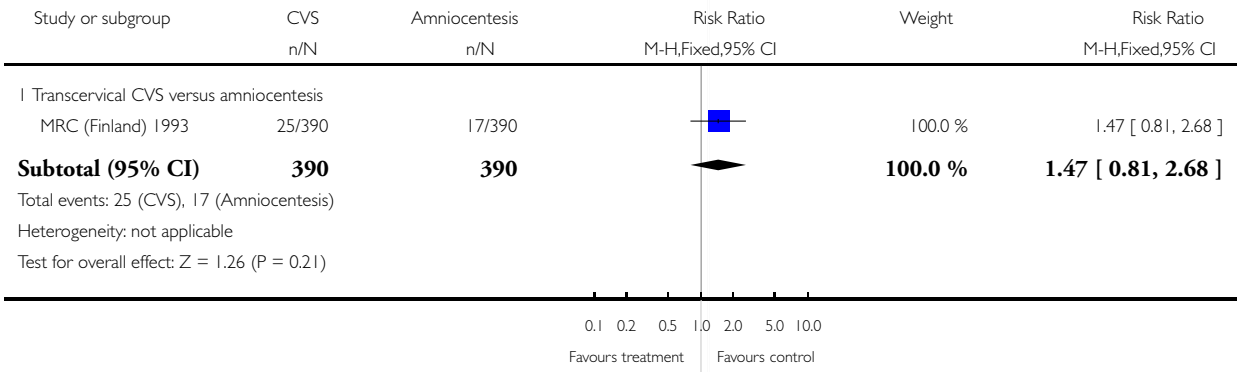
Outcome: 17 Antenatal hospital admission



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

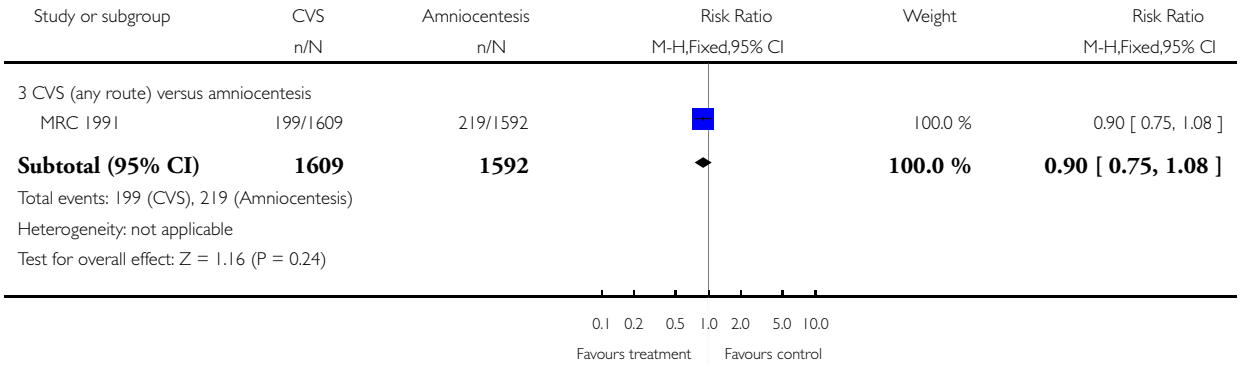
Outcome: 17 Antenatal hospital admission



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 17 Antenatal hospital admission

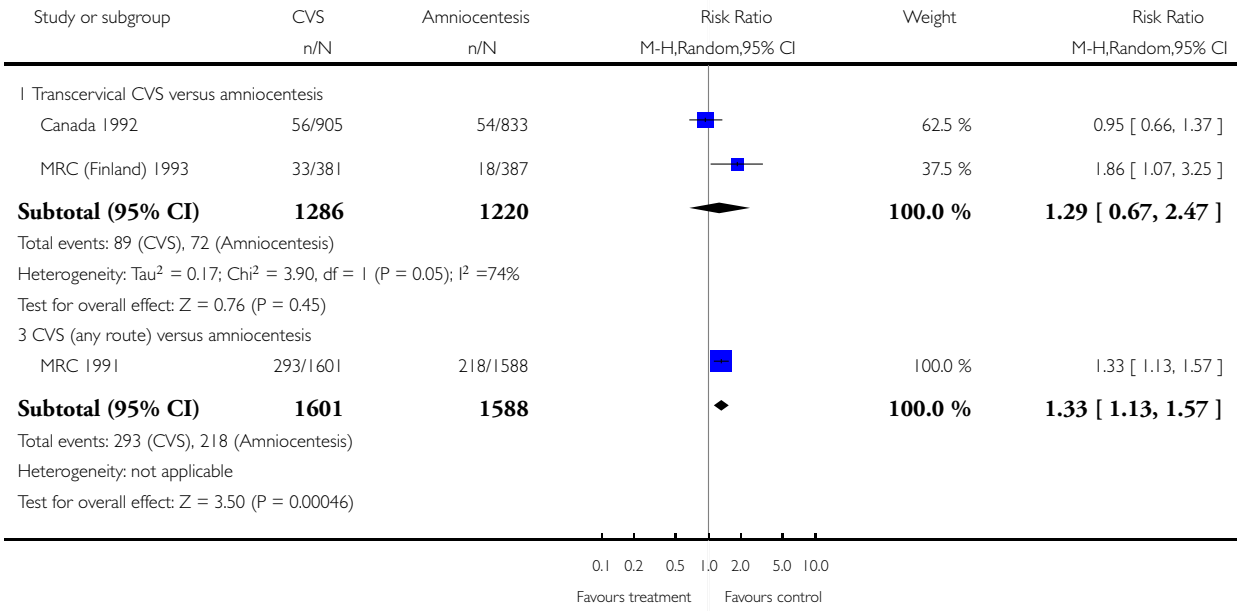


Analysis 3.18. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 18 Delivery before 37 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

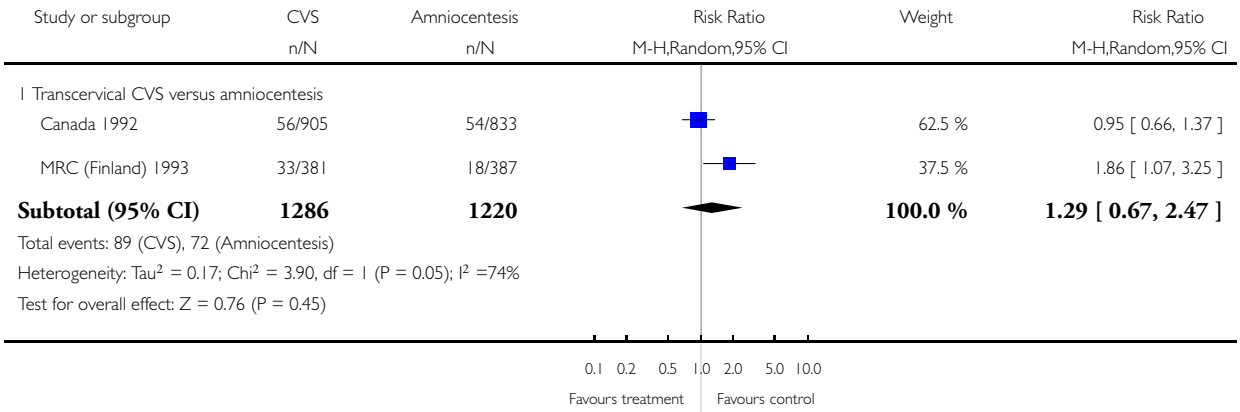
Outcome: 18 Delivery before 37 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

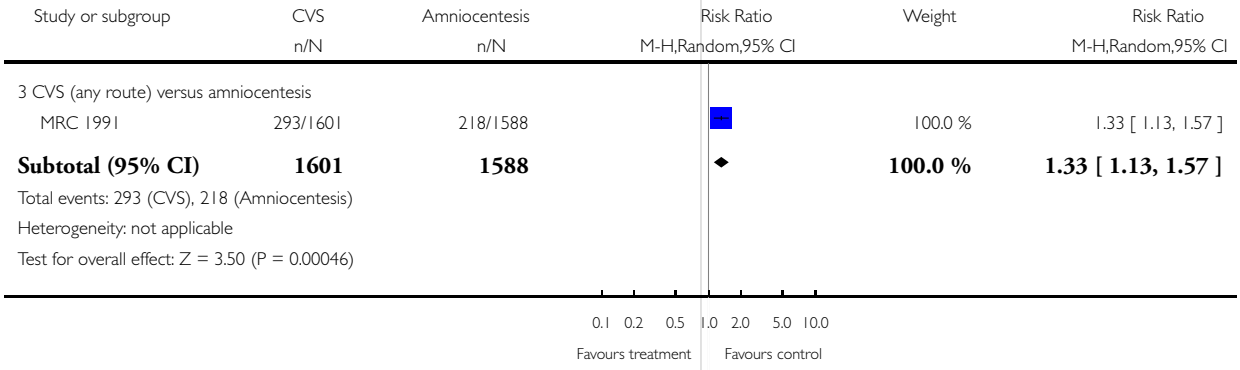
Outcome: 18 Delivery before 37 weeks



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 18 Delivery before 37 weeks



Analysis 3.19. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 19 Delivery before 33 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 19 Delivery before 33 weeks

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.069)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours treatment Favours control

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 19 Delivery before 33 weeks

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.069)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0

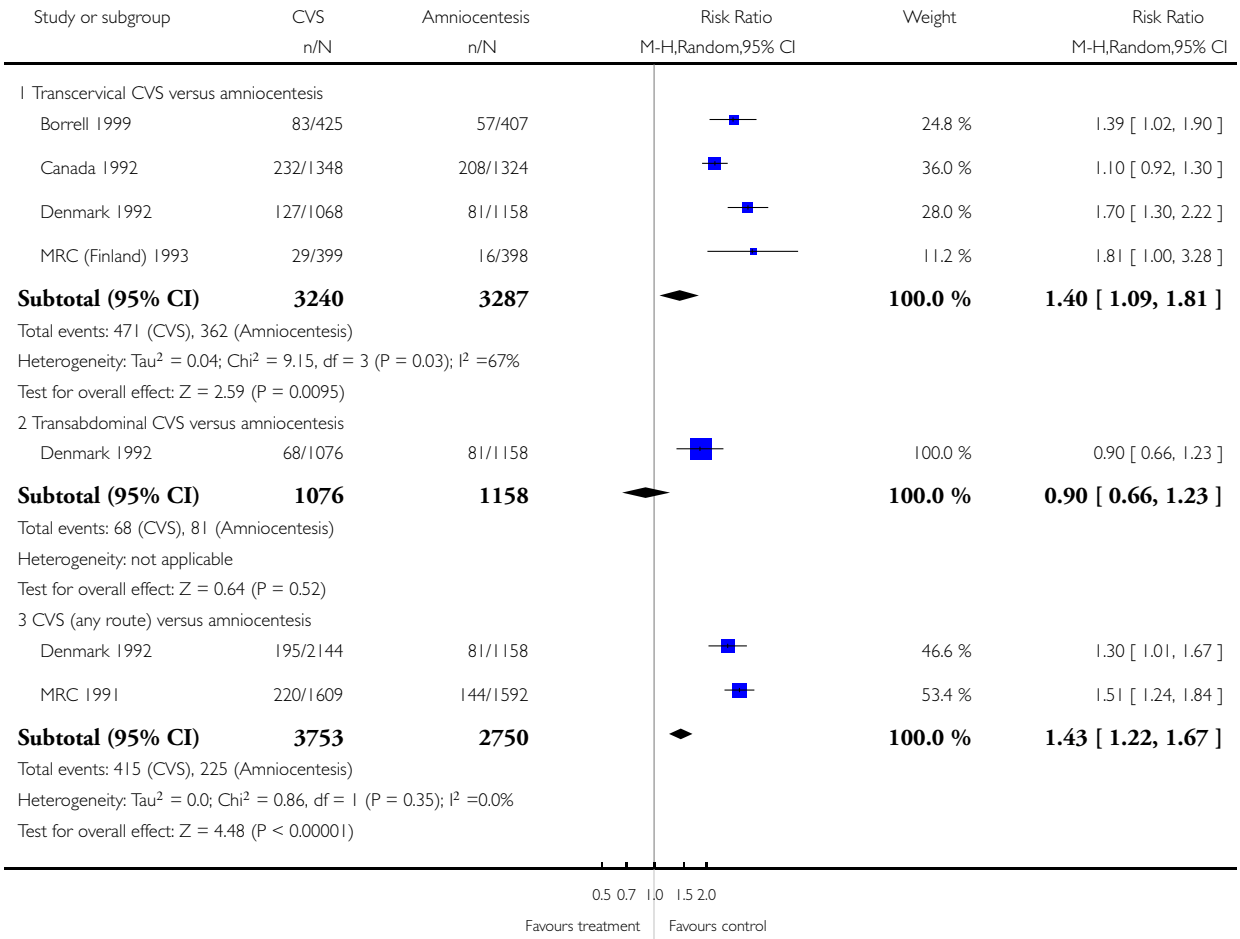
Favours treatment Favours control

Analysis 3.20. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

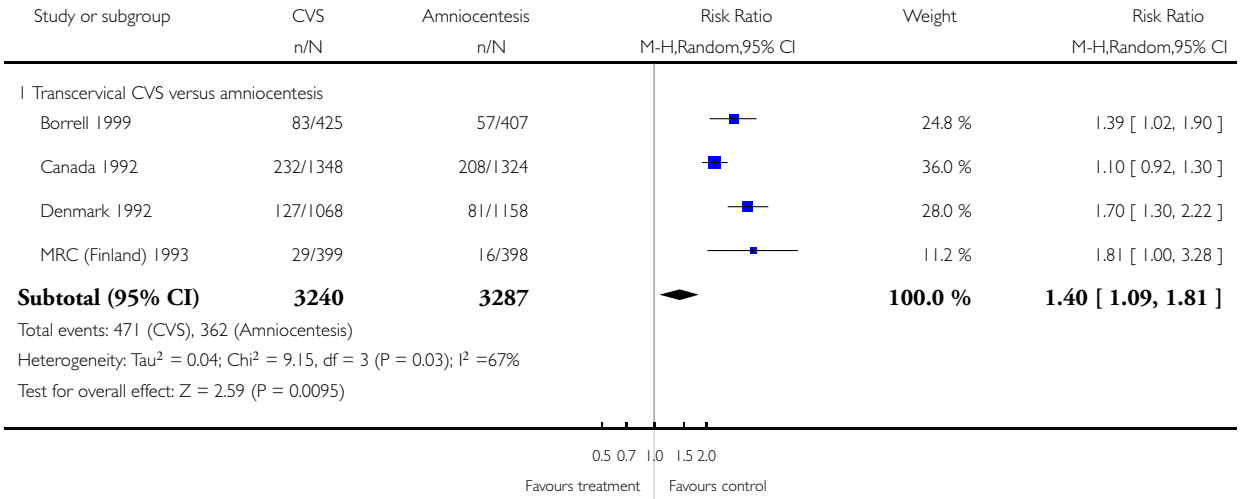
Outcome: 20 All known pregnancy loss (including termination of pregnancy)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

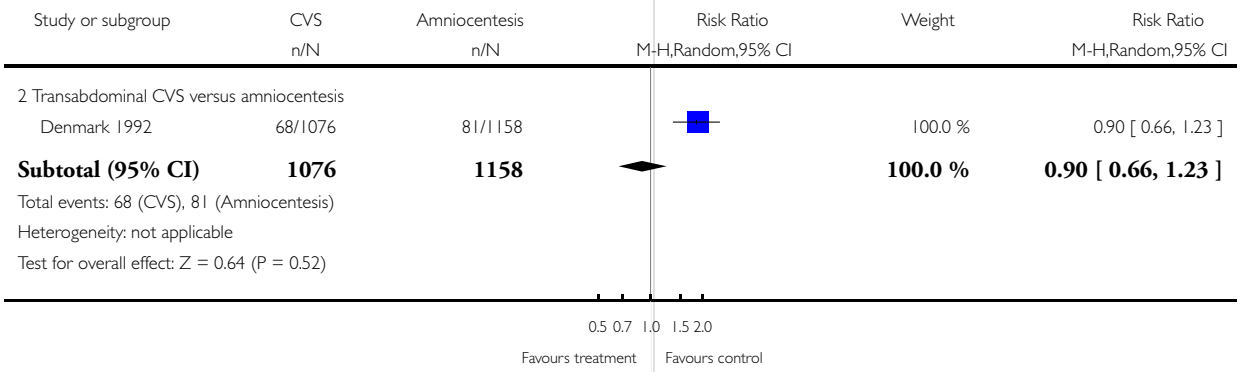
Outcome: 20 All known pregnancy loss (including termination of pregnancy)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

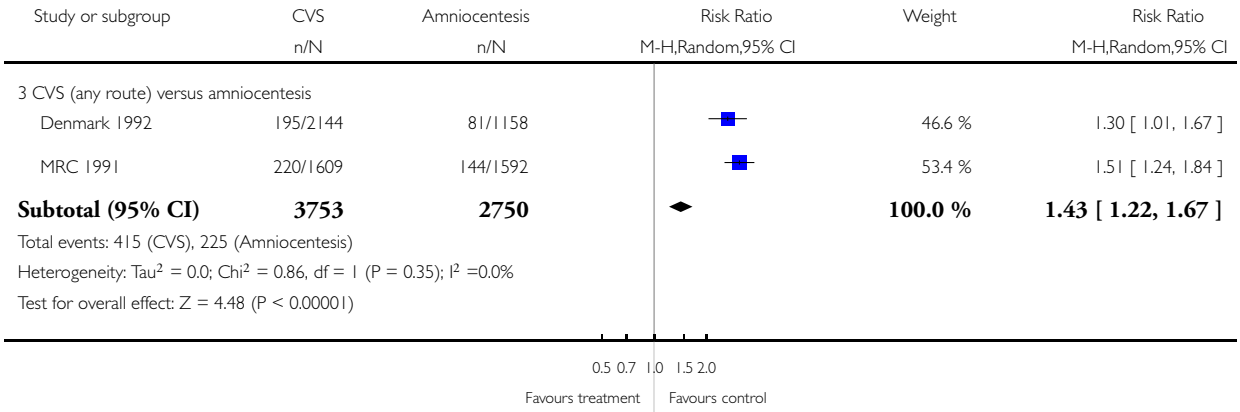
Outcome: 20 All known pregnancy loss (including termination of pregnancy)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

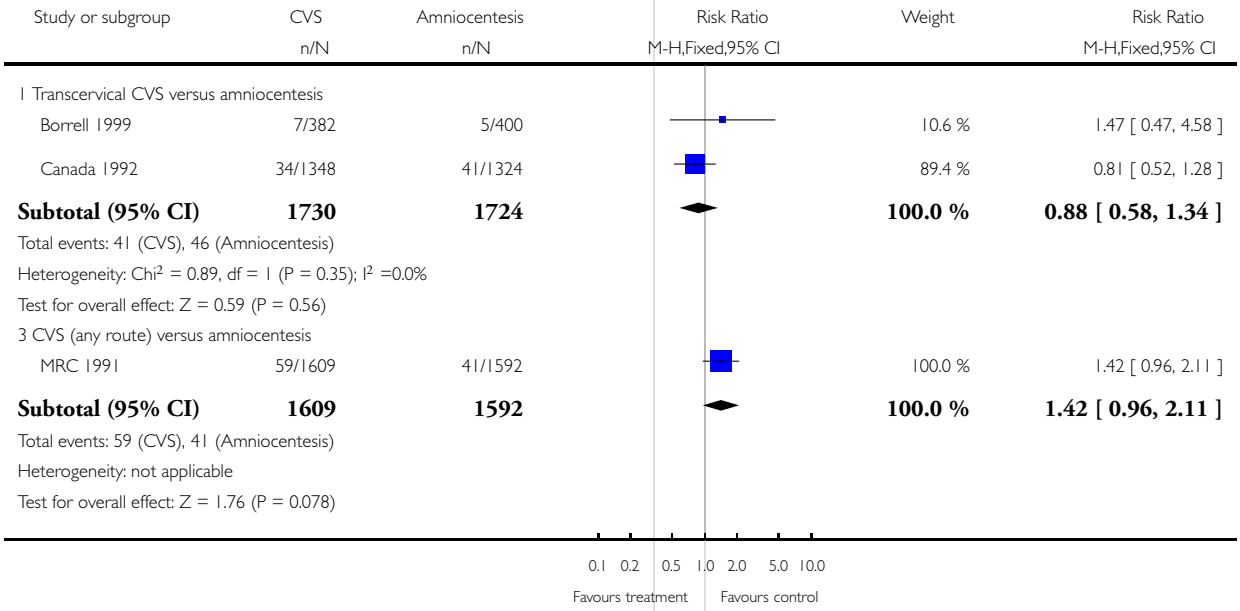


Analysis 3.21. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 21 Termination of pregnancy (all).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

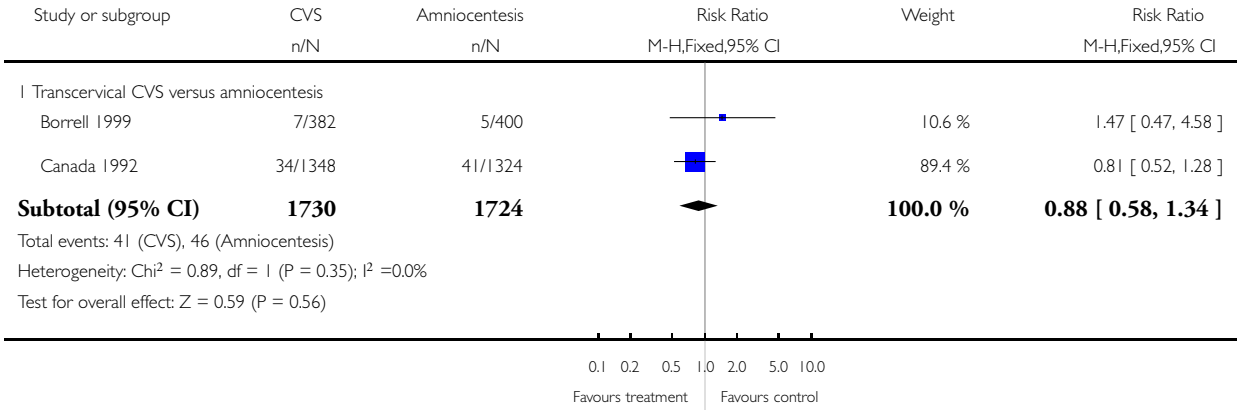
Outcome: 21 Termination of pregnancy (all)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

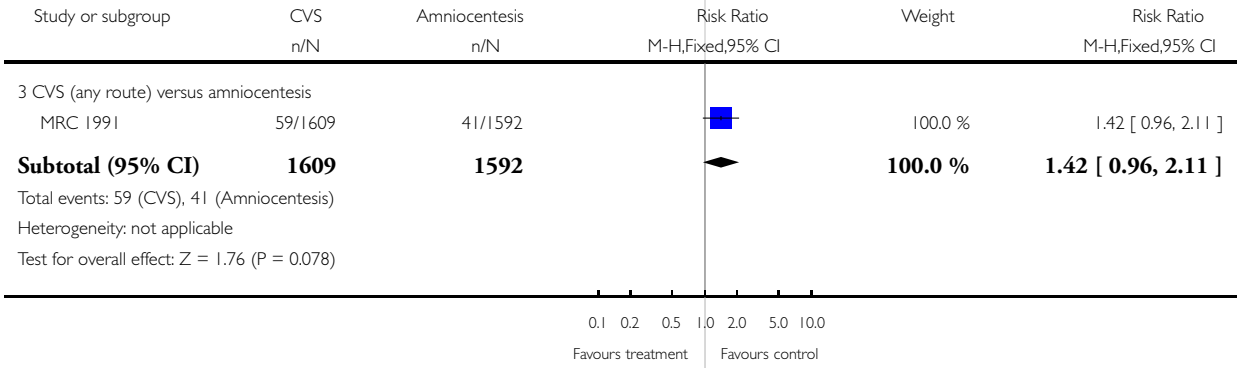
Outcome: 21 Termination of pregnancy (all)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 21 Termination of pregnancy (all)

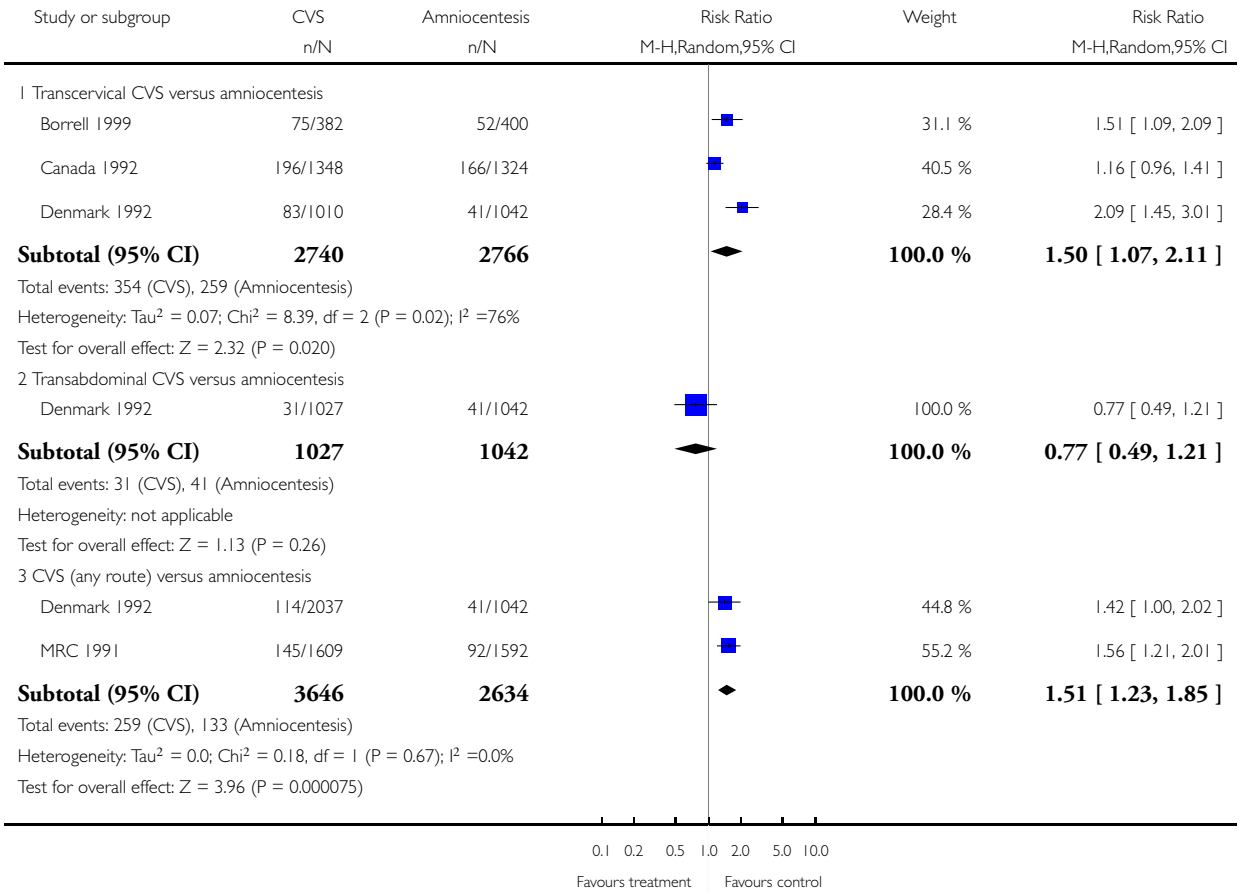


Analysis 3.24. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

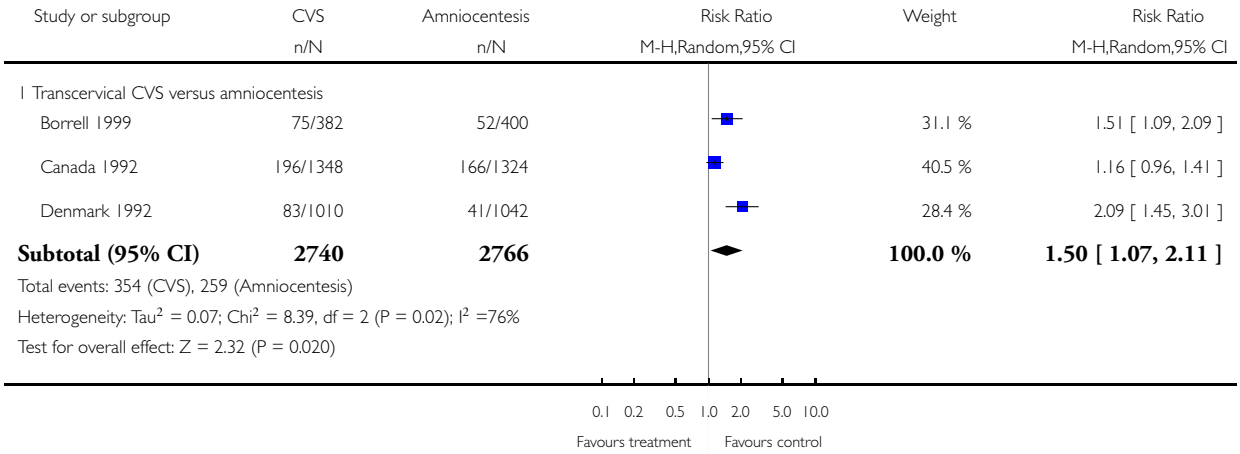
Outcome: 24 Spontaneous miscarriage



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

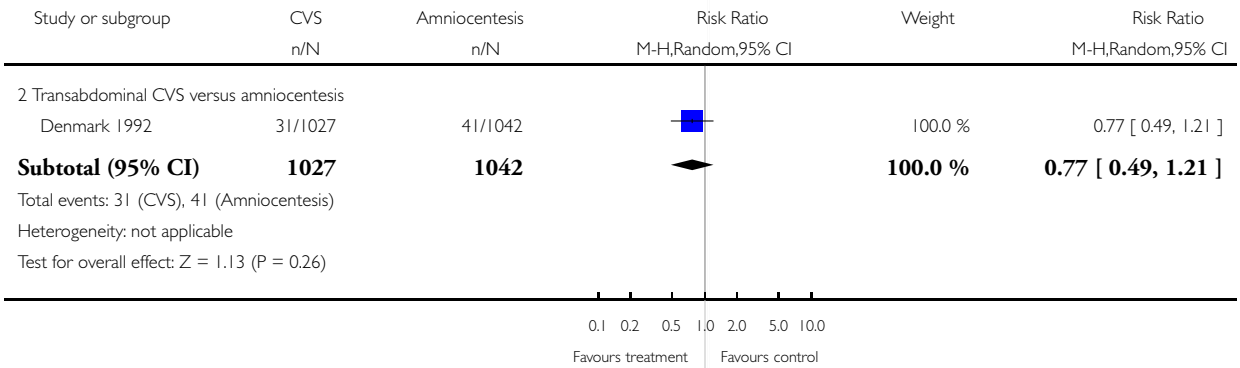
Outcome: 24 Spontaneous miscarriage



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

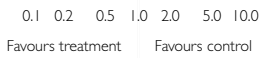


Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 CVS (any route) versus amniocentesis					
Denmark 1992	114/2037	41/1042		44.8 %	1.42 [1.00, 2.02]
MRC 1991	145/1609	92/1592		55.2 %	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)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.96 (P = 0.000075)					



Analysis 3.25. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

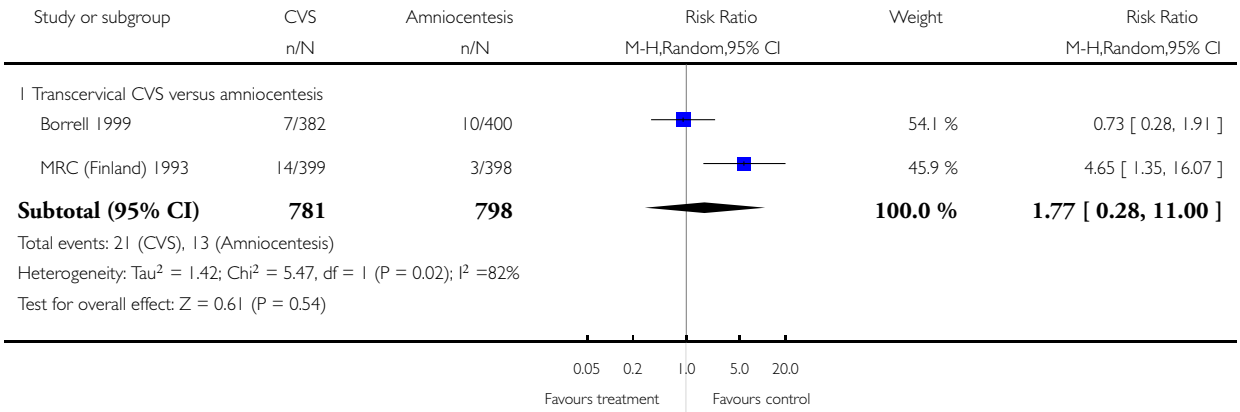
Outcome: 25 Spontaneous miscarriage after test

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transcervical CVS versus amniocentesis					
Borrell 1999	7/382	10/400		54.1 %	0.73 [0.28, 1.91]
MRC (Finland) 1993	14/399	3/398		45.9 %	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)					
Heterogeneity: $Tau^2 = 1.42$; $Chi^2 = 5.47$, df = 1 (P = 0.02); $I^2 = 82\%$					
Test for overall effect: Z = 0.61 (P = 0.54)					
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.43 (P < 0.00001)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

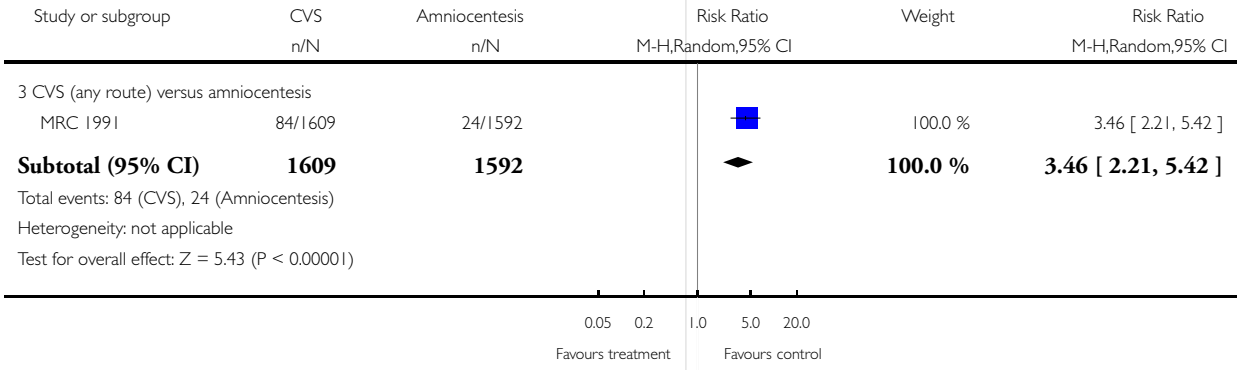
Outcome: 25 Spontaneous miscarriage after test



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

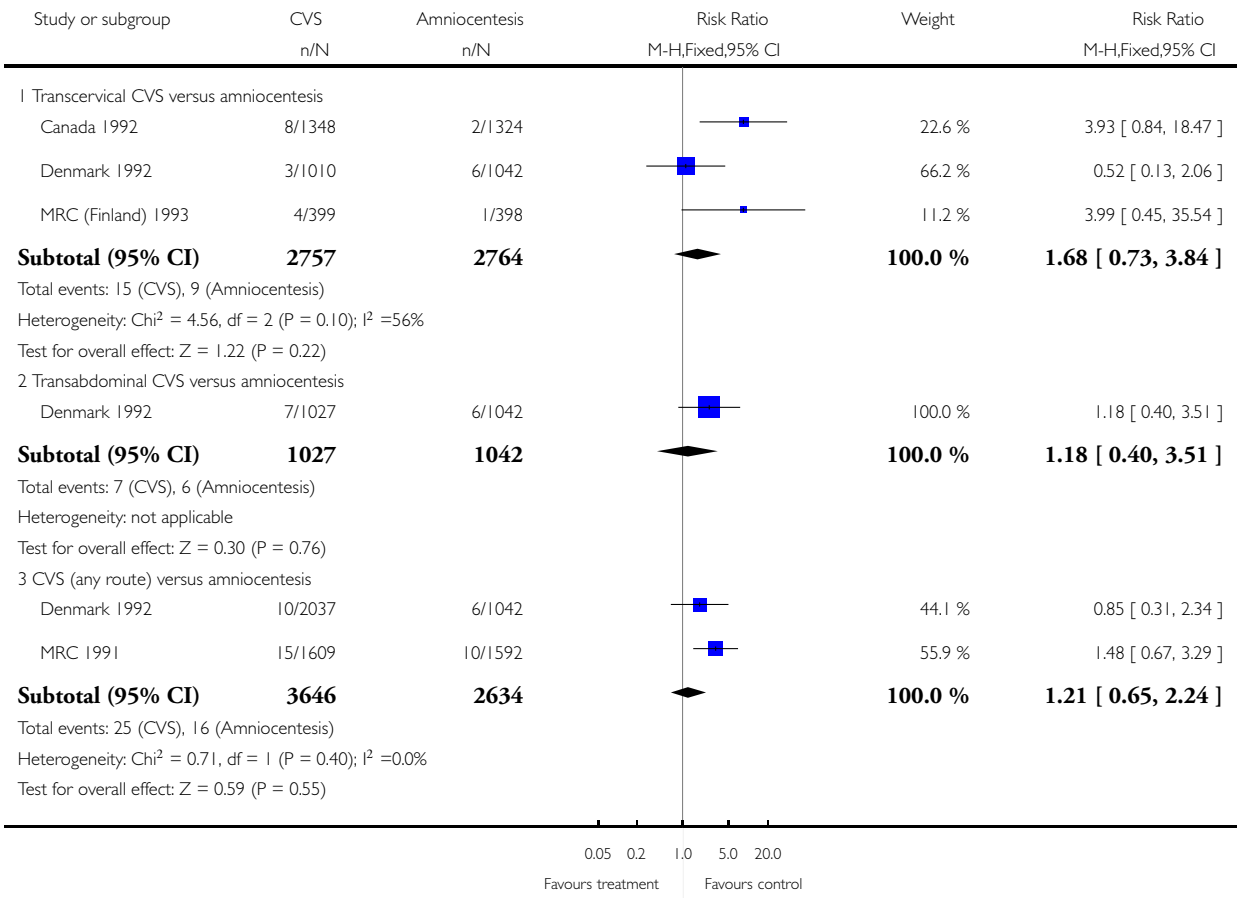


Analysis 3.26. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 26 Perinatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

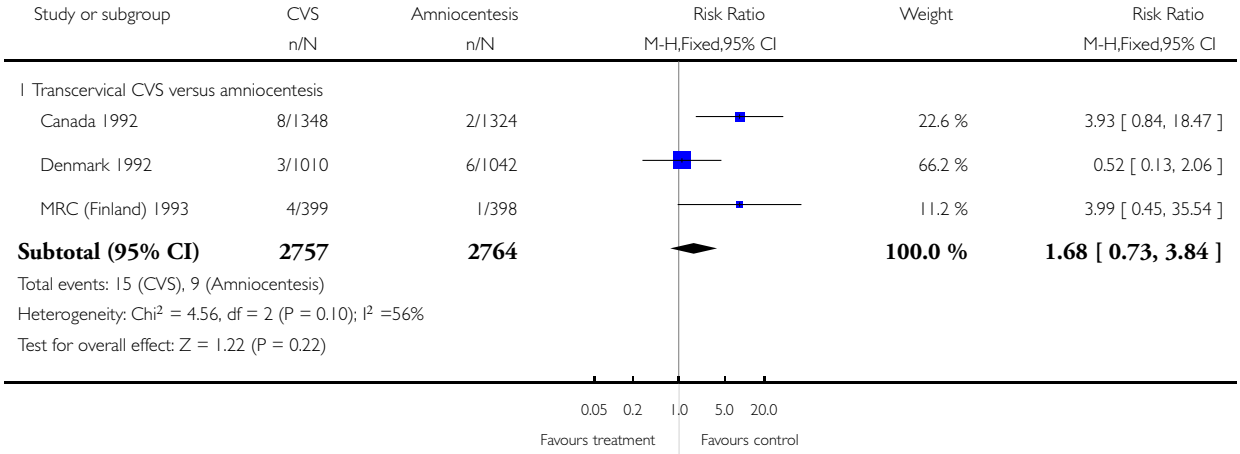
Outcome: 26 Perinatal deaths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

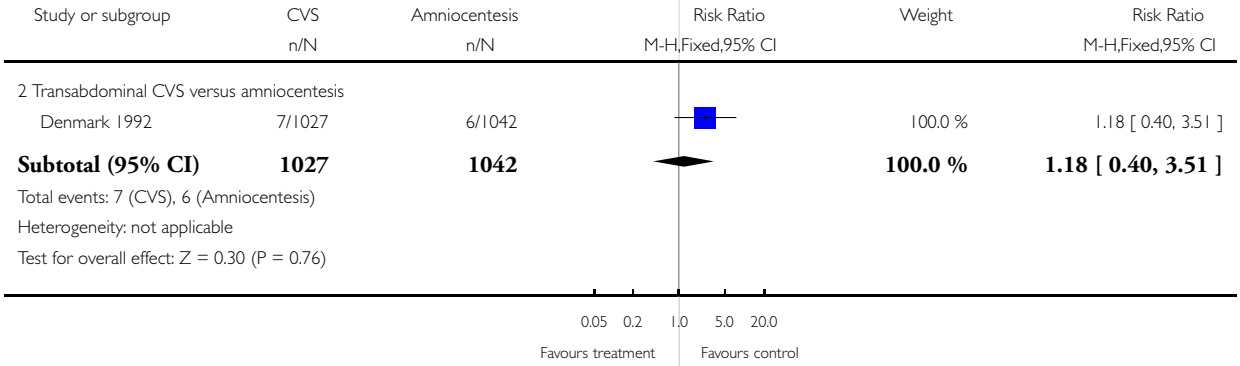
Outcome: 26 Perinatal deaths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

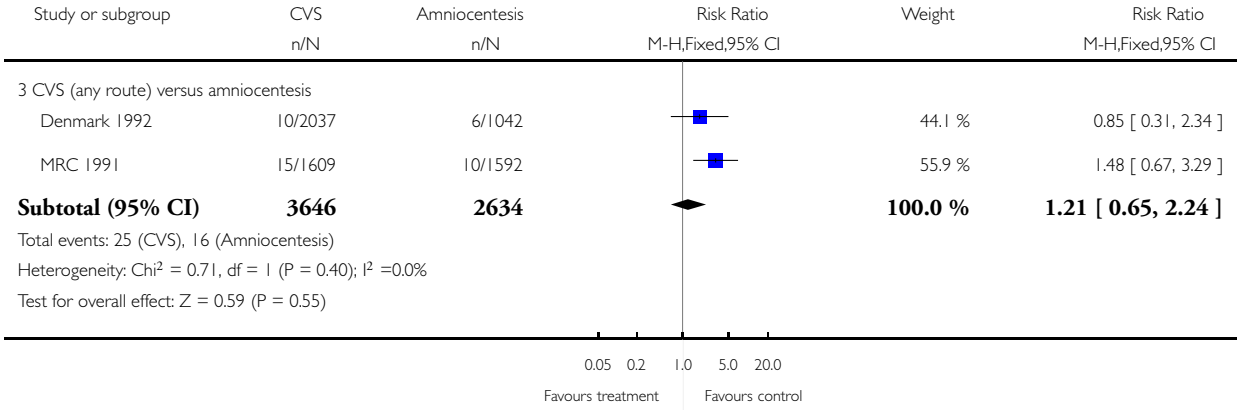
Outcome: 26 Perinatal deaths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 26 Perinatal deaths

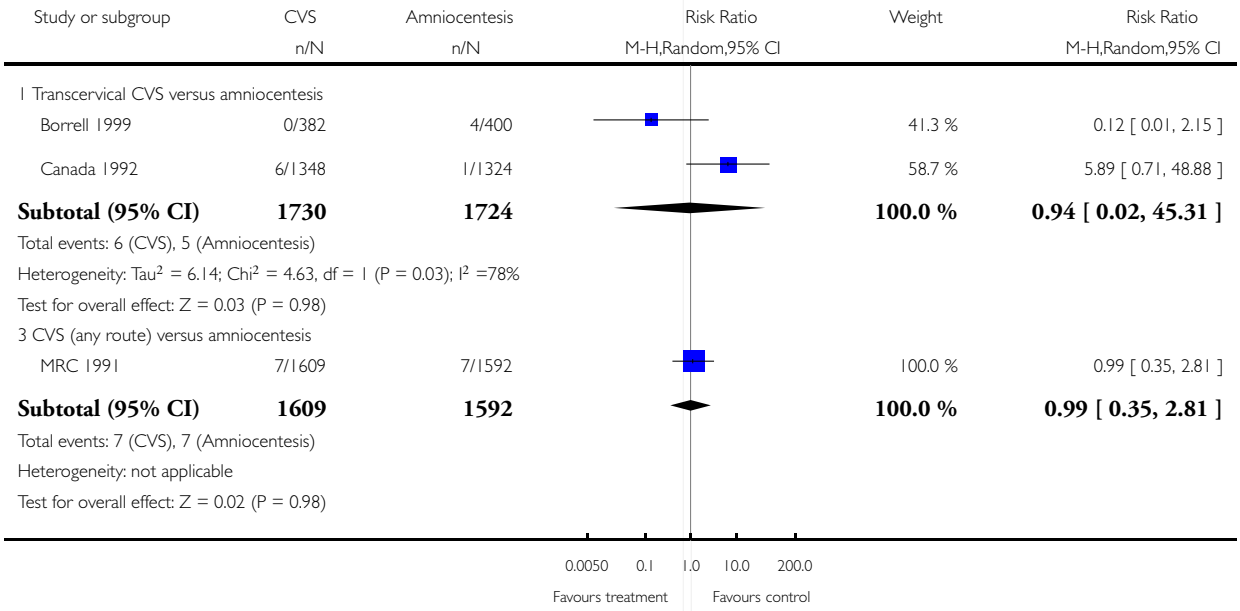


Analysis 3.27. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 27 Stillbirths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

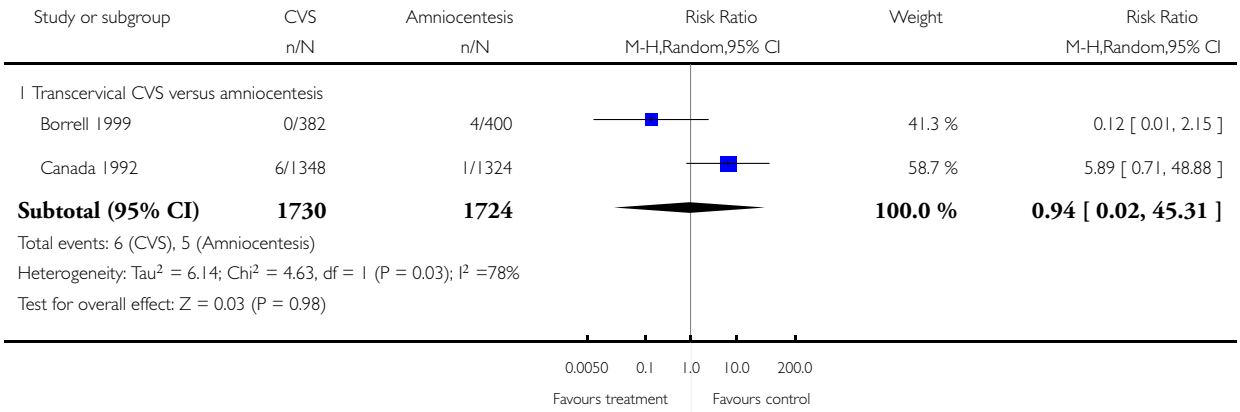
Outcome: 27 Stillbirths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

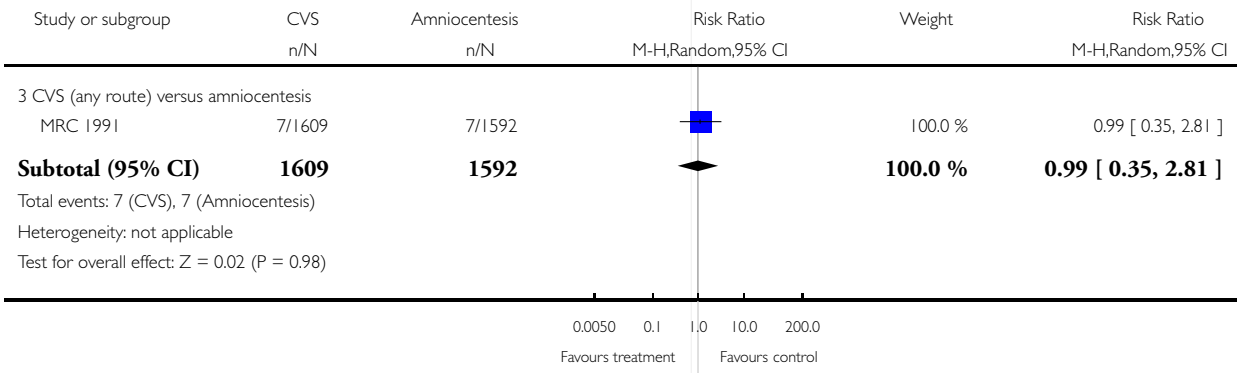
Outcome: 27 Stillbirths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 27 Stillbirths

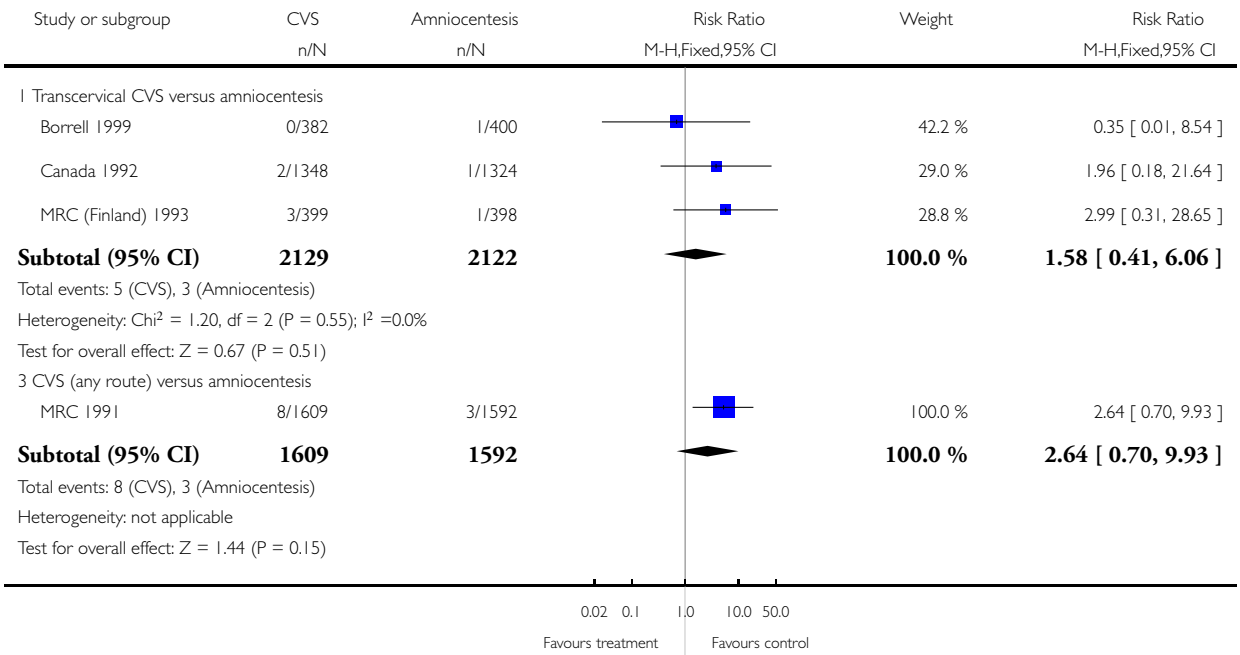


Analysis 3.28. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 28 Neonatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

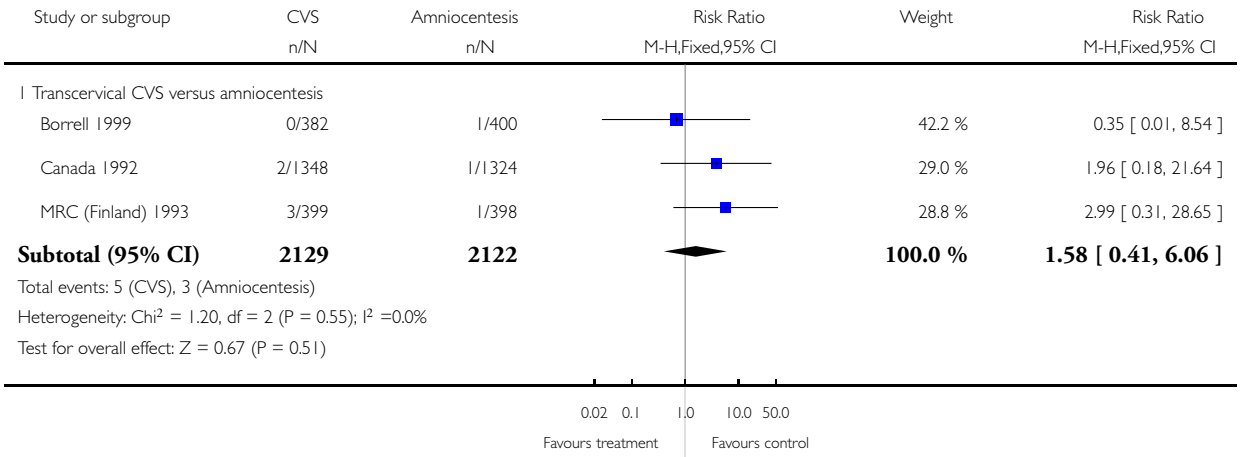
Outcome: 28 Neonatal deaths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

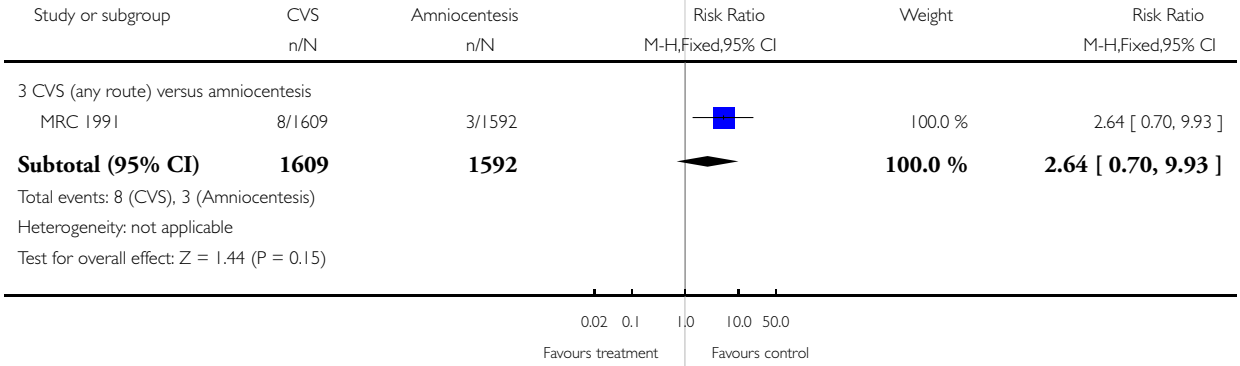
Outcome: 28 Neonatal deaths



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 28 Neonatal deaths

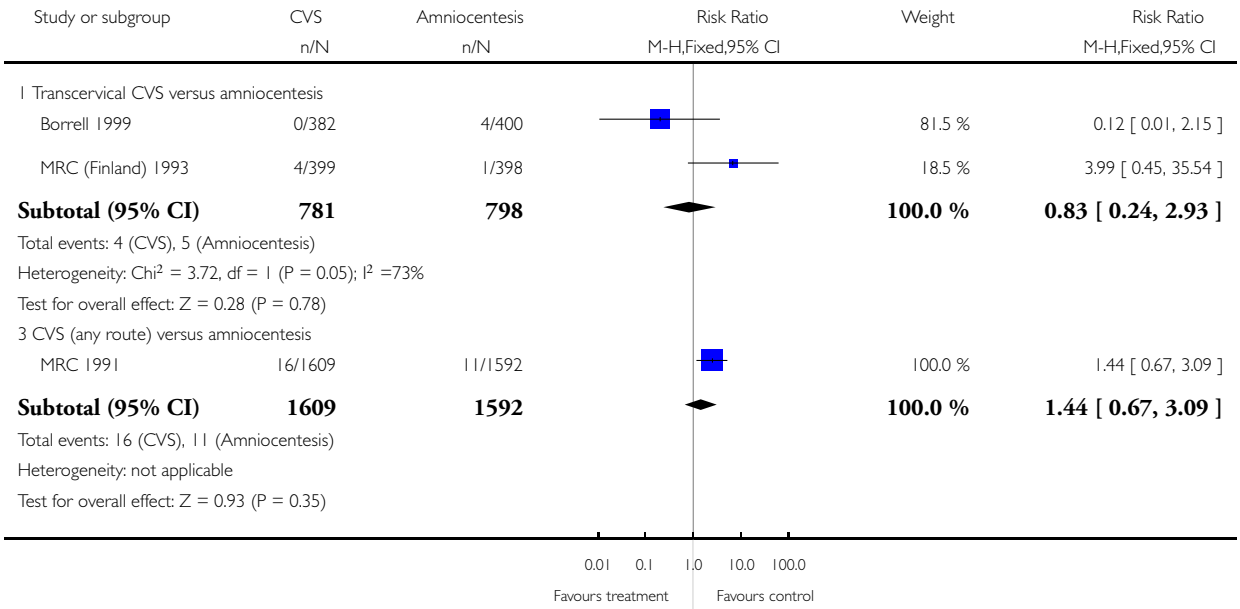


Analysis 3.29. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 29 All recorded deaths after viability.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

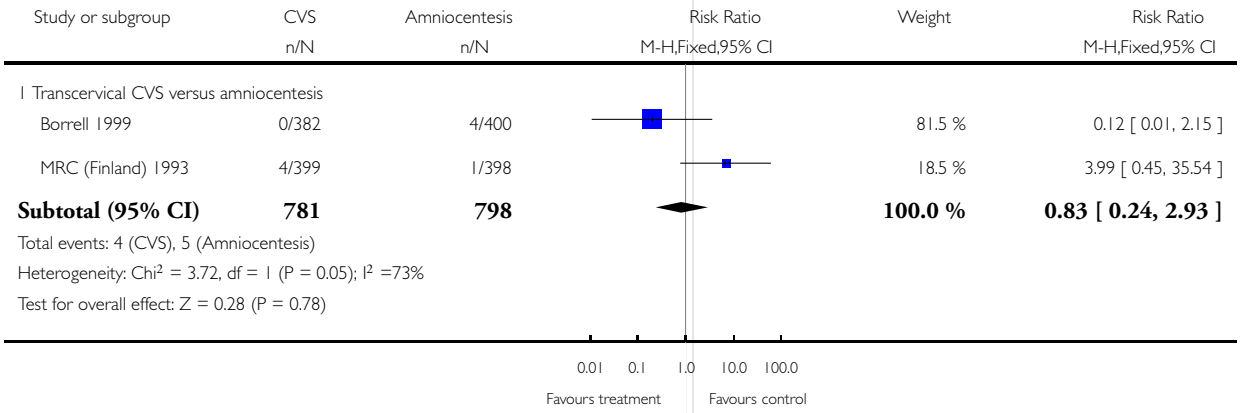
Outcome: 29 All recorded deaths after viability



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

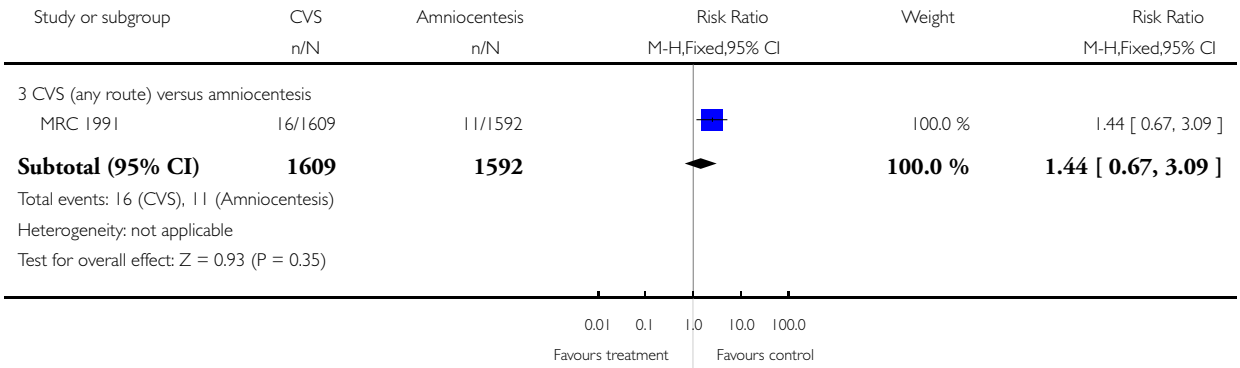
Outcome: 29 All recorded deaths after viability



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 29 All recorded deaths after viability



Analysis 3.30. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 30 Congenital anomalies (all recorded).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

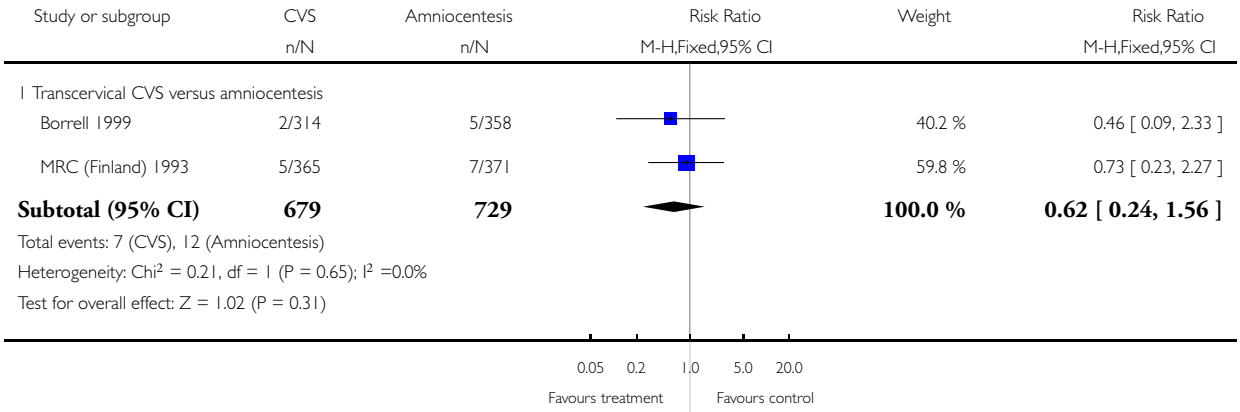
Outcome: 30 Congenital anomalies (all recorded)

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Transcervical CVS versus amniocentesis					
Borrell 1999	2/314	5/358		40.2 %	0.46 [0.09, 2.33]
MRC (Finland) 1993	5/365	7/371		59.8 %	0.73 [0.23, 2.27]
Subtotal (95% CI)	**679**	**729**		**100.0 %**	**0.62 [0.24, 1.56]**
Total events: 7 (CVS), 12 (Amniocentesis)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 1.02 (P = 0.31)					
3 CVS (any route) versus amniocentesis					
Canada 1992	63/95	77/87		65.8 %	0.75 [0.64, 0.88]
MRC 1991	38/1609	41/1547		34.2 %	0.89 [0.58, 1.38]
Subtotal (95% CI)	**1704**	**1634**		**100.0 %**	**0.80 [0.66, 0.96]**
Total events: 101 (CVS), 118 (Amniocentesis)					
Heterogeneity: Chi^2 = 0.82, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 2.35 (P = 0.019)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

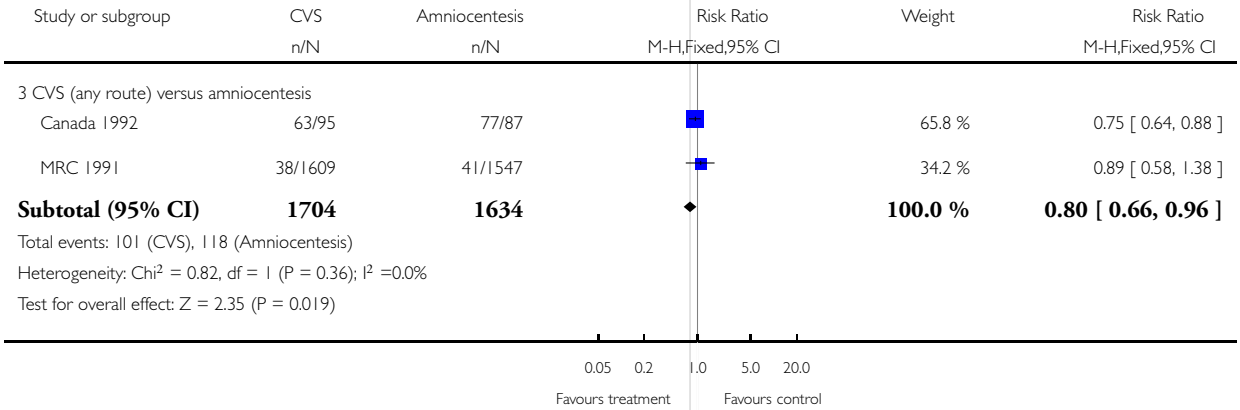
Outcome: 30 Congenital anomalies (all recorded)



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 30 Congenital anomalies (all recorded)



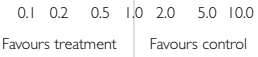
Analysis 3.31. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 31 Talipes.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 31 Talipes

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	0/399	0/398		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**399**	**398**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (CVS), 0 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 31 Talipes

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Transcervical CVS versus amniocentesis					
MRC (Finland) 1993	0/399	0/398		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**399**	**398**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (CVS), 0 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0
Favours treatment
Favours control

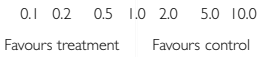
Analysis 3.32. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 32 Hemangiomas (localised vascular lesions of the skin and subcutaneous tissue).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 32 Hemangiomas (localised vascular lesions of the skin and subcutaneous tissue)

Study or subgroup	CVS n/N	AC n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Canada 1992	28/95	19/87		100.0 %	1.35 [0.81, 2.24]
Total (95% CI)	**95**	**87**		**100.0 %**	**1.35 [0.81, 2.24]**
Total events: 28 (CVS), 19 (AC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.24)					



Analysis 3.33. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 33 Limb reduction defects.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

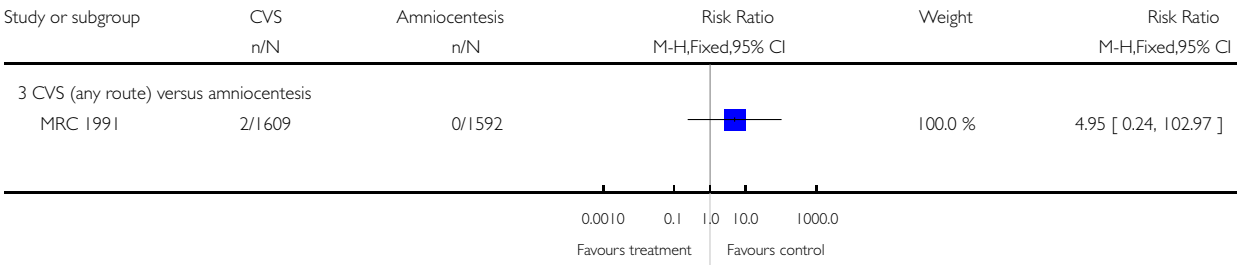
Outcome: 33 Limb reduction defects

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

Outcome: 33 Limb reduction defects

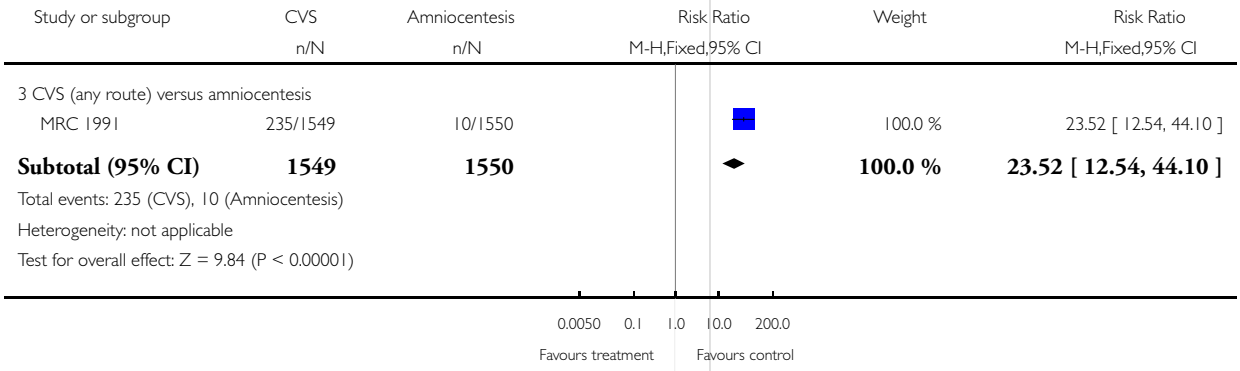


Analysis 3.38. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 38 Result given in less than 7 days (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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



Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.84 (P < 0.00001)					

Analysis 3.39. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 39 Result given in less than 14 days (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

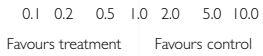
Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 CVS (any route) versus amniocentesis					
MRC (Finland) 1993	348/1549	88/1550		100.0 %	3.96 [3.17, 4.95]
Subtotal (95% CI)	**1549**	**1550**		**100.0 %**	**3.96 [3.17, 4.95]**
Total events: 348 (CVS), 88 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 12.09 (P < 0.00001)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 12.09 (P < 0.00001)					



Analysis 3.40. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 40 Result given in less than 21 days (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

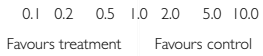
Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 CVS (any route) versus amniocentesis					
MRC (Finland) 1993	282/1549	392/1550		100.0 %	0.72 [0.63, 0.82]
Subtotal (95% CI)	**1549**	**1550**		**100.0 %**	**0.72 [0.63, 0.82]**
Total events: 282 (CVS), 392 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.74 (P < 0.00001)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.74 (P < 0.00001)					



Analysis 3.41. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 41 Result given in more than 21 days (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

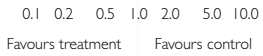
Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 CVS (any route) versus amniocentesis					
MRC 1991	167/1549	505/1550		100.0 %	0.33 [0.28, 0.39]
Subtotal (95% CI)	**1549**	**1550**		**100.0 %**	**0.33 [0.28, 0.39]**
Total events: 167 (CVS), 505 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 13.53 (P < 0.00001)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

Study or subgroup	CVS n/N	Amniocentesis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 CVS (any route) versus amniocentesis					
MRC 1991	167/1549	505/1550		100.0 %	0.33 [0.28, 0.39]
Subtotal (95% CI)	**1549**	**1550**		**100.0 %**	**0.33 [0.28, 0.39]**
Total events: 167 (CVS), 505 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 13.53 (P < 0.00001)					



Analysis 3.42. Comparison 3 Chorionic villus sampling versus second trimester amniocentesis, Outcome 42 Not wanting another baby at 22 weeks' gestation (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

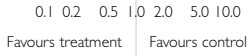
Study or subgroup	CVS n/N	Amniocentesis n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Transcervical CVS versus amniocentesis					
Canada 1992	7/26	13/25		100.0 %	0.34 [0.11, 1.09]
Subtotal (95% CI)	**26**	**25**		**100.0 %**	**0.34 [0.11, 1.09]**
Total events: 7 (CVS), 13 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 3 Chorionic villus sampling versus second trimester amniocentesis

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

Study or subgroup	CVS n/N	Amniocentesis n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Transcervical CVS versus amniocentesis					
Canada 1992	7/26	13/25		100.0 %	0.34 [0.11, 1.09]
Subtotal (95% CI)	**26**	**25**		**100.0 %**	**0.34 [0.11, 1.09]**
Total events: 7 (CVS), 13 (Amniocentesis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					



Analysis 4.1. Comparison 4 Transcervical versus transabdominal CVS, Outcome 1 Not complied with allocated procedure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 1 Not complied with allocated procedure

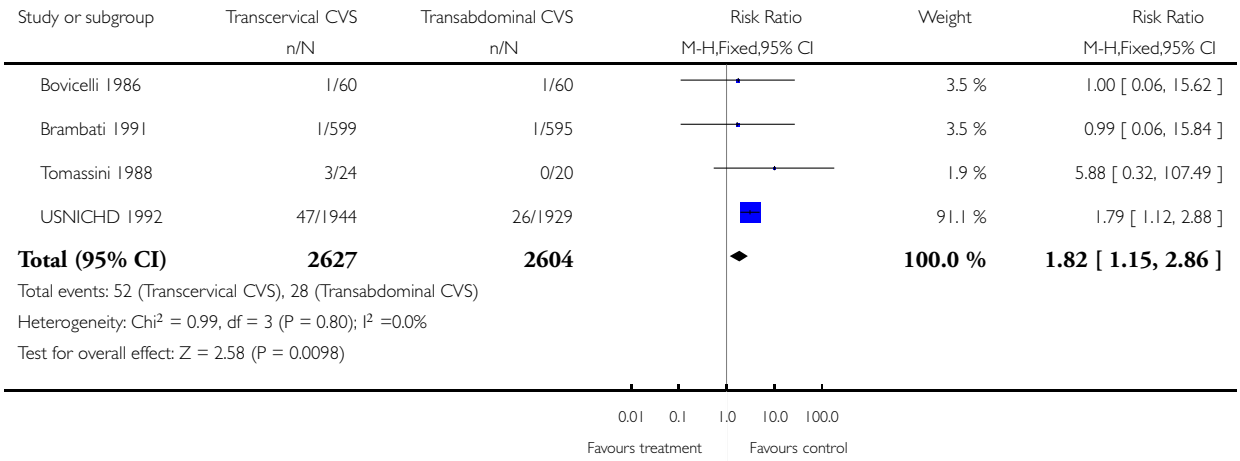
Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bovicelli 1986	0/60	0/60		0.0 %	0.0 [0.0, 0.0]
Brambati 1991	110/599	38/595		49.2 %	2.88 [2.02, 4.08]
USNICHD 1992	130/1944	130/1929		50.8 %	0.99 [0.78, 1.25]
Total (95% CI)	**2603**	**2584**		**100.0 %**	**1.68 [0.59, 4.76]**
Total events: 240 (Transcervical CVS), 168 (Transabdominal CVS)					
Heterogeneity: Tau^2 = 0.54; Chi^2 = 24.47, df = 1 (P<0.00001); I^2 =96%					
Test for overall effect: Z = 0.97 (P = 0.33)					

Analysis 4.2. Comparison 4 Transcervical versus transabdominal CVS, Outcome 2 Sampling failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 2 Sampling failure

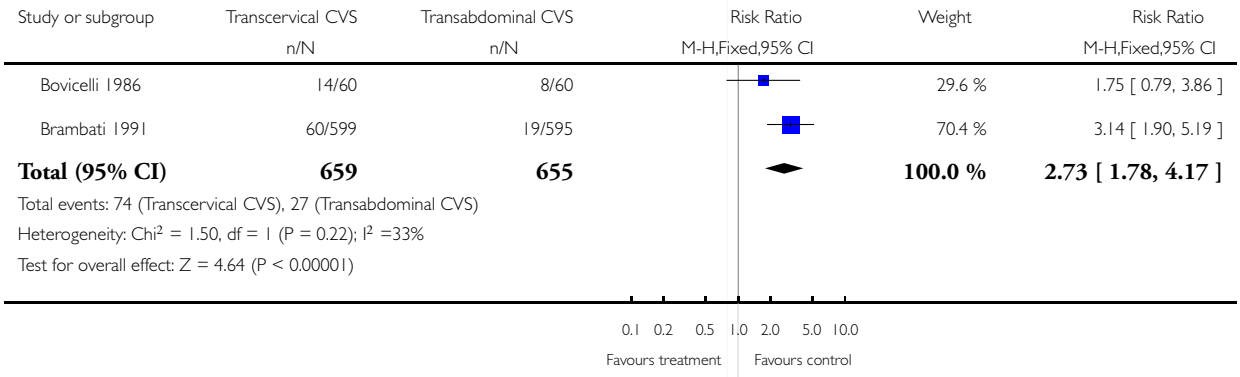


Analysis 4.3. Comparison 4 Transcervical versus transabdominal CVS, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 3 Multiple insertions

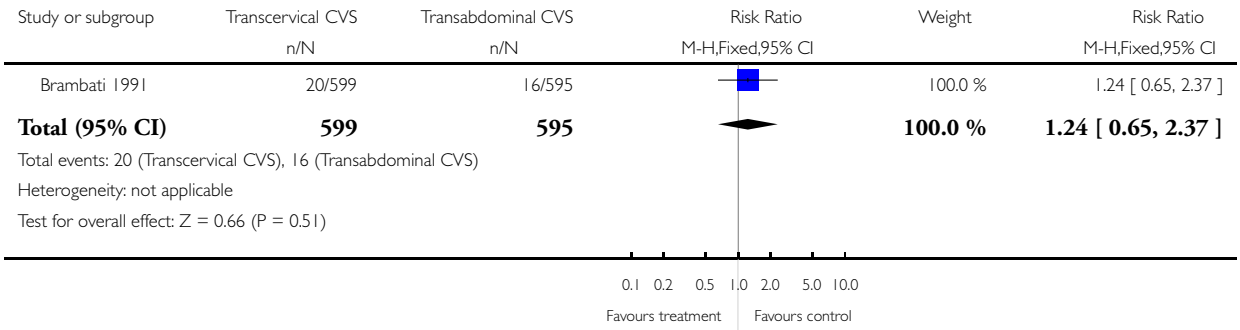


Analysis 4.4. Comparison 4 Transcervical versus transabdominal CVS, Outcome 4 Second test performed.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 4 Second test performed

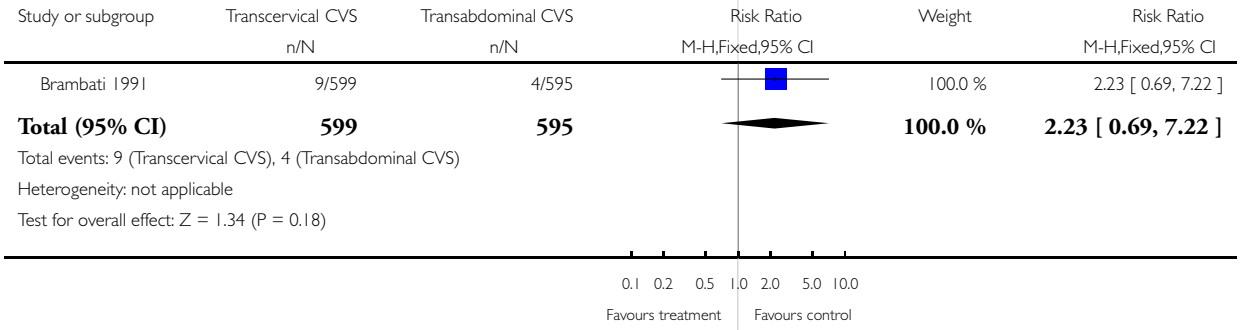


Analysis 4.5. Comparison 4 Transcervical versus transabdominal CVS, Outcome 5 Laboratory failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 5 Laboratory failure



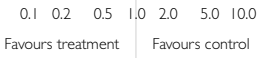
Analysis 4.6. Comparison 4 Transcervical versus transabdominal CVS, Outcome 6 All non-mosaic abnormalities.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 6 All non-mosaic abnormalities

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.23)					



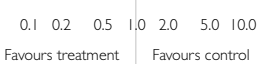
Analysis 4.7. Comparison 4 Transcervical versus transabdominal CVS, Outcome 7 True mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 7 True mosaics

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					

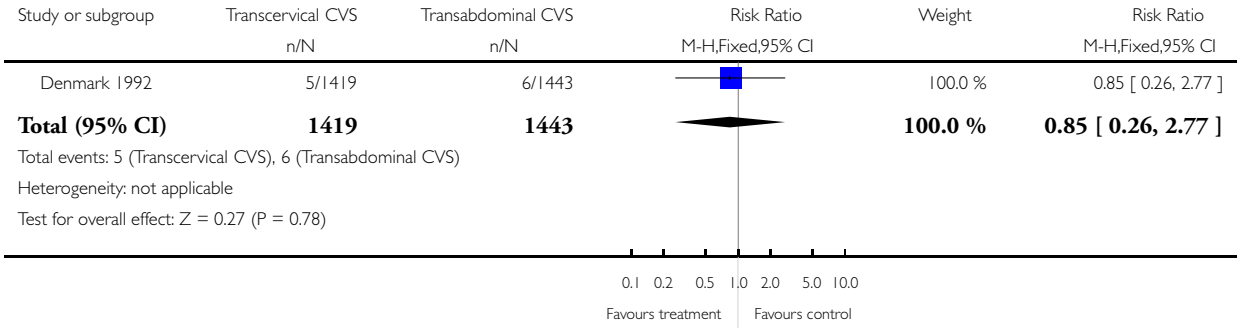


Analysis 4.8. Comparison 4 Transcervical versus transabdominal CVS, Outcome 8 Confined mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 8 Confined mosaics

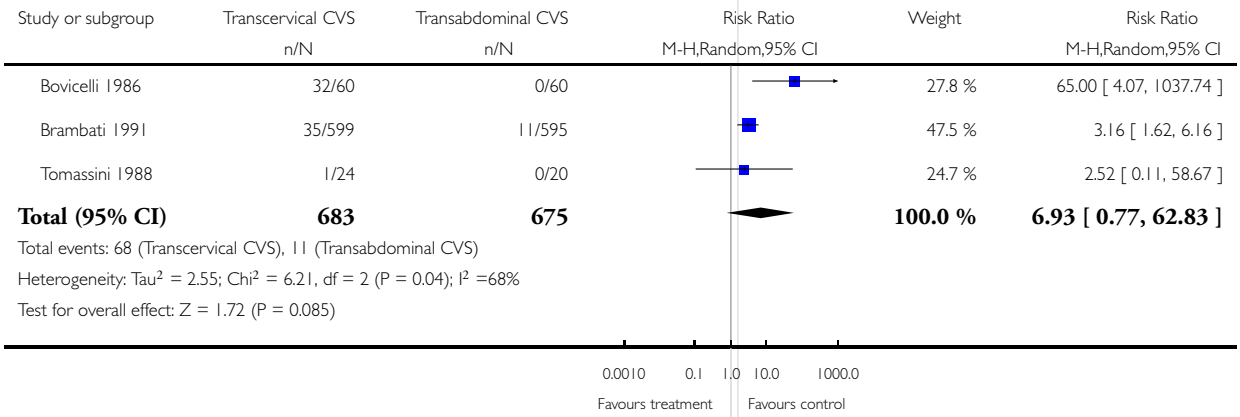


Analysis 4.13. Comparison 4 Transcervical versus transabdominal CVS, Outcome 13 Vaginal bleeding after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 13 Vaginal bleeding after test

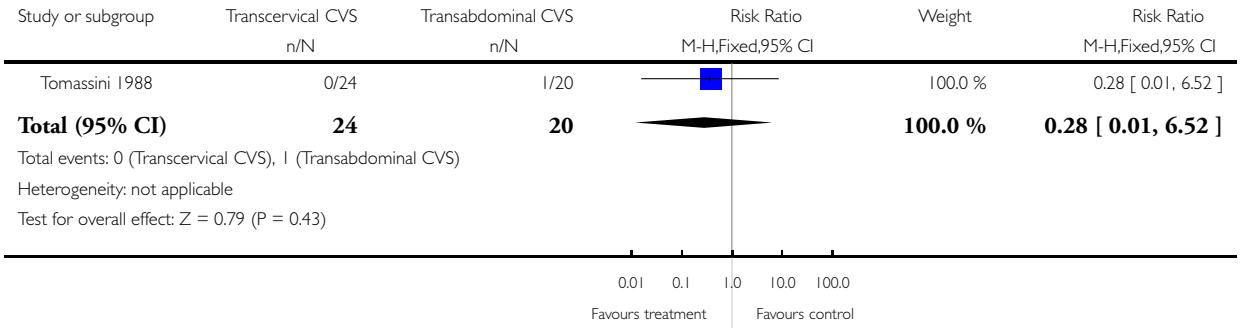


Analysis 4.14. Comparison 4 Transcervical versus transabdominal CVS, Outcome 14 Amniotic leakage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 14 Amniotic leakage after test

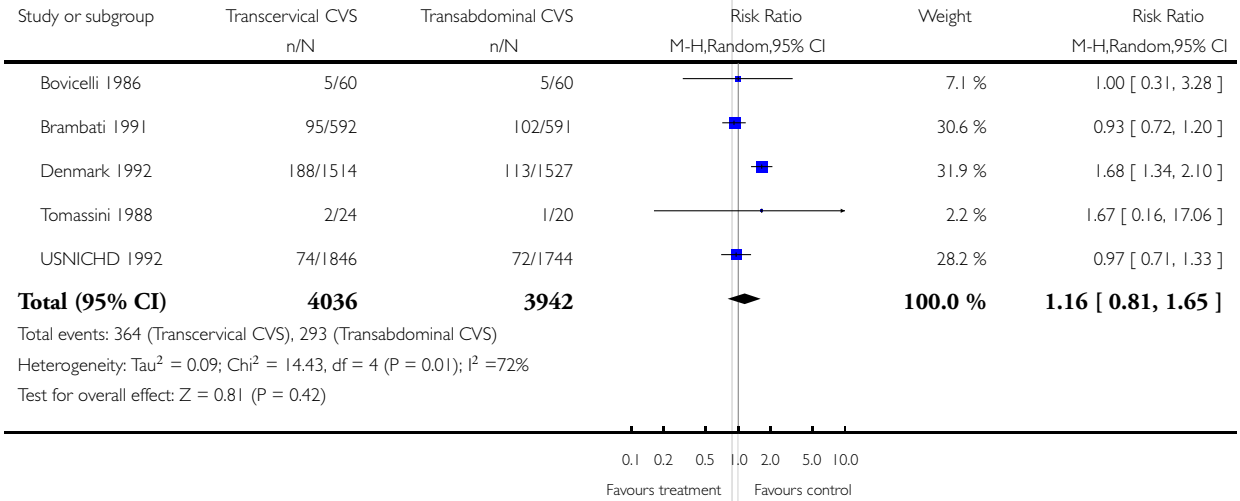


Analysis 4.20. Comparison 4 Transcervical versus transabdominal CVS, Outcome 20 All known pregnancy loss (including termination of pregnancy).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

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



Analysis 4.21. Comparison 4 Transcervical versus transabdominal CVS, Outcome 21 Termination of pregnancy (all).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

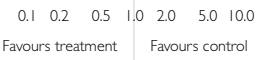
Outcome: 21 Termination of pregnancy (all)

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 0.95 (P = 0.34)



Analysis 4.24. Comparison 4 Transcervical versus transabdominal CVS, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

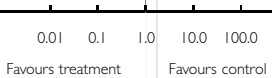
Outcome: 24 Spontaneous miscarriage

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: Tau^2 = 0.32; Chi^2 = 11.30, df = 3 (P = 0.01); I^2 =73%

Test for overall effect: Z = 1.35 (P = 0.18)



Analysis 4.25. Comparison 4 Transcervical versus transabdominal CVS, Outcome 25 Spontaneous miscarriage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 25 Spontaneous miscarriage after test

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: $Chi^2 = 0.70$, df = 2 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.88 (P = 0.38)

Analysis 4.26. Comparison 4 Transcervical versus transabdominal CVS, Outcome 26 Perinatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

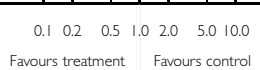
Outcome: 26 Perinatal deaths

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: not applicable

Test for overall effect: Z = 1.21 (P = 0.23)



Analysis 4.27. Comparison 4 Transcervical versus transabdominal CVS, Outcome 27 Stillbirths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 27 Stillbirths

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² =46%

Test for overall effect: Z = 0.69 (P = 0.49)

Analysis 4.28. Comparison 4 Transcervical versus transabdominal CVS, Outcome 28 Neonatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

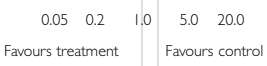
Outcome: 28 Neonatal deaths

Study or subgroup	Transcervical CVS n/N	Transabdominal CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² =0.0%

Test for overall effect: Z = 0.71 (P = 0.48)

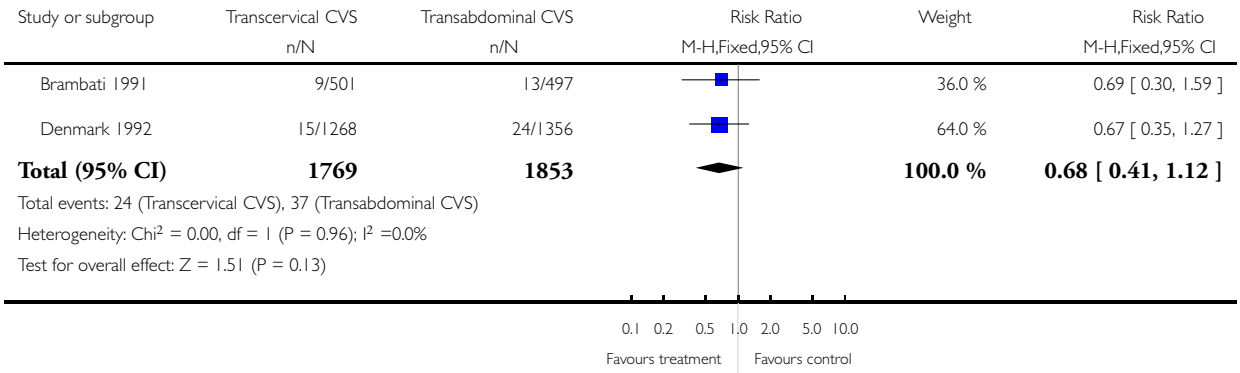


Analysis 4.30. Comparison 4 Transcervical versus transabdominal CVS, Outcome 30 Anomalies (all recorded).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 30 Anomalies (all recorded)

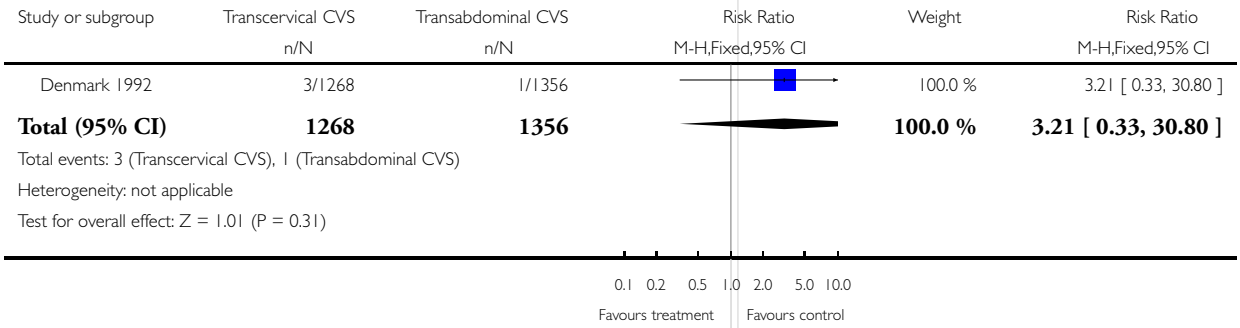


Analysis 4.31. Comparison 4 Transcervical versus transabdominal CVS, Outcome 31 Talipes.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 4 Transcervical versus transabdominal CVS

Outcome: 31 Talipes



Analysis 5.1. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 1 Not complied with allocated procedure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

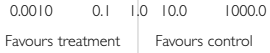
Outcome: 1 Not complied with allocated procedure

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	0/559	4/562		21.4 %	0.11 [0.01, 2.07]
King's 1996	0/278	0/277		0.0 %	0.0 [0.0, 0.0]
Leiden 1998	1/55	10/60		45.6 %	0.11 [0.01, 0.82]
NICHD EATA 2004	3/1861	7/1914		32.9 %	0.44 [0.11, 1.70]
Total (95% CI)	**2753**	**2813**		**100.0 %**	**0.22 [0.08, 0.60]**

Total events: 4 (Early amniocentesis), 21 (CVS)

Heterogeneity: Chi^2 = 1.69, df = 2 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 2.94 (P = 0.0032)



Analysis 5.2. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 2 Sampling failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 2 Sampling failure

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	3/559	11/562		47.1 %	0.27 [0.08, 0.98]
King's 1996	0/278	2/277		10.8 %	0.20 [0.01, 4.13]
Leiden 1998	1/55	2/60		8.2 %	0.55 [0.05, 5.85]
NICHD EATA 2004	9/1861	8/1914		33.9 %	1.16 [0.45, 2.99]
Total (95% CI)	**2753**	**2813**		**100.0 %**	**0.59 [0.30, 1.14]**

Total events: 13 (Early amniocentesis), 23 (CVS)

Heterogeneity: Chi^2 = 3.83, df = 3 (P = 0.28); I^2 =22%

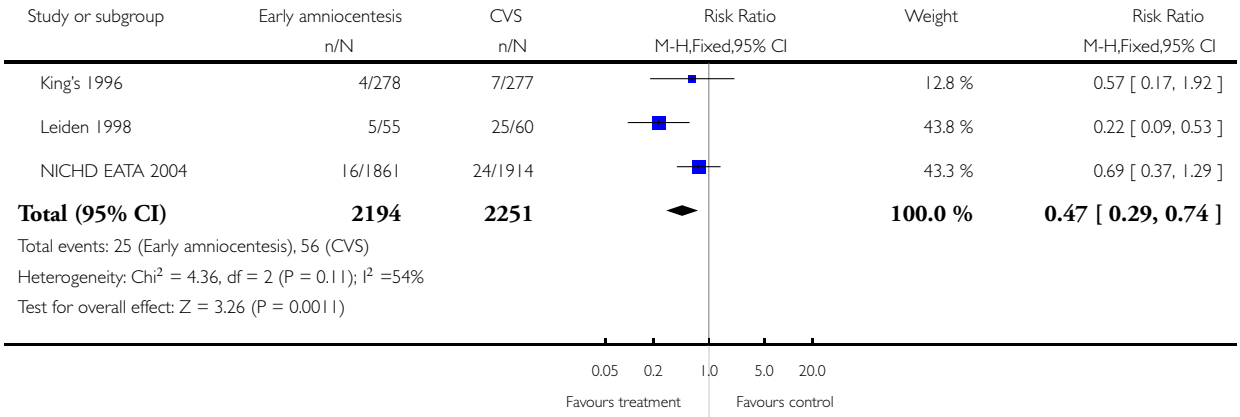
Test for overall effect: Z = 1.57 (P = 0.12)

Analysis 5.3. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 3 Multiple insertions

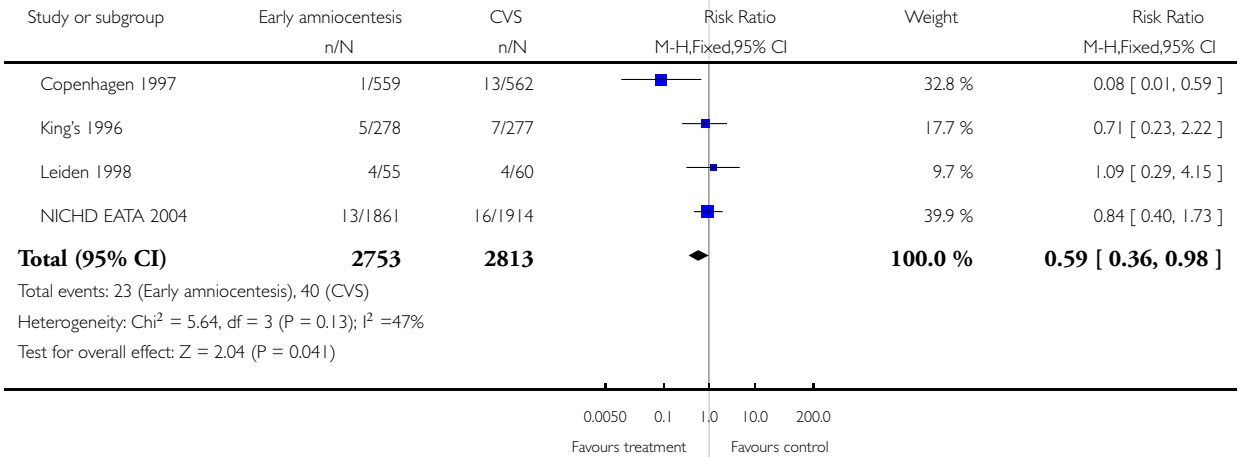


Analysis 5.4. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 4 Second test performed.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 4 Second test performed



Analysis 5.5. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 5 Laboratory failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

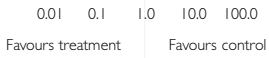
Outcome: 5 Laboratory failure

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	1/559	5/562		30.4 %	0.20 [0.02, 1.72]
King's 1996	5/278	7/277		42.7 %	0.71 [0.23, 2.22]
Leiden 1998	1/55	0/60		2.9 %	3.27 [0.14, 78.58]
NICHD EATA 2004	4/1861	4/1914		24.0 %	1.03 [0.26, 4.11]
Total (95% CI)	**2753**	**2813**		**100.0 %**	**0.71 [0.34, 1.49]**

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

Heterogeneity: Chi^2 = 2.49, df = 3 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 0.91 (P = 0.36)



Analysis 5.6. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 6 All non-mosaic abnormalities.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 6 All non-mosaic abnormalities

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	4/559	11/562		23.3 %	0.37 [0.12, 1.14]
King's 1996	5/278	5/277		10.7 %	1.00 [0.29, 3.40]
Leiden 1998	2/55	0/60		1.0 %	5.45 [0.27, 111.01]
NICHD EATA 2004	37/1861	31/1914		65.0 %	1.23 [0.76, 1.97]
Total (95% CI)	**2753**	**2813**		**100.0 %**	**1.04 [0.70, 1.55]**

Total events: 48 (Early amniocentesis), 47 (CVS)

Heterogeneity: Chi^2 = 4.87, df = 3 (P = 0.18); I^2 =38%

Test for overall effect: Z = 0.22 (P = 0.83)

Analysis 5.7. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 7 True mosaics.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

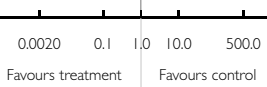
Outcome: 7 True mosaics

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	1/559	1/562		18.3 %	1.01 [0.06, 16.03]
King's 1996	0/278	1/277		27.5 %	0.33 [0.01, 8.12]
NICHD EATA 2004	1/1861	3/1914		54.2 %	0.34 [0.04, 3.29]
Total (95% CI)	**2698**	**2753**		**100.0 %**	**0.46 [0.10, 2.06]**

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

Heterogeneity: Chi^2 = 0.41, df = 2 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 1.02 (P = 0.31)



Analysis 5.8. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 8 Abnormalities confined to non-fetal tissues.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 8 Abnormalities confined to non-fetal tissues

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	0/559	3/562		11.6 %	0.14 [0.01, 2.77]
King's 1996	0/278	2/277		8.3 %	0.20 [0.01, 4.13]
Leiden 1998	2/55	0/60		1.6 %	5.45 [0.27, 111.01]
NICHD EATA 2004	24/1861	24/1914		78.5 %	1.03 [0.59, 1.80]
Total (95% CI)	**2753**	**2813**		**100.0 %**	**0.93 [0.56, 1.55]**

Total events: 26 (Early amniocentesis), 29 (CVS)

Heterogeneity: Chi^2 = 3.97, df = 3 (P = 0.26); I^2 =24%

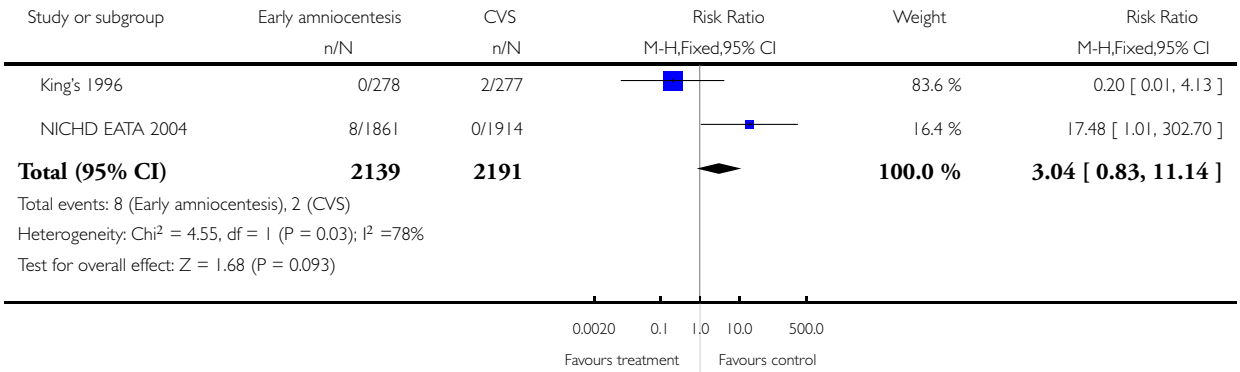
Test for overall effect: Z = 0.29 (P = 0.77)

Analysis 5.9. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 9 Maternal contamination.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 9 Maternal contamination

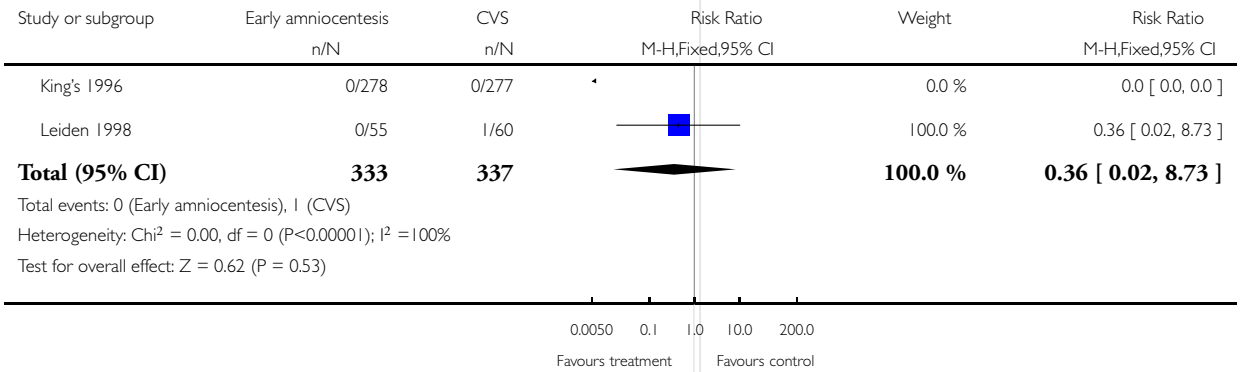


Analysis 5.10. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 10 Known false positive after birth.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 10 Known false positive after birth



Analysis 5.11. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 11 Known false negative after birth.

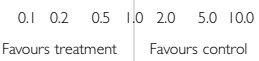
Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 11 Known false negative after birth

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
King's 1996	0/277	0/278		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**277**	**278**		**0.0 %**	**0.0 [0.0, 0.0]**

Total events: 0 (Early amniocentesis), 0 (CVS)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 5.12. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 12 Reporting time.

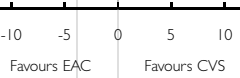
Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 12 Reporting time

Study or subgroup	EAC N	Mean(SD)	CVS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
NICHD EATA 2004	1861	10.3 (2.5)	1914	6.3 (3)		100.0 %	4.00 [3.82, 4.18]
Total (95% CI)	**1861**		**1914**			**100.0 %**	**4.00 [3.82, 4.18]**

Heterogeneity: not applicable
Test for overall effect: Z = 44.55 (P < 0.00001)



Analysis 5.13. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 13 Vaginal bleeding after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 13 Vaginal bleeding after test

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	23/559	40/562		71.7 %	0.58 [0.35, 0.95]
Leiden 1998	3/55	1/60		1.7 %	3.27 [0.35, 30.54]
NICHD EATA 2004	11/1820	15/1878		26.5 %	0.76 [0.35, 1.64]
Total (95% CI)	**2434**	**2500**		**100.0 %**	**0.67 [0.45, 1.01]**

Total events: 37 (Early amniocentesis), 56 (CVS)

Heterogeneity: Chi^2 = 2.37, df = 2 (P = 0.31); I^2 =16%

Test for overall effect: Z = 1.92 (P = 0.055)

Analysis 5.14. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 14 Amniotic leakage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

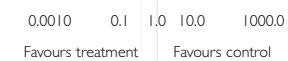
Outcome: 14 Amniotic leakage after test

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Copenhagen 1997	24/559	0/562		27.3 %	49.26 [3.00, 808.08]
Leiden 1998	0/55	1/60		24.1 %	0.36 [0.02, 8.73]
NICHD EATA 2004	195/1820	90/1878		48.6 %	2.24 [1.76, 2.85]
Total (95% CI)	**2434**	**2500**		**100.0 %**	**3.35 [0.37, 30.09]**

Total events: 219 (Early amniocentesis), 91 (CVS)

Heterogeneity: Tau^2 = 2.57; Chi^2 = 6.43, df = 2 (P = 0.04); I^2 =69%

Test for overall effect: Z = 1.08 (P = 0.28)

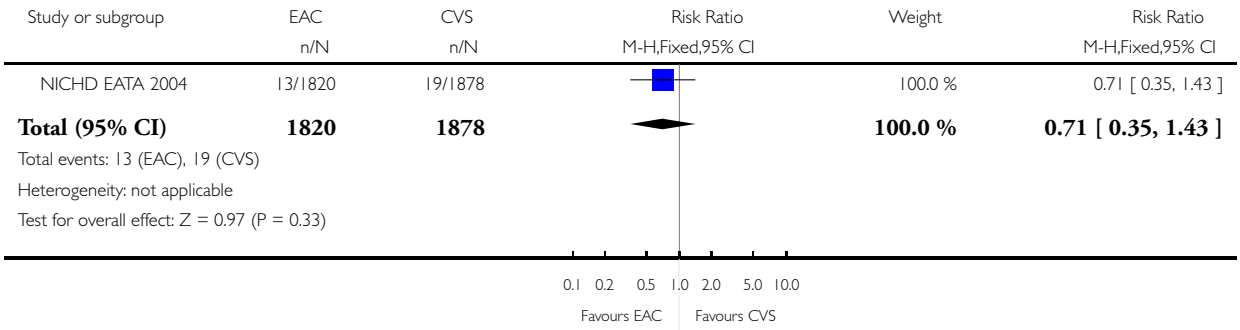


Analysis 5.15. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 15 Vaginal bleeding after 20 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 15 Vaginal bleeding after 20 weeks

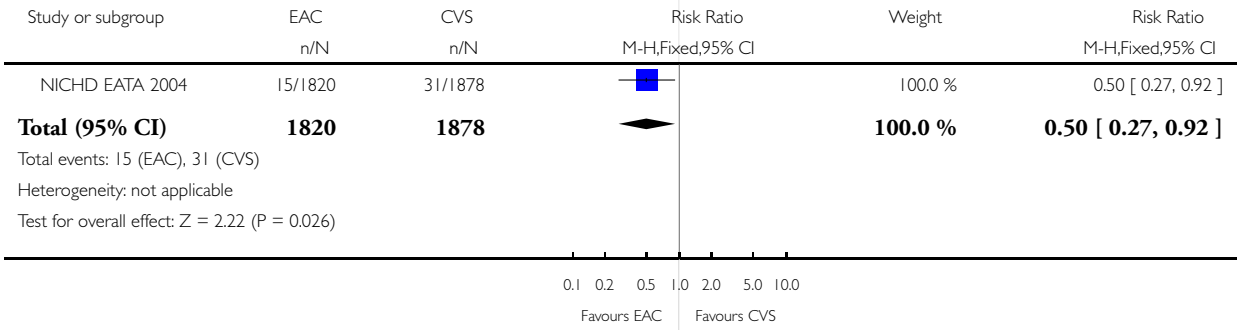


Analysis 5.16. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 16 Prelabour ruptured membranes less than 28 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 16 Prelabour ruptured membranes less than 28 weeks



Analysis 5.18. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 18 Delivery before 37 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 18 Delivery before 37 weeks

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: $Chi^2 = 0.38$, df = 2 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Analysis 5.19. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 19 Delivery before 33 weeks.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 19 Delivery before 33 weeks

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,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)

Heterogeneity: not applicable

Test for overall effect: Z = 0.80 (P = 0.43)

Analysis 5.20. Comparison 5 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: 5 Early amniocentesis versus transabdominal CVS

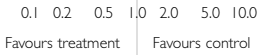
Outcome: 20 All known pregnancy loss (including termination of pregnancy)

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	30/559	27/562		32.4 %	1.12 [0.67, 1.85]
King's 1996	22/278	15/277		18.1 %	1.46 [0.77, 2.76]
Leiden 1998	4/56	3/61		3.5 %	1.45 [0.34, 6.21]
NICHD EATA 2004	39/1820	39/1878		46.1 %	1.03 [0.67, 1.60]
Total (95% CI)	**2713**	**2778**		**100.0 %**	**1.15 [0.86, 1.54]**

Total events: 95 (Early amniocentesis), 84 (CVS)

Heterogeneity: $Chi^2 = 0.89$, df = 3 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 0.96 (P = 0.34)



Analysis 5.21. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 21 Termination of pregnancy (all).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

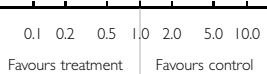
Outcome: 21 Termination of pregnancy (all)

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	9/559	13/562		38.3 %	0.70 [0.30, 1.62]
King's 1996	6/278	10/277		29.6 %	0.60 [0.22, 1.62]
Leiden 1998	0/55	0/60		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	10/1820	11/1878		32.0 %	0.94 [0.40, 2.20]
Total (95% CI)	**2712**	**2777**		**100.0 %**	**0.74 [0.45, 1.24]**

Total events: 25 (Early amniocentesis), 34 (CVS)

Heterogeneity: $Chi^2 = 0.49$, df = 2 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 1.13 (P = 0.26)



Analysis 5.24. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

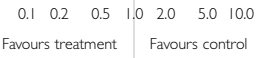
Outcome: 24 Spontaneous miscarriage

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	20/559	13/562		36.4 %	1.55 [0.78, 3.08]
King's 1996	16/278	5/277		14.1 %	3.19 [1.18, 8.58]
Leiden 1998	4/56	3/61		8.1 %	1.45 [0.34, 6.21]
NICHD EATA 2004	22/1820	15/1878		41.5 %	1.51 [0.79, 2.91]
Total (95% CI)	**2713**	**2778**		**100.0 %**	**1.76 [1.17, 2.64]**

Total events: 62 (Early amniocentesis), 36 (CVS)

Heterogeneity: Chi^2 = 1.79, df = 3 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 2.72 (P = 0.0066)



Analysis 5.25. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 25 Spontaneous miscarriage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

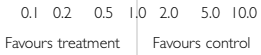
Outcome: 25 Spontaneous miscarriage after test

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	17/559	12/562		35.6 %	1.42 [0.69, 2.95]
King's 1996	16/278	5/277		14.9 %	3.19 [1.18, 8.58]
Leiden 1998	3/55	2/60		5.7 %	1.64 [0.28, 9.43]
NICHD EATA 2004	22/1820	15/1878		43.9 %	1.51 [0.79, 2.91]
Total (95% CI)	**2712**	**2777**		**100.0 %**	**1.74 [1.14, 2.64]**

Total events: 58 (Early amniocentesis), 34 (CVS)

Heterogeneity: Chi^2 = 1.91, df = 3 (P = 0.59); I^2 =0.0%

Test for overall effect: Z = 2.58 (P = 0.0098)



Analysis 5.26. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 26 Perinatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 26 Perinatal deaths

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	1/527	1/531		7.2 %	1.01 [0.06, 16.07]
King's 1996	0/278	0/277		0.0 %	0.0 [0.0, 0.0]
Leiden 1998	0/56	0/61		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	14/1820	13/1878		92.8 %	1.11 [0.52, 2.36]
Total (95% CI)	**2681**	**2747**		**100.0 %**	**1.10 [0.53, 2.28]**

Total events: 15 (Early amniocentesis), 14 (CVS)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 0.27 (P = 0.79)

Analysis 5.27. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 27 Stillbirths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

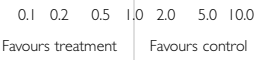
Outcome: 27 Stillbirths

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	0/527	0/531		0.0 %	0.0 [0.0, 0.0]
King's 1996	0/278	0/277		0.0 %	0.0 [0.0, 0.0]
Leiden 1998	0/56	0/61		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	14/1820	13/1878		100.0 %	1.11 [0.52, 2.36]
Total (95% CI)	**2681**	**2747**		**100.0 %**	**1.11 [0.52, 2.36]**

Total events: 14 (Early amniocentesis), 13 (CVS)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.27 (P = 0.78)



Analysis 5.28. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 28 Neonatal deaths.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

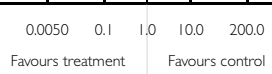
Outcome: 28 Neonatal deaths

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	1/559	1/562		22.4 %	1.01 [0.06, 16.03]
King's 1996	0/257	0/262		0.0 %	0.0 [0.0, 0.0]
Leiden 1998	0/56	0/61		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	0/1820	3/1878		77.6 %	0.15 [0.01, 2.85]
Total (95% CI)	**2692**	**2763**		**100.0 %**	**0.34 [0.05, 2.17]**

Total events: 1 (Early amniocentesis), 4 (CVS)

Heterogeneity: $Chi^2 = 0.89$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 1.14 (P = 0.25)



Analysis 5.29. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 29 All recorded deaths after viability.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 29 All recorded deaths after viability

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	1/559	1/562		14.4 %	1.01 [0.06, 16.03]
King's 1996	0/257	0/262		0.0 %	0.0 [0.0, 0.0]
Leiden 1998	0/55	0/60		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	7/1820	6/1878		85.6 %	1.20 [0.41, 3.58]
Total (95% CI)	**2691**	**2762**		**100.0 %**	**1.18 [0.43, 3.23]**

Total events: 8 (Early amniocentesis), 7 (CVS)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.75)

Analysis 5.30. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 30 Anomalies (all recorded).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

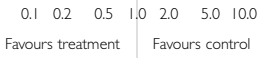
Outcome: 30 Anomalies (all recorded)

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Copenhagen 1997	21/527	8/531		24.3 %	2.64 [1.18, 5.92]
King's 1996	11/257	8/262		22.6 %	1.40 [0.57, 3.43]
Leiden 1998	5/52	16/58		21.9 %	0.35 [0.14, 0.89]
NICHD EATA 2004	41/1776	36/1842		31.3 %	1.18 [0.76, 1.84]
Total (95% CI)	**2612**	**2693**		**100.0 %**	**1.14 [0.57, 2.30]**

Total events: 78 (Early amniocentesis), 68 (CVS)

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 10.58$, df = 3 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 0.38 (P = 0.71)



Analysis 5.32. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 32 Talipes equinovarus.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 32 Talipes equinovarus

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	9/527	0/531		9.3 %	19.14 [1.12, 328.08]
King's 1996	5/257	1/262		18.4 %	5.10 [0.60, 43.33]
Leiden 1998	1/52	1/58		17.6 %	1.12 [0.07, 17.39]
NICHD EATA 2004	9/1776	3/1842		54.8 %	3.11 [0.84, 11.47]
Total (95% CI)	**2612**	**2693**		**100.0 %**	**4.61 [1.82, 11.66]**

Total events: 24 (Early amniocentesis), 5 (CVS)

Heterogeneity: $Chi^2 = 2.35$, df = 3 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 3.23 (P = 0.0012)

Analysis 5.33. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 33 Haemangioma.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

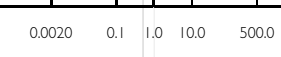
Outcome: 33 Haemangioma

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	3/527	1/531		0.7 %	3.02 [0.32, 28.97]
King's 1996	0/257	1/262		1.1 %	0.34 [0.01, 8.30]
Leiden 1998	0/52	7/58		5.1 %	0.07 [0.00, 1.27]
NICHD EATA 2004	115/1776	132/1842		93.1 %	0.90 [0.71, 1.15]
Total (95% CI)	**2612**	**2693**		**100.0 %**	**0.87 [0.69, 1.10]**

Total events: 118 (Early amniocentesis), 141 (CVS)

Heterogeneity: $Chi^2 = 4.48$, df = 3 (P = 0.21); $I^2 = 33\%$

Test for overall effect: Z = 1.15 (P = 0.25)



Analysis 5.35. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 35 Neonatal respiratory distress syndrome.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

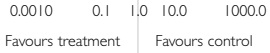
Outcome: 35 Neonatal respiratory distress syndrome

Study or subgroup	Early amniocentesis n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Copenhagen 1997	5/527	4/531		33.3 %	1.26 [0.34, 4.66]
King's 1996	0/74	6/86		50.3 %	0.09 [0.01, 1.56]
Leiden 1998	0/52	0/58		0.0 %	0.0 [0.0, 0.0]
NICHD EATA 2004	4/1667	2/1730		16.4 %	2.08 [0.38, 11.32]
Total (95% CI)	**2320**	**2405**		**100.0 %**	**0.80 [0.34, 1.89]**

Total events: 9 (Early amniocentesis), 12 (CVS)

Heterogeneity: Chi^2 = 3.92, df = 2 (P = 0.14); I^2 =49%

Test for overall effect: Z = 0.50 (P = 0.62)



Analysis 5.36. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 36 Birthweight below 10th centile.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

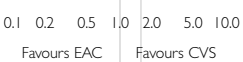
Outcome: 36 Birthweight below 10th centile

Study or subgroup	EAC n/N	CVS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
NICHD EATA 2004	118/1776	146/1842		100.0 %	0.84 [0.66, 1.06]
Total (95% CI)	**1776**	**1842**		**100.0 %**	**0.84 [0.66, 1.06]**

Total events: 118 (EAC), 146 (CVS)

Heterogeneity: not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

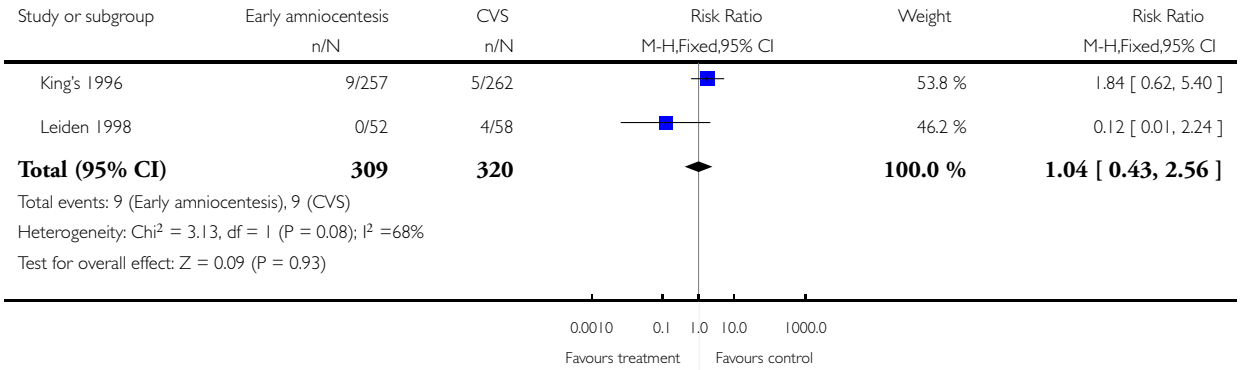


Analysis 5.37. Comparison 5 Early amniocentesis versus transabdominal CVS, Outcome 37 Birthweight below 5th centile.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 5 Early amniocentesis versus transabdominal CVS

Outcome: 37 Birthweight below 5th centile

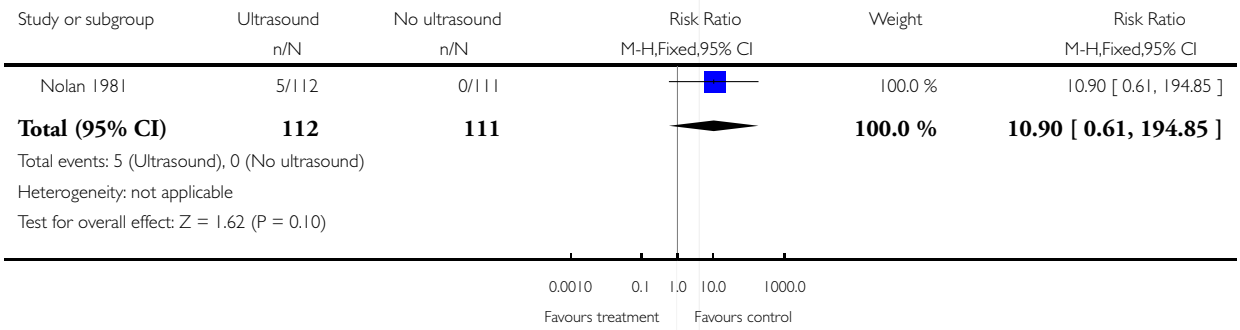


Analysis 6.2. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 2 Sampling failure.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

Outcome: 2 Sampling failure

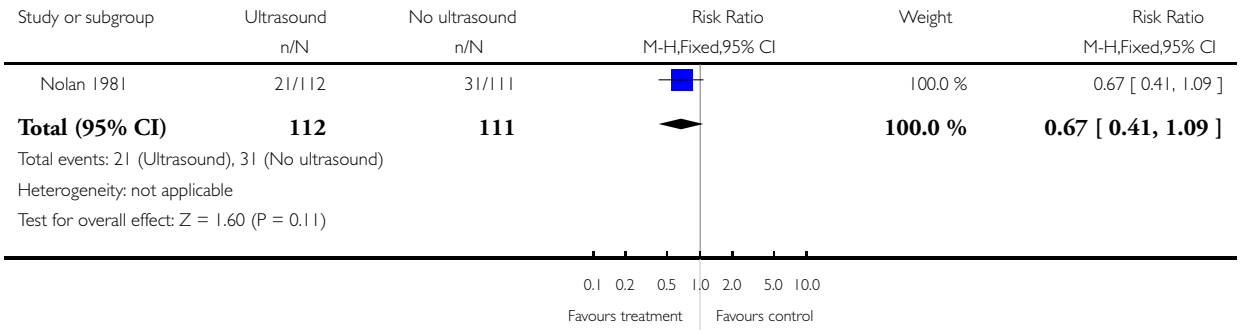


Analysis 6.3. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 3 Multiple insertions.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

Outcome: 3 Multiple insertions

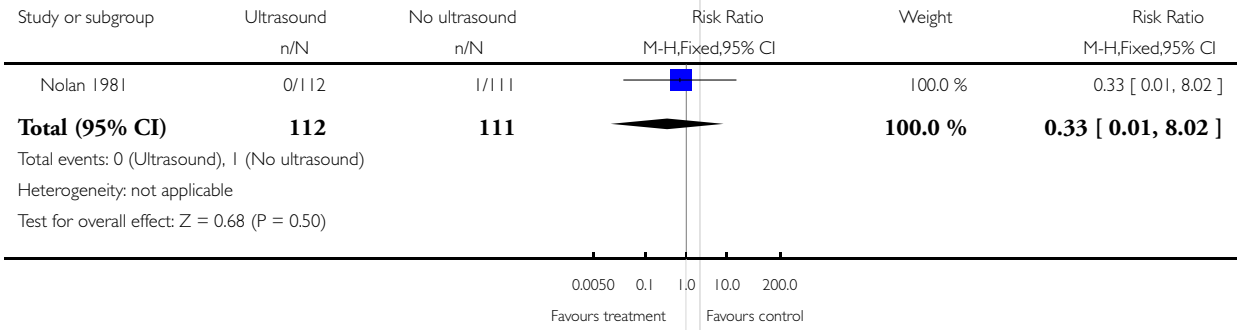


Analysis 6.20. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 20 All known pregnancy loss (including termination of pregnancy).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

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

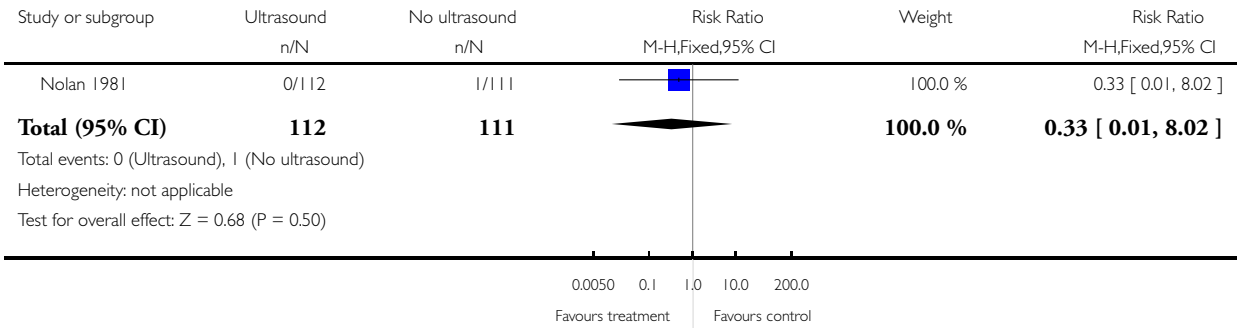


Analysis 6.24. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 24 Spontaneous miscarriage.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

Outcome: 24 Spontaneous miscarriage

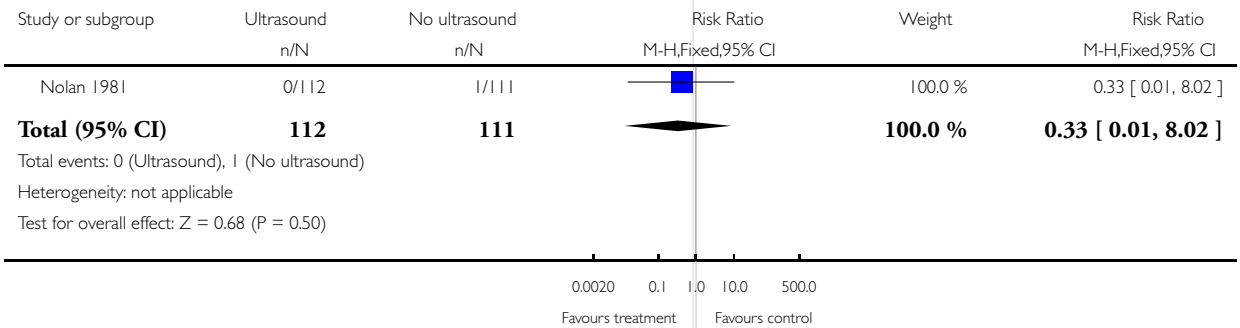


Analysis 6.25. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 25 Spontaneous miscarriage after test.

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

Outcome: 25 Spontaneous miscarriage after test

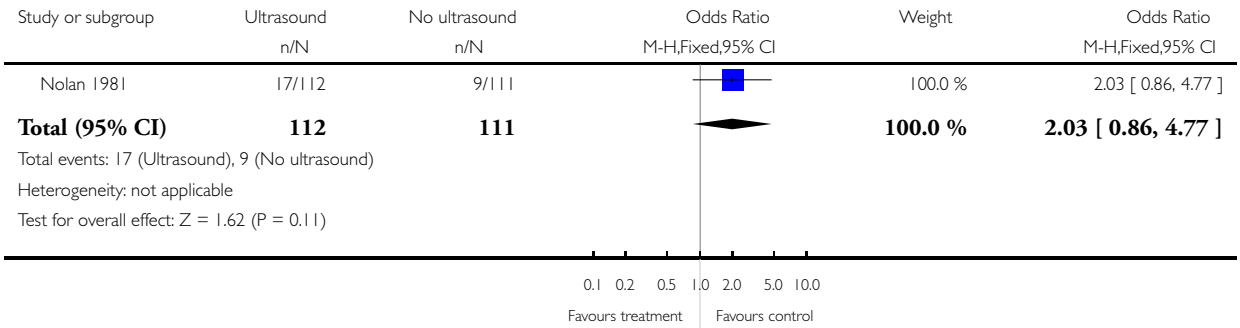


Analysis 6.38. Comparison 6 Ultrasound versus no ultrasound before second trimester amniocentesis, Outcome 38 Bloody tap (not prespecified).

Review: Amniocentesis and chorionic villus sampling for prenatal diagnosis

Comparison: 6 Ultrasound versus no ultrasound before second trimester amniocentesis

Outcome: 38 Bloody tap (not prespecified)



WHAT'S NEW

Last assessed as up-to-date: 28 June 2008.

29 June 2009	New search has been performed	New included study added (NICHD EATA 2004). Other minor amendments made including updating the reference list. There are no significant changes to the conclusions.
29 December 2007	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 3, 2003

CONTRIBUTIONS OF AUTHORS

Z Alfirevic developed the protocol, interpreted the data and wrote the review. K Sundberg and F Mujezinovic extracted the data and co-wrote the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The University of Liverpool, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy