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Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission (Review)

McIntyre PG, Tosh K, McGuire W

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[Intervention Review]

Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission

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ABSTRACT

Background

Observational studies have generally not provided evidence that delivery by caesarean section reduces perinatal hepatitis C virus (HCV) transmission. However, these studies have methodological weaknesses with potential for bias and their findings should be interpreted with caution.

Objectives

To assess the evidence from randomised controlled trials that a policy of delivery by planned caesarean section versus vaginal delivery reduces mother to infant HCV transmission.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2010).

Selection criteria

Controlled trials using random or quasi-random participant allocation that compared a policy of planned elective caesarean section versus vaginal birth for mothers with HCV infection.

Data collection and analysis

We did not identify any randomised controlled trials.

Main results

We did not identify any randomised controlled trials.

Authors' conclusions

Currently, there is no evidence from randomised controlled trials upon which to base any practice recommendations regarding planned caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. In the absence of trial data, evidence to inform women and carers is only available from observational studies that are subject to biases. Systematic review of these studies is needed. There is a need to determine whether women and healthcare providers would support a large pragmatic randomised controlled trial to provide evidence regarding the benefits and harms of planned elective caesarean section versus planned vaginal birth for women with HCV infection.

PLAIN LANGUAGE SUMMARY

Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission

No good evidence to support using caesarean section for reducing mother to baby transmission of hepatitis C during labour and birth.

Hepatitis C is a viral infection that causes liver damage. Mother to infant transmission is the commonest route of hepatitis C virus (HVC) infection in children. Most infected children remain well but are at high risk of developing chronic liver problems during adulthood. HCV is transmitted by the mixing of blood or body fluids, and this can occasionally happen during pregnancy, or during labour and birth. The rate of transmission from mother to baby is about 5%. The review aimed to assess whether there was any evidence that using caesarean section rather than letting women labour might reduce mother to infant HCV transmission for women with HCV infection. No trials were found. Hence, there is no evidence to support the use of caesarean section in these circumstances. It is important to consider whether a randomised controlled trial would be warranted and acceptable.

BACKGROUND

Most infants who acquire hepatitis C virus (HCV) infection do so in utero or in the peripartum period (Mok 2005; Resti 1998). Specifically, breastfeeding is not thought to be an important mode of transmission (Conte 2000; Resti 1998; Ruiz-Extremera 2000). Infants who acquire HCV in utero or at birth do not develop clinically apparent liver problems in early childhood but most do develop chronic HCV infection and are likely to be at risk of longer-term problems related to chronic liver disease, including hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (Rerksuppaphol 2004; Resti 2003; Tovo 2000). There is no available vaccine for preventing HCV infection. Pharmacological treatment regimens are successful in eradicating infection in more than half of the treated individuals but these are not used in pregnancy (Gluud 2002).

The overall prevalence of HCV infection among pregnant women in Europe and North America ranges from about 0.2% to 3% (Ades 2000; Conte 2000; Kim 2002). HCV seroprevalence is higher among pregnant women who live in economically deprived areas because of the high prevalence of specific major risk factors for transmission, especially injecting drug misuse (Goldberg 2001; Hutchinson 2002; Hutchinson 2004; McIntyre 2001). The HCV seroprevalence rate is also very high (more than 10%) in some developing countries where the practice of re-use of unsterilised injecting equipment in healthcare settings is common (Ahmad 2004; Kumar 1997).

The rate of mother to infant transmission of HCV is about 5% (Schwimmer 2000; Thomas 1998). Observational studies indicate that mother to infant transmission occurs predominantly in those women who have HCV ribonucleic acid detectable in their blood and that the risk of transmission is highest in those mothers who have a high hepatitis C viral load at the time of birth (Ceci 2001; Dal Molin 2002; Dore 1997; Resti 1998). Co-infection with the human immunodeficiency virus (HIV) may also be a risk factor for transmission (Tovo 1997). The HCV genotype does not appear to affect the rate of perinatal HCV transmission (Resti 1998).

Observational studies have generally not provided evidence that the mode of delivery (caesarean section versus vaginal delivery) affects the risk of mother to infant HCV transmission (Ceci 2001; Conte 2000; Dal Molin 2002; EPHCVN 2001; EPHCVN 2005; Granovsky 1998; Resti 1998; Resti 2002; Spencer 1997; Tajiri 2001; Thomas 1998; Tovo 1997). Consensus statements and guidelines have concluded that elective caesarean section does not afford the infant protection from HCV infection and that routine screening for HCV in pregnancy is not warranted (NICE 2004; Seeff 2003). However, in these observational studies some of the caesarean sections occurred in labour following rupture of amniotic membranes. Uterine contractions may facilitate perinatal transmission of blood borne viruses by causing placental breaks that allow maternal blood to be passed to the fetus. The duration of membrane rupture has been shown to correlate with the incidence of mother to infant HCV transmission (Spencer 1997). Data from other observational studies have suggested that the estimated rate of perinatal HCV infection might be reduced if infants are delivered by caesarean section prior to rupture of membranes (Gibb 2000; Paccagnini 1995). The findings of the larger study should be interpreted with caution as the HCV status of some infants in the cohort was not ascertained and analyses were not stratified by HIV status of the mother (Gibb 2000).

Given the uncertainty of findings from observational studies, we aim to determine if there is any evidence from randomised controlled trials that offering elective caesarean section to mothers who are infected with HCV affects the risk of mother to infant HCV transmission. We recognise that a policy of offering delivery by elective caesarean section for women infected with HCV may have other consequences for mothers and infants in addition to the possible prevention of HCV transmission (Lilford 1990; Morrison 1995). These are important to consider given that the absolute risk of perinatal HCV transmission is low. These issues are explored in a Cochrane review of caesarean section for non-medical reasons at term (Lavender 2006).

OBJECTIVES

To evaluate the available evidence from randomised controlled trials that a policy of elective caesarean delivery versus vaginal delivery reduces the incidence of perinatal transmission of the hepatitis C virus.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random participant allocation. Unpublished studies and studies published only as abstracts will be included only if assessment of study quality is possible and if other criteria for inclusion are fulfilled. We will contact authors of studies published as abstracts for further information.

Types of participants

Pregnant women with serological evidence of hepatitis C virus (HCV) infection. We plan separate comparisons of studies in which only women who had HCV detectable by ribonucleic acid (RNA) polymerase chain reaction (PCR) in blood participated and in which women co-infected with HIV and HCV participated.

Types of interventions

Planned delivery by elective caesarean section (that is, planned to take place before rupture of membranes, or onset of labour or both) versus planned vaginal delivery. Data should be available for intention-to-treat analyses.

Types of outcome measures

Primary outcomes

HCV transmission-related

1. Hepatitis C infection: positive HCV-RNA PCR in blood on two separate occasions (including one at more than three months after birth), or positive anti-HCV serology at age 18 months or more (Dunn 2001; Gibb 2000).
2. Liver disease: clinical, biochemical, or histological evidence of chronic hepatitis, hepatic fibrosis, cirrhosis, or hepato-cellular carcinoma.
3. Need for treatment for chronic HCV infection or chronic liver disease.

Secondary outcomes

morbidities related to the actual method of delivery

1. Maternal morbidity: admission to an intensive care unit; postpartum haemorrhage or anaemia requiring blood transfusion, or both; deep venous thrombosis or pulmonary embolism, or both; postpartum infection (wound-site, genito-urinary tract, chest); postpartum haematoma (wound-site, perineal); women's negative views of their birth experience assessed using a validated tool; postnatal depression or post-traumatic stress syndrome assessed using a validated tool; other urogynaecological complications (for example, dyspareunia; uterovaginal prolapse; urinary, flatus, or faecal incontinence); subsequent pregnancy complications (ectopic pregnancy, abruption, sub-fertility, miscarriage, hysterectomy, major obstetric haemorrhage).
2. Infant morbidity: neonatal intensive care unit admission; respiratory distress syndrome requiring mechanical ventilation or surfactant replacement therapy, or both; transient tachypnoea of the newborn requiring supplemental oxygen therapy; neonatal encephalopathy (as defined by trial authors).

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 (March 2010).

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 Cochrane Pregnancy and Childbirth Group.

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.

For details of additional searching carried out for the initial version of the review, *see:* Appendix 1.

We did not apply any language restrictions. Trials that were reported only as abstracts would have been eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We did not identify any randomised controlled trials. If we identify trials in the future, we plan to use the following methods.

1. Two authors will screen the title and abstract of all studies identified by the above search strategy and obtain the full articles for all potentially relevant trials. Both authors will independently re-assess the full text of these reports using an eligibility form based on the prespecified inclusion criteria. We will exclude those studies that do not meet all of the inclusion criteria and will state the reasons for exclusion. We will request additional information from the trial author to clarify methodology. Where it is not possible to evaluate the study because of language problems or missing information, we will classify the study as a 'study awaiting assessment' until a translation or further information can be obtained. The authors will resolve any disagreements by discussion until consensus is achieved.
2. Two authors will assess the studies independently for selection bias (allocation concealment), performance bias (although it is unlikely that women or clinicians will be blind to the nature of the intervention), and attrition bias (completeness of assessment in all randomised individuals) (Alderson 2004).
3. Two authors will use a data collection form to aid extraction of relevant information and data from each included study. Each author will extract the data separately, compare data, and resolve differences by discussion until consensus is achieved. If data from the trial reports are insufficient, we will contact the trial authors for information. We will include individual outcome data in the analysis if they meet the prestated criteria in Types of outcome measures.
4. We will process included trial data as described in the *Cochrane Reviewers' Handbook* (Alderson 2004). We will present outcomes for categorical data as risk ratio, risk difference, and number needed to treat, with respective 95% confidence intervals. For continuous data, we will use the mean difference with 95% confidence intervals.
5. We will estimate the treatment effects of individual trials and examine heterogeneity between trial results by inspecting the forest plots and quantifying the impact of heterogeneity in any meta-analysis using a measure of the degree of inconsistency in the studies' results (I^2 statistic). If we detect statistical heterogeneity, we will explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using post hoc subgroup analyses. We plan to use a fixed-effect model for meta-analyses. We will examine publication bias using a funnel plot, and a regression approach to assess funnel plot asymmetry (Egger 1997).

RESULTS

Description of studies

We did not identify any randomised controlled trials.

Risk of bias in included studies

We did not identify any randomised controlled trials.

Effects of interventions

We did not identify any randomised controlled trials.

DISCUSSION

In the absence of data from randomised controlled trials, decisions regarding the mode of delivery of infants of mothers with hepatitis

C virus (HCV) infection will continue to be informed by the findings of observational studies. In general, data from cohort studies have not provided evidence that planned caesarean section prevents or reduces the incidence of mother to infant transmission of HCV. However, since these non-randomised studies have methodological weaknesses with potential for bias, their findings should be interpreted with caution. Several issues are important to consider.

1. Because the mode of delivery was not allocated randomly, there may be other factors associated with the decision to deliver by caesarean section versus the vaginal route that also affected the rate of mother to infant HCV transmission.
2. Most observational studies have not distinguished between elective (prelabour) and emergency (after the onset of labour) caesarean section. Since micro-transfusions during labour may be responsible for intrapartum HCV transmission (Mast 2005; Spencer 1997), it is more appropriate to compare outcomes for infants born following a planned vaginal delivery (whether this was successful or resulted in an emergency caesarean section) with infants born following a planned caesarean section (whether the elective caesarean section took place or whether vaginal delivery occurred prior to caesarean section). One observational study found that the estimated rate of HCV infection was statistically significantly lower in infants delivered by prelabour caesarean section compared with infants delivered by the vaginal route or by caesarean section after the onset of labour (Gibb 2000). However, this study was not able to account for the possible effect of HIV co-infection in a minority of the women in the cohort. Analysis of data from the large European Paediatric HCV Network study did not confirm this finding (EPHCVN 2005).
3. In general, observational studies have been under-powered to detect a small but potentially important effect of mode of delivery on the rate of HCV transmission. The largest reported study (EPHCVN 2005) was not powered sufficiently to detect a 50% reduction in rate of HCV transmission (with 80% power and 95% significance). Some studies were not able to determine the HCV-ribonucleic acid (RNA) status of women at the time of delivery. Since mother to infant transmission is very rare in the absence of HCV viraemia, inclusion of these women in the study cohorts will further reduce the power of the study to detect a difference between infants delivered by caesarean section versus the vaginal route. Systematic review and meta-analysis of data from the available cohort studies may provide a more precise estimate of the effect size.

The least biased assessment of the effect of planned caesarean section on mother to infant transmission of HCV would be provided by a randomised controlled trial. However, a trial would need to be large enough to detect a modest absolute risk reduction since the baseline risk of transmission is already low (about 5%). As a corollary, even if the intervention prevented all HCV transmission (an absolute risk reduction of about 5%), twenty caesarean sections would be required to prevent a single extra case of HCV transmission. Given the maternal and infant morbidity associated with caesarean section, the acceptability to women, their families, and their carers of undertaking a trial of this intervention should be explored. The implications for health services also need to be considered and evaluated. Modelling of cost-effectiveness in the United States using observational data to inform assumptions about prevalence and uptake of intervention suggest that a policy of offering elective cesarean delivery would only be cost-effective if it prevented at minimum 90% of HCV perinatal transmission (Plunkett 2004). For women who are co-infected with HIV and HCV (suppressed HIV RNA but detectable HCV RNA), the higher baseline risk of HCV transmission means that caesarean section may be a much more cost effective intervention (Schackman 2004).

AUTHORS' CONCLUSIONS

Implications for practice

At present there are not any data available from randomised trials to inform decisions. Although data from observational studies have generally not provided evidence that delivery by caesarean section prevent mother to infant HCV infection (unless there is HIV co-infection), these findings should be interpreted with caution.

Implications for research

There is a need to determine whether women and healthcare providers would support a large pragmatic randomised controlled trial to provide evidence regarding the benefits and harms of planned elective caesarean section versus planned vaginal birth for women with HCV infection. Such a trial should probably only include women who are HCV-RNA positive. The trial should adhere to intention-to-treat principles.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and a referee who is external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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APPENDICES

Appendix 1. Additional search strategy

For the initial version of the review, authors searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 4) using the following search strategy:

#1 hepatitis (all fields)
#2 Hepatitis (explode MeSH)
#3 cesarean or caesarean or cesarian or caesarian or cesarien or caesarien (all fields)
#4 Delivery,Obstetric (explode MeSH)
#5 (#1 OR #2) AND (#3 OR #4)

WHAT'S NEW

Date	Event	Description
23 April 2010	New search has been performed	Search updated. No new trials identified.

HISTORY

Protocol first published: Issue 4, 2005
Review first published: Issue 4, 2006

Date	Event	Description
13 February 2009	Amended	Author's contact details edited.
12 February 2008	Amended	Converted to new review format.
28 October 2007	New search has been performed	Search updated. No trials identified.
28 July 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Paul McIntyre, Karen Tosh, and William McGuire developed and completed the review jointly. William McGuire is the guarantor of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Ninewells Hospital and Medical School, Dundee, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Complications, Infectious; Cesarean Section; Delivery, Obstetric [*methods]; Hepatitis C [*prevention & control] [transmission]; Infectious Disease Transmission, Vertical [prevention & control]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy