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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	5
METHODS	5
RESULTS	7
DISCUSSION	7
AUTHORS' CONCLUSIONS	7
ACKNOWLEDGEMENTS	8
REFERENCES	9
WHAT'S NEW	11
CONTRIBUTIONS OF AUTHORS	11
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12
INDEX TERMS	12

[Intervention Review]

Maternal and foetal outcomes following natural vaginal versus caesarean section (c-section) delivery in women with bleeding disorders and carriers

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ABSTRACT

Background

Bleeding disorders are uncommon but may pose significant bleeding complications during pregnancy, labour and following delivery for both the woman and the foetus. While many bleeding disorders in women tend to improve in pregnancy, thus decreasing the haemorrhagic risk to the mother at the time of delivery, some do not correct or return quite quickly to their pre-pregnancy levels in the postpartum period. Therefore, specific measures to prevent maternal bleeding and foetal complications during childbirth, are required. The safest method of delivery to reduce morbidity and mortality in these women is controversial. This is an update of a previously published review.

Objectives

To assess the optimal mode of delivery in women with, or carriers of, bleeding disorders.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Coagulopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the Cochrane Pregnancy and Childbirth Group's Trials Register as well as trials registries and the reference lists of relevant articles and reviews.

Date of last search of the Group's Trials Registers: 16 February 2017.

Selection criteria

Randomised controlled trials and all types of controlled clinical trials investigating the optimal mode of delivery in women with, or carriers of, any type of bleeding disorder during pregnancy were eligible for the review.

Data collection and analysis

No trials matching the selection criteria were eligible for inclusion

Main results

No results from randomised controlled trials were found.

Authors' conclusions

The review did not identify any randomised controlled trials investigating the safest mode of delivery and associated maternal and foetal complications during delivery in women with, or carriers of, a bleeding disorder. In the absence of high quality evidence, clinicians need to use their clinical judgement and lower level evidence (e.g. from observational trials, case studies) to decide upon the optimal mode of delivery to ensure the safety of both mother and foetus.

Given the ethical considerations, the rarity of the disorders and the low incidence of both maternal and foetal complications, future randomised controlled trials to find the optimal mode of delivery in this population are unlikely to be carried out. Other high quality controlled studies (such as risk allocation designs, sequential design, and parallel cohort design) are needed to investigate the risks and benefits of natural vaginal and caesarean section in this population or extrapolation from other clinical conditions that incur a haemorrhagic risk to the baby, such as platelet alloimmunisation.

PLAIN LANGUAGE SUMMARY

Mother and baby outcomes following normal delivery and caesarean (c-section) delivery in women with bleeding disorders and carriers

Review question

We looked at the evidence on mother and baby outcomes following natural vaginal delivery and caesarean (c-section) section in women with bleeding disorders and carriers. This is an update of a previously published review.

Background

We wanted to review the safest way to deliver babies in women with bleeding disorders and carriers and assess problems that may occur during delivery for the mother and baby with either method of delivery.

Search date

The evidence is current to: 16 February 2017.

Key results

We did not find any randomised controlled trials to analyse the safest way (either natural vaginal delivery or c-section) to deliver babies and problems encountered during delivery to mothers and babies in this population. Given the rarity of the disorders and the challenge of performing trials in pregnancy, it is unlikely that randomised controlled trials will be carried out in the future. Therefore, clinicians will need to make decisions regarding treatment using lower level evidence.

BACKGROUND

Description of the condition

Bleeding disorders can pose significant challenges during pregnancy and childbirth. Pregnancy is a hypercoagulable state and may mask or balance the bleeding risk (if mild). Many bleeding disorders tend to improve in pregnancy, thus decreasing the haemorrhagic risk to the mother at the time of delivery. However, some do not correct or return relatively quickly to the pre-pregnancy levels in the postpartum period, thus requiring specific measures to prevent maternal and foetal bleeding complications during childbirth. Von Willebrand disease (VWD), haemophilia A and B, factor XI (FXI) and factor VII (FVII) deficiency account for almost 90% of the inherited bleeding disorders, whereas deficiency in fibrinogen, prothrombin factor (FII), factor V (FV), factor X (FX), factor XIII are relatively rare (Chi 2007). Idiopathic thrombocytopenic purpura (ITP) is a commonly acquired bleeding disorder during pregnancy and accounts for 3% to 4% of the cases of thrombocytopenia detected at this time (Gill 2000); whereas HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome is a rarer acquired bleeding disorder during pregnancy, occurring in approximately one to two per 1000 pregnancies (Geary 1997).

- Von Willebrand disease is caused by a quantitative or qualitative defect in Von Willebrand factor (VWF). An increase in VWF (with levels in blood plasma up to normal plasma levels) is often seen during pregnancy in women with VWD (except type 3), but intrapatient variability is very wide (Conti 1986). A drastic fall in VWF following delivery in women with VWD causes these women to be prone to primary and secondary postpartum haemorrhage (PPH) (James 2009).
- Congenital haemophilias are X-linked recessive bleeding disorders that result from deficiencies of the coagulation factors VIII (FVIII) and IX (FIX). Most female carriers of haemophilia have levels of FVIII (or FIX) within the normal range and are therefore protected against significant bleeding problems in day-to-day life (Giangrande 2009). Pregnant carriers of haemophilia A usually have low levels of FVIII at the beginning of pregnancy, but have almost normal levels of FVIII by the third trimester. In normal pregnancy, FIX levels do not rise significantly (Stirling 1984). Women with levels of FVIII (or FIX) under 50% (less than 0.50 international units (IU)/millilitre (mL)) are at increased risk of bleeding when facing haemostatic challenges (Lusher 1978). Female carriers of haemophilia A are at an increased risk of haemorrhagic complications, both early and late PPH, because of the rapid fall in the increased pregnancy-induced maternal clotting factor levels (FVIII) after delivery. The incidence of early and late PPH is increased among haemophilia A carriers (22% and 11%, respectively) (Kadir 1997) compared with the general population (5% and 0.7%, respectively) (Lee 1981). Risk of head bleeding in babies (cephalohaematoma, intracranial haemorrhage) is 3%, 64% and 15% following normal delivery, vacuum extraction and caesarean section (c-section) respectively (Ljung 1994).
- Factor XI deficiency (haemophilia C) and FVII deficiency are very rare inherited bleeding disorders in the general population, but FXI deficiency more commonly occurs in individuals of the Ashkenazi Jewish population compared to other populations (Bolton-Maggs 1988). Homozygous and compound heterozygous individuals with FXI and FVII deficiency develop

haemorrhagic manifestations; heterozygous individuals are usually asymptomatic but may present with profuse bleeding. Clinical prototypes vary from mild to severe and do not correlate with FXI and FVII levels. The levels of FXI and FVII do not change during pregnancy and there is a poor correlation between the level of FXI and bleeding tendency (Bolton-Maggs 1988). For both FXI and FVII deficiencies, the bleeding tendency is likely to be associated with levels of factor less than 15%, and varies in the same individual following different haemostatic challenges. As a consequence of the unpredictable nature of these diseases, their management during pregnancy and childbirth is quite difficult.

- Inherited fibrinogen abnormalities, factor II, FV, FX and FXIII deficiencies are the rarest bleeding disorders; bleeding tendencies are low in heterozygous groups but life-threatening in the homozygous group, and mostly occurring as PPH (Bolton-Maggs 1988; Fadel 1989).
- Congenital platelet dysfunction disorders, being autosomal recessive disorders, are rare. Better characterized defects are those in the platelet GPIb complex (Bernard-Soulier Syndrome) or the GPIIb-IIIa complex (Glanzmann thrombasthenia) or in the platelet secretion or thromboxane synthesis. Bleeding tendencies are severe in Bernard-Soulier Syndrome and Glanzmann thrombasthenia, usually requiring platelet transfusion. Bleeding is milder in platelet dysfunction disorders, which are due to abnormal platelet secretion or thromboxane synthesis, but can be life-threatening following surgery or trauma (George 1990; Peng 1991).
- A common cause of acquired bleeding disorder in pregnancy is ITP which occurs in 1000 to 2000 deliveries (Burrows 1990). The risk of spontaneous bleeding at birth in women with ITP is low and occurs particularly if the platelet count decreases to less than 20,000/ μ L (Webert 2003). The frequency of neonatal allo immunisation thrombocytopenia (NAIT) is estimated at one to two cases per 1000 deliveries (Blanchette 1990). This disorder develops in foetal life, with 25% to 50% of foetal intracranial haemorrhages detectable on prenatal ultrasound prior to the onset of labour (Herman 1986).
- The HELLP syndrome occurs in 10% to 20% of cases with severe pre-eclampsia (Geary 1997). Maternal mortality in pregnancy associated with HELLP syndrome is 1.1% (Sibai 1993) and the perinatal mortality is 34% before 32 weeks gestation, and 8% after this (Gul 2005). A total of 30% of HELLP syndromes develop after birth, the majority within the first 48 hours with the time of onset ranging from a few hours to seven days following delivery (Barton 2004).
- More common but still very serious maternal complications are placenta abruptio, disseminated intravascular coagulation (DIC) and subsequent severe PPH; whereas, prematurity, intrauterine growth restriction (IUGR) and abruptio placenta are the leading causes of neonatal death (Magann 1999). Hepatic rupture has a perinatal mortality that can reach 80% (Mihu 2007), the majority of which are observed during the antenatal period.

Pregnant women with bleeding disorders require a multidisciplinary approach, especially for those pregnant women with severe and rare bleeding disorders. The delivery is planned at a unit where the necessary expertise in the management of bleeding disorders is present and resources for laboratory testing and clotting factor treatments are readily available (Bolton-Maggs 2004).

During antenatal checkups in women with inherited bleeding disorders, affected fetuses can be diagnosed by non-invasive or invasive prenatal diagnostic methods such as analysis of foetal DNA in maternal blood using digital polymerase chain reaction or a relative mutation dosage approach (Tsui 2011) during early pregnancy. Relevant coagulation factor levels should be checked at pregnancy diagnosis, at 28 and at 34 weeks of gestation, and also prior to any invasive procedure, which allows treatment to be managed in acute situations when urgent assays may be difficult to obtain (Street 2008).

Prevention of bleeding is by undertaking prophylactic treatment, such as recombinant or plasma-derived clotting factor concentrates, tranexamic acid or desmopressin, when factor levels are less than 50 IU/decilitre (dL) for FVIII, FIX, Von Willebrand factor antigen (VWF:Ag) and Von Willebrand factor activity (VWF:Ac) or less than 70 IU/dL for FXI to cover invasive procedures, labour, delivery; treatment is usually continued for at least three days following vaginal delivery and at least five days following c-section (Ljung 1994).

In pregnant women with ITP, most experts opine that a platelet count in the range of 50,000/ μ L for vaginal delivery and 80,000/ μ L for epidural anaesthesia and c-section during and after delivery is adequate (Cines 2005; Stavrou 2009).

The optimal mode of delivery in women with bleeding disorders is chosen on an individual case basis. The risks and benefits involved in relation to both mother and foetus in each mode of delivery are discussed by a multidisciplinary team consisting of obstetricians, haematologists, paediatricians and anaesthesiologists (Chic 2008). In women with bleeding disorders, controlled delivery of the foetus by planned c-section has been suggested to reduce the risk of intracranial haemorrhage (ICH) by an estimated 85% compared with vaginal delivery, whereas maternal mortality and morbidity are not significantly different from those observed in vaginal delivery (James 2010).

Bleeding complications during delivery are estimated at 1% to 4% (intracranial haemorrhage, cephalo-haematoma) in infants with inherited bleeding disorders or ITP, and more commonly observed with traumatic delivery.

Description of the intervention

Pregnancy and childbirth management in women with bleeding disorders is a multidisciplinary approach consisting of obstetricians, haematologists, anaesthesiologists and neonatologists. Delivery is conducted in centres where laboratory testing and clotting factor concentrates are readily available. Optimal management of delivery has to take into account the health needs and goals for both the mother and the newborn. Indeed, the debate about the delivery modality optimizing the risk-to-benefit ratio for the mother and the newborn is fully open. While it is impossible to separate the two when making treatment choices, it might be appropriate to attempt to separate them when describing the intervention.

Certainly, one goal is to achieve delivery by the least traumatic method, and early recourse to c-section can be considered to minimise the risk of bleeding complications for both mother and newborn. Caesarean section is safer for the foetus and riskier for the mother, although the latter has not been proven in the context

of bleeding disorders (James 2010). Prolonged labour should be avoided whenever possible. Maternal genital and perineal trauma should be minimised in order to reduce the risk of excessive bleeding at delivery (Kadir 1998; McMahon 2001).

Conversely, vaginal delivery is considered a safe mode of delivery in women with bleeding disorders, and the indication for undertaking a c-section is an obstetric decision. Vaginal delivery also avoids surgical morbidity and anaesthesia-related complications (Lee 2006). Special attention to haemostasis is required to minimise bleeding during c-section.

For both c-section and vaginal delivery, administration of neuraxial or general anaesthesia are considered safe. In women with, or carriers of, bleeding disorders, the risk of spinal or epidural haematoma following administration of neuraxial anaesthesia may be increased with potential for permanent neurological injury (Vandermeulen 1994). The decision for neuraxial anaesthesia is individualised and the procedure is better performed after an optimum level of deficient clotting factor is achieved. When there is concern about the increased risk of spinal or epidural haematoma, patient-controlled analgesia with fentanyl is an alternative option (Campbell 2003). Caesarean section under general anaesthesia is considered in cases where neuraxial analgesia is contraindicated.

Instrumental delivery with low forceps is permissible, delivery by vacuum extraction or mid-cavity or rotational forceps delivery is not recommended and episiotomies and foetal scalp electrodes are tentatively avoided (Ljung 1994).

Prophylactic administration of a uterotonic drug (oxytocin, ergometrine, misoprostol, carboprost) along with active management of the third stage of labour are the main strategies to prevent PPH.

A deficient coagulation level persisting during pregnancy must be corrected to a safe level by supplementation in order to prevent bleeding during childbirth. If the goal is to normalize the haemostatic level before the procedure and to maintain it for at least five to seven days following either vaginal or c-section delivery, prophylactic replacement therapy in severe bleeding disorders and desmopressin in mild bleeding disorders is considered to prevent PPH. Lack of data from the literature in relation to fetuses with rare bleeding disorders and knowledge is extrapolated from experience of newborns with common bleeding disorders such as haemophilia (Ljung 1994).

Treatment of newborns affected, or at risk of being affected, by congenital coagulopathies are not the object of this review.

How the intervention might work

Choices regarding the modality of delivery, use of instruments, type of anaesthesia, administration of prophylactic factor concentrates or treatment or active bleeding during obstetrical procedures are all interventions aimed at preventing, reducing or treating obstetrical bleeding complications. Evidence about the risk-benefit ratio for the mother and the fetus is scanty, and no strong recommendations are available in the field. The safest method of delivery for fetuses at risk is controversial (James 2010; Towner 1999). Low forceps delivery is considered less traumatic compared to c-section when the head is deeply engaged in the pelvis and an easy outlet delivery is anticipated (Kadir 1998; McMahon 2001). Any, or different combinations of these interventions, can be associated

with clinically significant outcomes. This review will focus on the specific role of vaginal versus c-section delivery.

Why it is important to do this review

At present, there is an ongoing debate about the best way to deliver babies in women with, or at risk of, congenital bleeding disorders. The evidence for vaginal versus surgical delivery is limited. This review will investigate the safety and efficacy associated with the mode of delivery in women with bleeding disorders and carriers, taking into account the effects on both the mother and the foetus. This is an update of a Cochrane review first published in 2015 (Karanth 2015)

OBJECTIVES

To assess the optimal mode of delivery in women with, or carriers of, bleeding disorders.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised control trials and quasi-randomised control trials.

Types of participants

Pregnant women with, or carriers of, any type of bleeding disorder.

Types of interventions

Vaginal delivery compared to elective c-section delivery.

Types of outcome measures

Primary outcomes

1. Maternal death (any cause, within 42 days following delivery)
2. Post-partum haemorrhage (women with total blood loss 500 mL or more within 24 hours after birth, and severe PPH defined as a blood loss of 1000 mL or more within the same timeframe) (WHO 2012).
3. Infant death (within one year of birth)

Secondary outcomes

1. Severe maternal morbidity (WHO 2011), e.g.
 - a. major surgery
 - b. vital organ failure
 - c. intensive care unit (ICU) admission
2. Other maternal morbidity
 - a. wound infection
 - b. wound haematoma
 - c. low genital tract haematoma
3. Instrumental delivery
4. Foetal morbidity
 - a. head bleeding (e.g. cephalhaematoma, intracranial haemorrhage)
5. Other anaesthesia complications
 - a. spinal haematoma
 - b. epidural haematoma
6. Length of the stay

Search methods for identification of studies

We will not adopt any language or publication restrictions.

Electronic searches

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register using the term: pregnancy.

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE and the prospective handsearching of one journal - *Haemophilia*. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 16 February 2017.

We searched the Cochrane Pregnancy and Childbirth's Trials Register, date of the most recent search: 21 February 2017.

We also searched the following trial registries for ongoing trials: the ClinicalTrials.gov (<http://clinicaltrials.gov/>); the International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr/en/); and the ISRCTN Register (www.controlled-trials.com/isrctn). Date of the last search of the registries of ongoing trials: 08 April 2017.

Searching other resources

For future updates of the review, we will also check the reference lists of all the trials identified by the above methods.

Data collection and analysis

No trials are currently eligible for inclusion, the following methods will be employed should trials be included in future updates of this review.

Selection of studies

Two authors will independently check the titles and abstracts identified from the searches. All authors will obtain the full text of all potentially relevant trials and decide which of these fit the inclusion criteria. We aim to resolve any disagreement by discussion. We will contact trial authors for clarification where necessary.

Data extraction and management

Two review authors will independently extract data from included trials using forms provided by the Cochrane Cystic Fibrosis and Genetic Disorders Group. For each included trial we will collect information regarding the patients, the nature of the interventions and data relating to the outcomes specified above. When information regarding any of the above is unclear, we will contact the trial authors for further details. We will enter data into

the Review Manager software and pool outcome measures where appropriate (at one month, three months, one year and beyond one year) ([RevMan 2014](#)).

Assessment of risk of bias in included studies

Two authors (KLK,SK) will independently assess the risk of bias of each included trial using Cochrane's risk of bias assessment tool ([Higgins 2011a](#)). We plan to resolve any disagreements between the two review authors by discussion. The risk of bias of assessment will include: generation of allocation sequence; allocation concealment; blinding (of participants, personnel and outcome assessors); incomplete outcome data; selective outcome reporting; and other potential threats to validity. In relation to each of these domains, we will explicitly judge each of the included trials as having either a low, high or unclear risk of bias (as defined in the *Cochrane Handbook For Systematic Reviews of Interventions* ([Higgins 2011a](#))). For included trials, we will note levels of attrition.

Measures of treatment effect

We will present the results for categorical data (maternal death, post partum haemorrhage, neonatal death, major surgery, vital organ failure, intensive care unit admission, wound infection, wound haematoma, low genital tract haematoma, instrumental delivery, foetal morbidity, anaesthesia complications) as risk ratios (RR) with 95% confidence intervals (CI). For continuous data (length of the stay) if outcomes are measured in the same way, we will use the mean difference (MD) and when the same outcome is measured using different methods, we will use the standardised mean difference (SMD), both with 95% CI.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. In an attempt to account for any unit of analysis error, we plan to use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similarly designed trial or from a trial of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster randomised trials and individually-randomised trials, we plan to pool the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the trial designs and we consider an interaction between the effect of intervention and the choice of randomisation unit to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. Where information is missing or unclear, we will contact the trial author(s).

Assessment of heterogeneity

We will assess heterogeneity among trials by inspecting the forest plots and using the χ^2 test and I^2 statistic for heterogeneity with a statistical significance level of P less than 0.10 and the interpretation of I^2 is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Final interpretation of the I^2 value depends on number of trials and sample size, and we will discuss this after the analysis.

Assessment of reporting biases

If any trial protocols are available, we will compare these to the published reports. Where the trial protocol is not available, we will judge the completeness of reported outcomes based on clinical common sense. If 10 or more trials are eligible, we will investigate potential reporting biases using a funnel plot. We will use a linear regression approach to measure funnel plot asymmetry on the logarithm scale of the RR. If we obtain an asymmetrical funnel plot, we will explore alternative causes in addition to publication bias ([Sterne 2011](#)).

Data synthesis

We will perform statistical analysis in accordance with the guidelines developed by Cochrane ([Deeks 2011](#)). We will perform our statistical analysis using Review Manager software ([RevMan 2014](#)). If there is no significant heterogeneity, we will use the fixed-effect model. In the presence of at least moderate heterogeneity (over 30%), we will use the random-effects model and subgroup analyses as described below to investigate the source of heterogeneity.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses as detailed below.

1. Any congenital bleeding disorders (including platelet defect) versus ITP, HELLP syndrome, acquired haemophilia or other acquired coagulation inhibitors.
2. Pre-term and term birth.
3. Type of anaesthesia, e.g. spinal or epidural (across compared interventions).

We will consider meta-regression if, in future updates, there are more than 10 trials in a meta-analysis and we will use the Comprehensive Meta-analysis Software ([Comprehensive Meta Analysis 2015](#)).

Sensitivity analysis

We will perform a sensitivity analysis (on the primary outcomes only) if we find the included trials are not of 'high quality', i.e. trials defined as having a low risk of bias relating to random sequence generation, adequate allocation concealment and where the percentage of missing data less than 20%, given the stated importance of attrition as a quality measure.

If at least moderate statistical heterogeneity exists in outcomes between trials, we will explore the impact of including or excluding trials with high levels of missing data in the overall assessment of treatment effect.

Finally, as outlined in the 'Unit of analysis issues' section, if possible, we plan to conduct a sensitivity analysis on the choice of ICC.

RESULTS

Description of studies

No trials were identified which were eligible for inclusion in the review.

Risk of bias in included studies

No trials were identified which were eligible for inclusion in the review.

Effects of interventions

No results from randomised controlled trials were found.

DISCUSSION

No randomised controlled trials were identified which met the inclusion criteria for this review.

Summary of main results

No results from randomised controlled trials were found.

Agreements and disagreements with other studies or reviews

Due to the absence of trial-based evidence, in this section we are not able to compare our results with other published systematic reviews or excluded trials, but will instead provide a concise summary of the current relevant observational evidence.

Due to limited information available in the literature, the general principles of the management of labour and delivery in women with rare bleeding disorders are not differentiated on the basis of the underlying bleeding disorder. Pregnant women with a bleeding disorder, especially if severe and rare, should be advised to deliver in a tertiary centre, where the requisite coagulation laboratory tests are available. Delivery is better planned by a multidisciplinary team. Maternal safety considerations are usually taken into account first, and obstetrical considerations are, in general, not dissimilar from women without bleeding disorders, provided the bleeding defect has been properly corrected. For prophylactic treatment with clotting factors to prevent postpartum haemorrhage, the treatment needs to raise the deficient factor levels to above 50 international units (IU)/decilitre (dL) for factor VIII (FVIII), factor IX (FIX), Von Willebrand factor antigen (VWF:Ag) and Von Willebrand factor activity (VWF:Ac) or to 30 to 70 IU/dL for FXI during labour and delivery and to maintain this for at least three days after vaginal delivery and at least five days after c-section (Lee 2006; Srivastava 2013). Concomitant use of factor XI concentrates with tranexamic acid is generally avoided because it has a prothrombotic effect. Minimizing maternal genital and perineal trauma in order to reduce the risk of excessive bleeding at delivery should be considered (McMahon 2001). Active management of the third stage of labour

has demonstrated a significant reduction in blood loss and the need for blood transfusion (Begley 2011).

The use of regional anaesthesia or analgesia in women with bleeding disorders is controversial because of the potential risk of epidural or spinal haemorrhage and haematoma, which can lead to permanent neurological damage. A regional block is preferred in women with bleeding disorders, provided their coagulation defect has normalized during pregnancy or been corrected by prophylactic treatment (Kadir 1997). An experienced anaesthesiologist should perform the regional block (Anim-Somuah 2011). General anaesthesia is preferred whenever regional anaesthesia is contraindicated (e.g. when the coagulation defect cannot be corrected by replacement therapy). When epidural anaesthesia is adopted, the catheter is best removed after assessing that the deficient factor level has been normalized.

Moving on to considerations about foetal safety, the safest method of delivery is largely debatable even when the foetus is supposed, or known to be affected by, a bleeding disorder (James 2010; Towner 1999). The rate of intracranial haemorrhage may be higher among infants delivered by vacuum extraction, forceps, or emergency c-section initiated during labour than among infants delivered spontaneously (Towner 1999). Elective c-section has been found to have an 85% chance of a lower rate of intracranial haemorrhage compared to vaginal delivery (James 2010). Delivery should be achieved by the least traumatic method and early recourse to c-section should be considered to minimize the risk of neonatal bleeding complications. Risk of head bleeding is slightly higher following vaginal delivery compared to c-section, but c-section does not appear to eliminate the risk of serious neonatal bleeding complications (Ljung 1994). Invasive intrapartum monitoring techniques, such as foetal scalp electrodes and foetal blood sampling, should be avoided in pregnancies where the foetus is at risk of a bleeding disorder because of the risk of serious scalp bleeding, cephalohaematoma and intracranial haemorrhage during the birth process. The use of vacuum extraction or forceps, or prolongation of labour (especially prolongation of the second stage of labour), should be avoided because of associated head bleeding in the foetus (Ljung 1994).

It may be worth highlighting that women with bleeding disorders are considered to have an inherently low risk for venous thromboembolism (VTE) (Dargaud 2004). Replacement therapy corrects the coagulation defect and, therefore, the risk of VTE in these women is likely to return closer to that of the general population (Dargaud 2004). Thromboprophylaxis post delivery should be considered in the presence of selected risk factors, and can be either pharmacological or mechanical, depending on risk factors and presence or absence of concomitant replacement therapy.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review reveals that randomised control trials to assess the optimal mode of delivery in pregnant women with any bleeding disorders are lacking.

In the absence of high quality evidence, clinicians need to use their clinical judgement and refer to lower level evidence (e.g.

from observational trials) to decide between vaginal or c-section delivery in this population.

Implications for research

The number of cases of pregnant women with bleeding disorders is very small, and the number of those suffering from bleeding complications is even lower. To ensure that any trial undertaken has sufficient statistical power, it needs to be carried out over long periods of time (several years) and will require combining data from several centres. Bleeding complications can be life-threatening to the mother as well as the foetus and this makes the ethical issues regarding randomised trials more complex (Temple 1982). Therefore, randomised controlled trials are unlikely to be conducted. Patient-important outcomes can be evaluated by studying international prospective registries which have collected and maintained data scientifically (Gliklich 2014). Epidemiological parameters, safety effectiveness, cost effectiveness can be obtained by studying the registries in detail and this will help in decision-making and developing treatment protocols (Lipscomb 2009). Other high quality controlled studies

(such as risk allocation designs, sequential design, and parallel cohort design) to investigate the risks and benefits of natural vaginal versus c-section delivery in this population are needed.

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Date	Event	Description
15 June 2017	New search has been performed	Minor changes have been made throughout the review.
15 June 2017	New citation required but conclusions have not changed	New searches undertaken in 2017 did not identify any potentially-relevant trials for inclusion in the review.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
<i>Protocol stage:</i> draft the protocol	Karanth KL
<i>Review stage:</i> select which trials to include (2 + 1 arbiter)	Karanth KL, Sachchithananthum K + Adinegara BL Abas
<i>Review stage:</i> extract data from trials (2 people)	Karanth KL, Adinegara BL Abas
<i>Review stage:</i> enter data into RevMan	Karanth KL

<i>Review stage:</i> carry out the analysis	Karanth KL, Adinegara BL Abas
<i>Review stage:</i> interpret the analysis	Karanth KL
<i>Review stage:</i> draft the final review	Karanth KL, Sachchithananthum K, Adinegara BL Abas
<i>Update stage:</i> update the review	Karanth KL, Sachchithananthum K, Adinegara BL Abas

DECLARATIONS OF INTEREST

All authors: none known.

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INDEX TERMS

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*Blood Coagulation Disorders [genetics]; *Heterozygote; *Pregnancy Complications, Hematologic [genetics]; Cesarean Section; Delivery, Obstetric [*methods]; Fetus

MeSH check words

Adult; Female; Humans; Pregnancy