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Desmopressin acetate (DDAVP) for preventing and treating acute bleeds during pregnancy in women with congenital bleeding disorders (Review)

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[Intervention Review]

Desmopressin acetate (DDAVP) for preventing and treating acute bleeds during pregnancy in women with congenital bleeding disorders

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ABSTRACT

Background

Congenital bleeding disorders can cause obstetric haemorrhage during pregnancy, labour and following delivery. Desmopressin acetate (DDAVP) is found to be an effective drug which can reduce the risk of haemorrhage and can also stop bleeding in certain congenital bleeding disorders. Its use in pregnancy has been controversial. Hence beneficial and adverse effects of DDAVP in these groups of pregnant women should be evaluated.

This is an update of a Cochrane Review first published in 2013 and updated in 2015.

Objectives

To evaluate the efficacy and safety of DDAVP in preventing and treating acute bleeding in pregnant women with bleeding disorders.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coaguopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant and abstract books of conferences proceedings. We also searched several clinical trial registries and grey literature (27 August 2017).

Date of most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coaguopathies Trials Register: 01 October 2018.

Selection criteria

Randomised and quasi-randomised controlled trials investigating the efficacy of DDAVP versus tranexamic acid or factor VIII or rFactor VII or fresh frozen plasma in preventing and treating congenital bleeding disorders during pregnancy were eligible.

Data collection and analysis

No trials matching the selection criteria were eligible for inclusion.

Main results

No trials matching the selection criteria were eligible for inclusion.

Authors' conclusions

No randomised controlled trials were identified investigating the relative effectiveness of DDAVP for bleeding during pregnancy in women with congenital bleeding disorders. In the absence of high-quality evidence, clinicians need to use their clinical judgement and lower level evidence (e.g. from observational trials) to decide whether or not to treat women with congenital bleeding disorders with DDAVP.

Given the ethical considerations, future randomised controlled trials are unlikely. However, other high-quality controlled studies (such as risk allocation designs, sequential design, parallel cohort design) to investigate the risks and benefits of using DDAVP in this population are needed.

Given that there are unlikely to be any trials published in this area, this review will no longer be regularly updated.

PLAIN LANGUAGE SUMMARY

Desmopressin acetate (DDAVP) for preventing and treating acute bleeds during pregnancy in women with congenital bleeding disorders

Review question

We reviewed the evidence about the effect and safety of desmopressin acetate (DDAVP) in preventing and treating acute bleeding in pregnant women with bleeding disorders. This is an update of previously published versions of this Cochrane Review.

Background

Congenital bleeding disorders cause problems with bleeding during pregnancy, labour and delivery. Bleeding complications in women with congenital bleeding disorders are an important cause of disease and death linked to childbirth. Agents to stop the flow of blood are used for women with these bleeding disorders during pregnancy. DDAVP is a drug used to effectively increase the concentration of factor VIII in the blood and to increase the clumping together of platelets to stop bleeding. It does not come from human plasma and it carries no risk of infection. It might be a precious resource in people with von Willebrand disease, haemophilia A or congenital platelet disorders to prevent and treat bleeding episodes related to pregnancy.

Search date

The evidence is current to: 01 October 2018.

Study characteristics

We did not find any randomised controlled trials assessing desmopressin acetate in this group of women.

Key results

There were no trials included in the review. Given the ethical considerations, future randomised controlled trials are unlikely. Evidence is needed to show the risks and benefits of DDAVP when used to prevent and treat bleeding during pregnancy in women with congenital bleeding disorders. While there is evidence from observational trials that shows the drug is effective in stopping and preventing bleeding, we conclude that there is still a need to generate other high-quality controlled evidence. Given that there are unlikely to be any trials published in this area, this review will no longer be regularly updated.

BACKGROUND

Description of the condition

Congenital bleeding disorders are relatively uncommon, however, they may be challenging during acute episodes. During pregnancy these disorders may present a haemostatic challenge resulting in excessive bleeding and as a cause of obstetric haemorrhage, bleeding disorders are often underestimated. Inherited bleeding disorders, mainly von Willebrand disease (VWD), haemophilia A and B factor XI and factor VII deficiency account for almost 90% of all women with inherited bleeding disorders (Chi 2007). Deficiencies in factors such as fibrinogen, prothrombin, factor V, FX, FXIII are comparatively rare.

Von Willebrand disease results from either a quantitative or qualitative defect in von Willebrand factor (VWF). A physiological increase in VWF (with levels in blood plasma up to normality) is often seen during pregnancy in women with a severe form of VWD (excluding type 3), but intrapatient variability is wide (Conti 1986). A rapid fall of VWF occurs following delivery in women with VWD, and they are more prone to both early haemorrhage (blood loss of more than 500 mL within 24 hours of delivery of the baby) and late haemorrhage (any significant loss between 24 hours and 6 weeks after the birth) in the puerperium. The occurrence of early and late postpartum haemorrhage (PPH) among VWD is 16% to 29% and 20% to 29%, respectively (Greer 1991; Kadir 1998).

Congenital haemophilias are X-linked recessive bleeding disorders that result from deficiencies of coagulation factors VIII and IX. Most female carriers of haemophilia have levels of factor VIII (or IX) within the normal range, but a significant proportion have a modest reduction in the baseline level. The baseline level is seldom lower than 20% of the normal level and should therefore be enough to protect against significant bleeding problems in day-to-day life (Giangrande 2003). Female carriers of haemophilia A who are pregnant, usually have normal levels of factor VIII by the third trimester, because even in those with low levels at the beginning, factor VIII increases as gestation advances. However, those with levels of factor VIII (or IX) less than 50% (< 0.50 IU/mL) are at increased risk of bleeding when facing haemostatic challenges (Lusher 1978). In normal pregnancy, levels of factor VIII nearly double over the normal baseline value, whereas factor IX levels do not rise significantly (Stirling 1984). Female carriers of haemophilia A are at increased risk of haemorrhagic complications, both early and late PPH, after invasive procedures, miscarriage and delivery 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).

Factor XI deficiency (haemophilia C) is a very rare inherited bleeding disorder in the general population but is very common in the Ashkenazi Jewish population (Bolton-Maggs 1988). It can be homozygous or heterozygous. The level of factor XI does not rise during pregnancy and there is poor correlation between level of factor XI and bleeding tendency (Bolton-Maggs 1988). Bleeding tendency is likely to be associated with a level less than 15% and varies in the same individual following different haemostatic challenges. Therefore, the unpredictable nature of this disease makes its management during pregnancy and childbirth difficult.

Inherited factor VII deficiency is a very rare autosomal recessive disorder. Only homozygous and compound heterozygous individuals develop haemorrhagic manifestations, heterozygous individuals are usually asymptomatic. Clinical prototypes vary from mild to severe and do not correlate with factor VII levels.

Congenital platelet dysfunction disorders, being autosomal recessive disorders, are rare. Defects are in the platelet GPIb complex (Bernard-Soulier Syndrome) or GPIIb-IIIa complex (Glanzmann thrombasthenia) or in abnormal secretion and thromboxane synthesis. Bleeding tendencies are severe in Bernard-Soulier Syndrome and Glanzmann thrombasthenia, which need platelet transfusion. Bleeding in platelet dysfunction disorders, due to abnormal secretion and thromboxane synthesis, is mild, but can be life-threatening following surgery or trauma.

Vaginal delivery is considered safe, although, if possible, procedures that could increase the risk of haemorrhage (episiotomies, fetal scalp electrodes, instrumental deliveries) should be avoided. It is also better to avoid prolonged second stage labour. Caesarean section is generally to be pursued for obstetric indications only (Lee 2006), but no strong evidence comparing vaginal and Caesarean delivery exists.

Description of the intervention

Desmopressin acetate (DDAVP) is a synthetic analogue (1-deamino-8-D-arginine vasopressin) of the antidiuretic hormone L-arginine-vasopressin with haemostatic properties. It induces VWF release from endothelial cells and is safe for the fetus, since it does not cross the placenta in detectable amounts (Mannucci 2005) and does not pass into breast milk in any significant amount. There have been no adverse effects on reproduction observed in animal studies (Sanofi-Aventis 2007).

In those with inherited bleeding disorders, DDAVP infusion results in a two- to six-fold increase from baseline in factor VIII and VWF plasma levels, although individuals have differing responses (Lethagen 1987). The therapeutic peak level is achieved in 30 to 90 minutes. When repeated DDAVP doses were given every 12 to 24 hours, there is generally a gradual diminishing of the initial factor VIII activity increase noted with the first dose. However, the initial response is reproducible in any particular person if two or three days elapse between administrations. The usual therapeutic dose is 0.3 to 0.4 µg/kg given intravenously over a period of 30 minutes; it may be administered subcutaneously or intranasally. As absorption is erratic, DDAVP is administered intravenously when administered prophylactically in surgical procedures (Nicholos 2008). Since its first clinical use in 1977, DDAVP has become the treatment of choice for people with haemophilia A with factor VIII between 5% and 50%. It increases the density of platelet surface glycoprotein receptors and increases plasma level of factor VIII (Levi 2003; Mannucci 1975; Wun 1995). An average two- to six-fold factor VIII increase is observed in most people and a return to baseline occurs usually within eight hours. It is also of potential value in VWD type 1 because it can increase VWF in the blood. It also increases platelet adhesiveness and shortens bleeding time. As a result of its antidiuretic effects, there is a risk of fluid overload and hyponatraemia (Mannucci 1997), which can lead to seizures in susceptible individuals, particularly young children and pregnant women (Mannucci 2005). Hence during therapy, fluid intake should be limited and plasma sodium levels frequently monitored. Treatment with DDAVP is not indicated for haemophilia

B and is of no value in type 3 VWD; a variable response would be expected in VWD types 2A and 2B, which overall account for approximately 20% of the VWD cases. It is also not indicated for treating people with a deficiency in factor XI or factor VII.

How the intervention might work

In people with some level of deficient factors (VWD type 1, some VWD type 2, mild and moderate haemophilia A) and in those with platelet function defects, DDAVP increases the plasma concentration of factor VIII and VWF through endogenous release of the individual's own stores. By increasing the concentration of the deficient factor to values in the normal range, DDAVP administration normalizes the haemorrhagic risk or stops the bleeding in responsive individuals.

Why it is important to do this review

This review is important given that bleeding complications in women with congenital bleeding disorders are an important cause of obstetrical morbidity and mortality. It is necessary to establish whether the use of DDAVP is safe, effective and affordable for people with VWD and haemophilia A for preventing and treating bleeding episodes related to pregnancy. In contrast to fresh frozen plasma and derivatives, DDAVP has no risks of blood-borne viral infections. There is currently no available systematic appraisal of the evidence of the use of DDAVP to prevent and treat bleeding complications in pregnancy-related bleeding.

This is an update of a Cochrane Review first published in 2013 and updated in 2015 (Karanth 2013; Karanth 2015).

OBJECTIVES

To evaluate the efficacy and safety of DDAVP in preventing and treating acute bleeding in pregnant women with bleeding disorders.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Types of participants

Pregnant women with congenital bleeding disorders (e.g. VWD, platelet function defects, carrier for haemophilia A) with documented diagnosis before pregnancy or who have undergone blood factor VIII or VWF estimation at first or second trimester.

Types of interventions

DDAVP versus tranexamic acid or factor VIII or rFactor VII or fresh frozen plasma.

Types of outcome measures

Primary outcomes

1. Maternal mortality
2. Post-partum haemorrhage (PPH) (defined as excessive bleeding occurring within six weeks after delivery and also judged on the basis of any intervention required (e.g. transfusion, surgery))
3. Infant mortality

Secondary outcomes

1. Red blood cell (RBC) transfusion
2. Reduction in bleeding (assessed by e.g. number of tampons, amount of bleeding in bed pan, gauze, or pads or differences in haemoglobin (Hb) prior to and after an episode of bleeding)
3. Number needing emergency Caesarean sections
4. Seizures
5. Severe hyponatraemia
6. Maternal hypertensive crisis
7. Delivery complications for the foetus

Search methods for identification of studies

We did not adopt any language or publication restrictions.

Electronic searches

We identified relevant studies from the Group's Coagulopathies Trials Register using the terms: DDAVP.

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.

We searched the following trial registries in an effort to identify ongoing clinical trials: ClinicalTrials.gov (www.ClinicalTrials.gov); the WHO International Clinical Trials Registry Platform (ICTRP) portal (www.who.int/ictrp/en/); and the ISRCTN Registry (www.isrctn.com/). We used a combination of medical subject headings (MeSH) such as 'desmopressin OR DDAVP AND congenital bleeding disorders AND pregnancy OR gestation OR delivery'. We also used these terms for searching the grey literature.

Date of the last search of the registries of ongoing trials: 27 August 2017.

Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register: 01 October 2018.

Searching other resources

We also aimed to check the reference lists of all the trials identified by the above methods. We contacted pharmaceutical companies for information on unpublished and ongoing trials.

Data collection and analysis

Selection of studies

Two authors aimed to independently check the titles and abstracts identified from the searches. However, to date, the authors have not identified any eligible randomised controlled trials. For future

updates, should any trials be included, the authors will adhere to the protocol outlined below.

Data extraction and management

Two review authors (KLK, AB) will independently extract data from included studies using forms provided by the Cochrane Cystic Fibrosis and Genetic Disorders Group. For each included study, we will collect information regarding the participants, 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 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, AB) will independently assess the risk of bias of each included study using the Cochrane Collaboration 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 studies as having either a low, high or unclear risk of bias. For included studies, we will note levels of attrition.

Measures of treatment effect

We will present the results for categorical data as risk ratio (RR) with 95% confidence intervals (CI). For continuous data, 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% CIs.

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 intracluster correlation co-efficient (ICC) derived from the study (if possible), from a similar (in design) study or from a study 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 study 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 sensitivity or subgroup analysis to investigate the effects of the randomisation unit.

Cross-over studies

The relevance of cross-over studies in preventing or treating acute haemorrhagic conditions in temporary situations such as pregnancy is minimal as they are usually carried out for stable chronic conditions. In the event that we identify cross-over studies, we will only analyse the data from the first arm.

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 studies by inspecting the forest plots and using the Chi^2 test and I^2 statistic for heterogeneity with a statistical significance level of $P < 0.10$ 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 study protocols are available, we will compare these to the published reports. We will investigate potential reporting biases using a funnel plot, provided a sufficient number of studies are available. 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.

Data synthesis

We will perform statistical analysis in accordance with Cochrane guidelines (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

We plan to conduct subgroup analyses by:

1. individual congenital bleeding disorder;
2. mode of delivery (vaginal, assisted and Caesarean sections);
3. type of PPH (early and late).

Sensitivity analysis

If there are sufficient comparable studies, we will perform sensitivity analyses excluding studies with clearly inadequate allocation of concealment, randomisation, or blinding (high risk of bias). Finally, we will also explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect.

RESULTS

Description of studies

Results of the search

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

Risk of bias in included studies

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

Effects of interventions

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

DISCUSSION

Summary of main results

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

Agreements and disagreements with other studies or reviews

Obstetric haemorrhage is a challenge observed during pregnancy, labour and delivery in women with congenital bleeding disorders. Many published studies have revealed that DDAVP is an effective drug in preventing and treating bleeding during pregnancies in women with VWD, haemophilia A and other rare functional platelet disorders (Huq 2011; Sanchez-Luceros 2007). This treatment has the benefit of avoiding the risk of blood-borne viruses associated with blood products. There is concern about the potential for serious adverse effects of using DDAVP during pregnancy, for example, because of its antidiuretic effect; water intoxication and hyponatraemia are reported side-effects (Chediaik 1986). Premature delivery or increased uterine activity has also been reported following DDAVP administration (Chediaik 1986; Rochelson 1991). However, other available data demonstrate the absence of structural abnormalities and fetal complications, such as intrauterine growth restriction, as well as the insignificant secretion of DDAVP in breast milk and these signify the safe use of DDAVP in pregnancy (Burrow 1981; Ray 1998). However, interestingly, no randomised trials are available to support the clinical use of DDAVP.

The absence of definitive randomised trials suggests that this is an area where more evidence is needed to inform the scientific community as
to the benefits and risks of this intervention in the treatment of acute bleeds during pregnancy in women with congenital bleeding disorders.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised controlled trials of desmopressin acetate (DDAVP) for bleeding in women with congenital bleeding disorders in pregnancy were found for inclusion in this review. Thus, there is no high level evidence on which to base recommendations for or against the routine use of DDAVP in this population. Decisions about the use of DDAVP must be based on observational evidence, which can substantiate claims of effectiveness and safety for this substitution-like therapy in the prevention and treatment of acute bleeding. Conversely, the same non-controlled evidence cannot provide any high-quality comparative evaluation on the efficacy and safety of DDAVP compared to other available treatments, which would require controlled observations as suggested below.

Implications for research

This systematic review has identified the lack of well-designed, adequately-powered randomised controlled trials to assess the benefits and risks of the use of DDAVP as a means of preventing or reducing bleeding in women with congenital bleeding disorders during pregnancy.

Formidable barriers exist to the proper planning and co-ordination of comparable trials. Due to the low absolute number of occurrences of pregnancy-related bleeding episodes in women with rare congenital bleeding disorders, trials of similar design can only be run over a long time period and across several centres in order to achieve the requisite statistical power. Also, ethical considerations make designing such trials (with the aim of a successful full-term pregnancy and delivery) very complex (Temple 1982). Nonetheless, any active drug could be compared with alternative treatment modalities, and specific controlled study designs (risk allocation designs, sequential design, parallel cohort design) can be used to address specific issues of safety and efficacy (Lilford 1995; National Academies Press 2001).

Meanwhile, international prospective registries collecting and maintaining data in agreement with high scientific standards would be beneficial, as long as they allow the evaluation of patient-important outcomes (Dreyer 2009). Simultaneously, patient registries designed explicitly to examine questions of comparative effectiveness could provide epidemiological, safety, comparative-effectiveness and cost-effectiveness data and can serve a wide spectrum of decision-making purposes (Lipscomb 2009; Temple 1982).

Given that there are unlikely to be any trials published in this area, this review will no longer be regularly updated.

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WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	A search for relevant studies was undertaken on 1 October 2018. None of the identified trials were eligible for inclusion in any section of the review. No new trials are expected in this area, therefore, we do not plan on updating this review.

HISTORY

Protocol first published: Issue 4, 2012
Review first published: Issue 4, 2013

Date	Event	Description
13 February 2019	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register identified two potentially eligible trials for inclusion, these were not eligible for any section of the review. Given that there are unlikely to be any trials published in this area, this review will no longer be regularly updated.
13 February 2019	New citation required but conclusions have not changed	Minor updates have been made throughout the review.
7 September 2015	New citation required but conclusions have not changed	No potentially eligible trials were identified by the searches.
7 September 2015	New search has been performed	The update contains minor changes throughout the text of the review. The 'Plain language summary' has been re-formatted.

CONTRIBUTIONS OF AUTHORS

The review and updates were performed by K. Laxminarayan Karanth assisted by Dr Ankur Barua in discussion with Prof Sachchithanantham Kanagasabai and Prof Sreekumaran Nair.

K. Laxminarayan Karanth wrote protocol in discussion with Prof Sachchithanantham Kanagasabai and Prof Sreekumaran Nair and assisted by Dr Ankur Barua.

DECLARATIONS OF INTEREST

All authors: none known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Blood Coagulation Disorders [congenital] [*drug therapy] [*prevention & control]; Deamino Arginine Vasopressin [*therapeutic use]; Hemostatics [*therapeutic use]; Pregnancy Complications, Hematologic [*drug therapy] [*prevention & control]

MeSH check words

Female; Humans; Pregnancy