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Which drug is best for treating excessive bleeding after childbirth?

Authors: Parry Smith WR, Papadopoulou A, Thomas E, Tobias A, Price MJ, Meher S, Alfirevic Z, Weeks AD, Hofmeyr GJ, Gülmezoglu AM, Widmer M, Oladapo OT, Vogel JP, Althabe F, Coomarasamy A, Gallos ID

What is the issue?

The most common reason why mothers die during childbirth is excessive bleeding, which is known as postpartum haemorrhage, when blood loss equals or exceeds 500 mL. This emergency condition is usually caused by failure of the uterus to contract and close the vessels that carried blood to the placenta. The World Health Organization (WHO) recommends giving drugs that make the uterus contract more effectively (uterotonic drugs) and reduce the risk for excessive bleeding. Although these drugs are given to the mother immediately after the birth of her baby, some women will still experience heavy bleeding and will require further treatment.

Why is this important?

The administration of uterotonic drugs is the main treatment when prevention fails, and excessive bleeding occurs. Available uterotonic treatments include oxytocin, carbetocin, ergometrine, misoprostol, injectable prostaglandins, and combinations of these drugs, which differ in terms of effectiveness and side-effects. The aim of this Cochrane Review is to identify the best drug with the least side-effects for treating excessive bleeding after childbirth.

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What evidence did we find?

We searched for evidence in May 2020 and found seven studies involving 3738 women. Women gave birth mostly vaginally in hospital settings and had received uterotonic drugs to prevent postpartum haemorrhage. The drugs used for treating heavy bleeding in these studies were misoprostol (tablets dissolved under the tongue, pills or rectal suppositories), oxytocin (given into a vein or muscle), a combination of misoprostol with oxytocin and a combination of Syntometrine® (ergometrine plus oxytocin combination injected into muscle) with oxytocin.

Two studies, involving 1787 women, compared misoprostol with oxytocin for the initial treatment of excessive bleeding after birth. We found that misoprostol probably increases the risk of requiring a blood transfusion compared with oxytocin and may also increase the risk of suffering an additional blood loss of 1000 mL or more after initiation of treatment and until the bleeding stops. From the available data, we cannot learn much for the outcomes of suffering an additional blood loss of 500 mL or more, maternal death or severe illness related to excessive blood loss, and the need for additional uterotonic drugs to stop the bleeding. In terms of side-effects, misoprostol increases the risk for vomiting and may also increase the incidence of fever compared with oxytocin.

Four studies, involving 1881 women, compared misoprostol given in combination with oxytocin against oxytocin given alone. The drug combination makes little or no difference to the use of additional uterotonics, and blood transfusion compared with oxytocin given alone. However, we were not able to identify which of these drugs works best for reducing additional blood loss of 500 mL or more, additional blood loss of 1000 mL or more, and maternal death or severe illness related to excessive blood loss. In terms of side-effects, the drug combination increases the occurrence of both fever and vomiting.

One trial with only 64 women compared misoprostol with Syntometrine® combined with oxytocin. The available evidence was of very low certainty and thus we were unable to identify the best performing drug among them.

We also compared the combination of misoprostol and oxytocin against misoprostol alone. These drugs have not been compared directly in studies. However, both drugs have been compared against oxytocin, and thus we were able to compare them indirectly. The drug combination probably reduces the risk of blood transfusion and may reduce the risk of additional blood loss of 1000 mL or more, but makes little or no difference to vomiting compared with misoprostol alone. However, we cannot learn much for the outcomes of additional blood loss of 500 mL or more, maternal death or severe illness related to excessive blood loss, use of additional uterotonic drugs, and fever.

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What does this mean?

We found that oxytocin is probably more effective than misoprostol and is also associated with less side-effects. Giving misoprostol together with oxytocin probably does not improve effectiveness and increases side-effects. The evidence for most available drugs used as first-line treatment of postpartum haemorrhage is limited, with no evidence found for several drugs currently in use.

Interventions for leg cramps during pregnancy

Authors: Luo L, Zhou K, Zhang J, Xu L, Yin W

What is the issue?

Leg cramps are experienced as sudden, intense involuntary contractions of the leg muscles. They are a common problem in pregnancy, especially in the third trimester. They are painful and can interfere with daily activities, disrupt sleep, and reduce quality of life. Various interventions have been used during pregnancy to treat leg cramps, including drug, electrolyte (magnesium, calcium, sodium) and vitamin therapies, and non-drug therapies such as muscle stretching.

Why is this important?

The goal of this review was to find out what is effective and safe for treating leg cramps during pregnancy.

What evidence did we find?

We searched for evidence in September 2019 and identified eight randomised controlled studies, with a total of 576 women who were 14 to 36 weeks pregnant, comparing either magnesium, calcium, calcium-vitamin D or vitamin B with placebo or no treatment, and comparing vitamin C with calcium. All treatments were given as tablets to be chewed or swallowed.

Magnesium supplements may reduce how often women experienced leg cramps when compared with placebo or no treatment, although findings were not consistent. Studies measured this in different ways, sometimes showing that magnesium helped reduce the number of leg cramps but sometimes showing that it made little or no difference. Likewise, evidence about whether magnesium reduced the intensity of pain was inconclusive with one study showing a reduction while others showed no difference. There was little or no difference in the experience of side effects, such as nausea and diarrhoea.

Calcium did not consistently reduce how often women experienced leg cramps after treatment compared to women who did not receive any treatment. The evidence was also found to be of very low quality and so we cannot be sure of the results.

More women who received vitamin B supplements fully recovered compared with those women receiving no treatment; however these results were from a small sample and the study had design limitations.

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The frequency of leg cramps was no different between women treated with calcium and those treated with vitamin C.

The calcium-vitamin D and the vitamin D supplements had no effect on the frequency, length, and pain intensity of leg cramps after treatment compared to women who received placebo.

What does this mean?

The level of evidence was found to be of low or very low quality. This was mainly due to the small sample size of studies and poor study design. Four studies were well-conducted and reported. The other four had design limitations: women were not allocated to different treatment groups in the best way in several studies, and in two studies women knew whether they were receiving treatment or not. Adverse effects such as any effect of the treatment on pregnancy complications, labour and the baby were not reported. Several of the studies focused mainly on serum calcium and magnesium levels. The frequency and intensity of cramps and the duration of pain were not reported in a consistent way and often information was lacking on how they were measured, either during treatment, at the end of treatment or after treatment had stopped.

It is not clear from the evidence reviewed whether any of the oral interventions (magnesium, calcium, calcium-vitamin D, vitamin B vitamin D or vitamin C) provide an effective and safe treatment for leg cramps in pregnancy. Supplements may have different effects depending on women's usual intake of these substances. No trials considered therapies such as muscle stretching, massage, relaxation or heat therapy.

Paracetamol for relief of perineal pain after birth

Authors: Abalos E, Sguassero Y, Gyte GML

What is the issue?

The aim of this Cochrane Review was to find out if a single dose of paracetamol (acetaminophen) reduces the incidence of perineal pain for women after giving birth vaginally. We collected and analysed all relevant studies to answer this question (search date December 2019).

Why is this important?

The birth of a baby should be a very special time for women and families. Perineal pain can sometimes interfere with women's well-being and cause them problems in looking after their babies.

The perineum is a diamond-shaped area between the vagina and the anus that can bruise or tear as the baby is born. Some women are given a cut to the perineum (an episiotomy) for the baby to be born. Episiotomies and natural tears require stitches (sutures). Forceps or suction (ventouse) may also need to be used to help the baby to be born. Any such intervention can cause perineal discomfort and pain. Reducing the chance of perineal trauma and often intense perineal pain is clearly important as it can reduce a woman's ability to move

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around, breastfeed, and care for her baby. It can also cause urinary or fecal incontinence and painful sex. The pain can persist for weeks, months, or sometimes more. Adequate pain control is therefore important.

This review on paracetamol is part of a series of reviews looking at medicines to help relieve perineal pain in the first few hours after giving birth.

What evidence did we find?

We found no new studies in this update, so the review still includes 10 studies involving 1301 women. The studies were quite old, ranging from the 1970s to the early 1990s. All the studies looked at perineal pain relief associated with trauma, and no studies where the pain was associated with intact perineum were found. Overall, the evidence was of low quality due to the unclear methodology reported and the variation of findings.

Paracetamol may reduce the number of women experiencing pain at four hours after birth (10 trials, 1279 women), and fewer women may need additional pain relief with paracetamol (eight trials, 1132 women).

Only one study reported the number of women experiencing nausea (feeling sick) or sleepiness with no clear differences identified. There were no other side effects and none of the studies looked at effects on the babies.

What does this mean?

Paracetamol is generally effective as painkiller and causes few side effects. This review showed there may be some benefit specifically with a single dose of paracetamol for perineal pain after vaginal birth. Lactating women should be advised about the little information available on the effects of paracetamol in breastfed babies.

Anti-inflammatory drugs for relief of perineal pain after childbirth

Authors: Wuytack F, Smith V, Cleary BJ

What is the issue?

Following childbirth, many women experience pain in the perineum, an area between the anus and vagina. This Cochrane Review asked if this pain can be reduced by one dose of a non-steroidal anti-inflammatory drug (NSAID), such as aspirin or ibuprofen.

Why is this important?

The pain some women experience in the perineum after childbirth can be particularly acute if the perineum tears during the birth, or needs to be cut (known as an episiotomy). Even a woman without tearing or surgery often experiences discomfort in her perineum, which can affect her mobility as well as her ability to care for her baby. This review is part of a series of reviews on the effectiveness of different drugs for pain relief for perineal pain immediately after birth. We are looking specifically at NSAIDs, such as aspirin and ibuprofen.

What evidence did we find?

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We found 35 studies with 5136 women that examined 16 different NSAIDs (aspirin, ibuprofen, etc.). We included studies up to 9 December 2019. The studies we found only included women who had trauma of the perineum and who were not breastfeeding. Studies were conducted between 1967 and 2013 and had few women in them. The studies showed that a single dose of a NSAID may provide greater pain relief at four hours (low-certainty evidence) after taking the drug when compared to a placebo (dummy pill) or no treatment in non-breastfeeding women who had sustained perineal trauma during childbirth. We are uncertain if there is any difference between NSAID and placebo in achieving **adequate pain relief** at six hours.

Women who received a single dose of NSAID are probably less likely to need additional pain relief at four hours (moderate-certainty evidence) after taking the drug compared to women who received placebo or no treatment. We are uncertain if there is any difference between NSAIDs and placebo for women needing additional pain relief at six hours (very low-certainty evidence). Not all of the studies assessed adverse effects of the drugs, but some studies reported maternal adverse effects such as drowsiness, headache, weakness, nausea, gastric discomfort. The evidence is very uncertain about the difference in maternal adverse effects between NSAIDs and placebo at six hours after administration (very low-certainty evidence). One small study (90 women) reported that there were no maternal adverse effects at four hours after administration. None of the studies measured possible adverse effects on the baby.

A NSAID may also be better than paracetamol in providing pain relief at four hours after administration. We are uncertain if there is any difference between NSAID and paracetamol in achieving **adequate pain relief** at six hours or in the number of women who need additional pain relief at four hours after administration. Women who receive NSAID may be less likely to need additional pain relief at six hours compared to women who received paracetamol. One study reported that no **maternal adverse effects** were observed at four hours (210 women). Three small studies reported maternal adverse effects at six hours after administration but we are uncertain if there is any difference between the groups. Adverse effects on the baby were not reported in any of the included studies and all studies excluded women who were breastfeeding.

Comparisons of different NSAIDs and different doses of the same NSAID did not demonstrate any clear differences in their effectiveness on any of the main outcomes measured in this review. However, little information was available for some NSAIDs.

None of the included studies reported on any of this review's secondary outcomes, including: extended hospital stay or readmission to hospital for perineal pain; breastfeeding; perineal pain at six weeks after having the baby; women's views, postpartum depression or measures of disability due to perineal pain.

What does this mean?

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For women who are not breastfeeding, a single dose of a NSAID may be better than placebo or paracetamol for perineal pain at four hours. No serious side effects were reported, but not all studies examined these. For women who breastfeed, there are no data and these women should seek help, as some NSAIDs are not recommended for women who breastfeed.

If you have any questions or comments with regard to the above document please feel free to contact me.

Kind regards

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