Cyclo-oxygenase (COX) inhibitors for threatenedmiscarriage (Protocol)

by Windy Wariki 3

Submission date: 11-Sep-2019 10:26AM (UTC+0700)
Submission ID: 1170598871
File name: 4._Cyclo-oxygenase_COX_inhibitors_for_threatened_miscarriage.pdf (204.23K)
Word count: 6117
Character count: 35879

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Wariki WMV, Goto Y, Ota E, Mori R.
Cyclo-oxygenase (COX) inhibitors for threatened miscarriage.
Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD011310.
DOI: 10.1002/14651858.CD011310.

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[Intervention Protocol]

Cyclo-oxygenase (COX) inhibitors for threatened miscarriage

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 9, 2014.

Citation: Wariki WMV, Goto Y, Ota E, Mori R. Cyclo-oxygenase (COX) inhibitors for threatened miscarriage. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No.: CD011310. DOI: 10.1002/14651858.CD011310.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and safety of COX inhibitors for threatened miscarriage, compared with other treatments, placebo or no intervention.

BACKGROUND

Description of the condition

Threatened miscarriage is defined as vaginal bleeding during the first 20 weeks' gestation, with or without lower abdominal pain and cramps, while the cervix is still closed and the fetus is also viable (Cunningham 2001). Vaginal bleeding during early gestation is a very common complication in the first trimester of pregnancy, occurring in up to 30% of all clinical pregnancies (Weiss 2004; Wijesiriwardana 2006). The incidence of miscarriage after detection of fetal activity is between 3.4% (Tannirandorn 2003) and 26.7% (Das 1996; Dede 2010).

Progression to miscarriage is a major outcome of threatened miscarriage (Calleja-Agius 2011; Herbert 2009). Miscarriage or spontaneous abortion is defined as "the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestational age or, if gestational age is unknown, the loss of an embryo/fetus of less than 400 g" (Zegers-Hochschild 2009). Some clinical investigations have reported the incidence of miscarriage to be between 2.3% (Wilson 1986) and 26.6% (Basama 2004; Dede 2010).

The rate of miscarriage incidence has been associated with genetic factors, immunological dysfunction, other maternal factors, and environmental factors. Genetic factors relate to mothers or fathers (Suzumori 2010), and include chromosomal abnormalities (Ogasawara 2000), antiphospholipid antibodies (Chauleur 2010), and congenital uterine abnormalities (Ekici 2013). Immunological factors include lower serum progesterone concentrations (below or equal to 12 ng/mL) (Arck 2008), maternal endocrine abnormalities or disorders such as uncontrolled diabetes (Dunne 2003) and polycystic ovary syndrome (Boomsma 2008), lower titres of thyroid autoimmunity (Kaprara 2008), and thrombophilic disorders (Sucak 2010). Maternal factors include maternal age over 33 years (Arck 2008), paternal age over 40 years (Kleinhaus 2006), previous miscarriage (Basama 2004) and lower body mass index (below or equal to 20 kg/m^2 (Arck 2008); maternal diseases include diabetes mellitus (Pearson 2007), uncontrolled thyroid disorders (Negro 2011) and bacterial vaginosis (Denney 2009); and maternal so-

cial habits include alcohol consumption (Chiodo 2012), smoking (Baba 2011) and use of drugs (Dingle 2008).

Not all threatened miscarriages progress to miscarriage, but increased myometrium contractility is always accompanied with threatened miscarriage and miscarriage, although whether this is as a cause or effect is unclear. Little is known about the role of prostaglandins in the pathophysiology of threatened miscarriage and miscarriage. However, prostaglandins play a major role in myometrium contraction.

If a miscarriage is avoided, threatened miscarriage is associated with increased adverse perinatal and maternal outcomes, compared with pregnant women who did not experience threatened miscarriage (Saraswat 2010). Perinatal outcomes include preterm delivery (delivery before 37 completed weeks) (Hossain 2007; Weiss 2004), and intrauterine growth restriction (IUGR) (Arafa 2000; Mulik 2004), presence of congenital malformation (Johns 2006; Wijesiriwardana 2006), and perinatal death (Mulik 2004; Wijesiriwardana 2006). Adverse maternal outcomes include increased risk of pre-eclampsia or pregnancy-induced hypertension (PIH) (Calleja-Agius 2011; Wijesiriwardana 2006), preterm prelabour rupture of membranes (PPPROM) (Johns 2006; Weiss 2004), placental praevia or abruption (Johns 2006; Mulik 2004), retained placenta (Calleja-Agius 2011), and caesarean delivery (Weiss 2004).

Threatened miscarriage is an important public health problem. Most women who have a threatened miscarriage experience depression and anxiety (Ban 2012), which may lead to serious physical and psychological morbidity among pregnant women (Lok 2007). Moreover, taking antidepressants during the first trimester of pregnancy to reduce depression and anxiety has been associated with an increased risk of miscarriage (Andrade 2008; Klieger-Grossmann 2012).

Description of the intervention

Cyclo-oxygenase (COX) is an enzyme that converts arachidonic acid to prostaglandins and is required for the production of prostaglandins (Warner 2004). Prostaglandins are well understood as the first step in prostanoid biosynthesis (Warner 2004) and play an important role in the maintenance of pregnancy and the onset of labour.

Two closely-related but distinct forms of COX isoenzymes have been identified, COX-1 and COX-2 (Smith 2001). COX-1 is responsible for serving a "house-keeping" function as a constitutive enzyme in most normal tissues (O'Neill 1993). COX-2 is induced by inflammatory process and serves a crucial role in the onset of labour (Loudon 2003).

The use of COX inhibitors has gained interest as a way to clinically manage threatened miscarriage due to its role in regulation of the onset of labour, in which COX inhibitors reduce uterine contractions (Van den Veyver 1993).

Non-steroidal anti-inflammatories (NSAIDs), which are the most commonly used non-specific COX inhibitors, are associated with several side effects including nausea, vomiting, oesophageal reflux, gastritis, and shortness of breath. Some individuals are allergic to NSAIDs. This medication is classified under pregnancy category B in the FDA Pregnancy Categories. Putative fetal effects include diminished renal blood flow with consequent oligohydramnios, and premature closure of the ductus arteriosus (Bloor 2013).

Previous research has demonstrated that COX-2 expression is up-regulated in fetal membranes and uterine tissues during onset of spontaneous labour, while at the same time, COX-1 expression remains unmodified (Doret 2002). Because COX-2 inhibitors selectively inhibit COX-2 enzymes, they do not inhibit COX-1, an enzyme that helps with the production of the protective gastrointestinal lining, and this can lead to a reduction in side effects. COX-2 inhibitors have been shown to be effective in preventing spontaneous preterm labour, decreasing maternal adverse effects, and also in reducing mortality and morbidity in preterm infants (Babay 1998).

How the intervention might work

Cyclo-oxygenase plays an important role in converting phospholipase-released arachidonic acid and producing prostaglandins through the COX pathway (Funk 2001). The role of this pathway in ovulatory processes is well known (Scherle 2000). Arachidonic acid induces COX expression during implantation and decidualisation of the embryo (Zhao 2012), while prostaglandins are essential for the maintenance of labour (Warner 2004). The effect of prostaglandin receptors on tissue targets may cause vasodilatation of vascular smooth muscle and actively contribute to myometrial relaxation (Woodcock 2006). There is some evidence supporting the use of COX inhibitors: first, COX-2 is associated with myometrial contractility (Bartlett 1999); and second, specific expression of prostaglandin receptors regulates uterine activation through specific relaxing effects on myometrium (Hilton 2010; Myatt 2004).

Cyclo-oxygenase (prostaglandin synthase) is critical in labour, and COX inhibitors are effective in the treatment of preterm labour by decreasing prostaglandin production (Khanprakob 2012). The hypothesis is that COX inhibitors decrease the intensity and frequency of myometrium contractions, hence reducing the risk of miscarriage.

Why it is important to do this review

Threatened miscarriage may progress to miscarriage, which is the worst outcome of threatened miscarriage. Miscarriage can be caused by multiple pathogenesis and mechanisms, the aetiology of which is unknown in almost all cases. Various conservative and hormonal therapies for threatened miscarriage have proven lim-

ited in their effectiveness to reduce the risk of miscarriage. There is no high-quality evidence that supports the use of progesterone, human chorionic gonadotropin, Chinese herbal medicines, uterine muscle relaxant drugs, or bed rest for preventing pregnancy loss in women with threatened miscarriage. When threatened miscarriage progresses to miscarriage, the condition is always accompanied by increased uterine contractility and cervical dilatation. COX inhibitors have been shown to be effective in the treatment and prevention of preterm labour. It is therefore important to systematically review the evidence from randomised controlled trials (RCTs) to assess the effectiveness, safety and tolerability of COX inhibitors for treating threatened miscarriage.

OBJECTIVES

To assess the effectiveness and safety of COX inhibitors for threatened miscarriage, compared with other treatments, placebo or no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) that examine the effectiveness of COX inhibitors for threatened miscarriage. We will also include cluster-randomised trials, but will exclude quasi-randomised trials. Trials employing a cross-over design will not be included in the review. We will include studies published in abstract form, only if sufficient information is presented in the abstract.

Types of participants

All pregnant women who present with vaginal bleeding during the first 20 weeks' gestation, with or without lower abdominal pain, while the cervix is closed and the fetus is viable.

Types of interventions

The intervention will be COX inhibitor drugs (oral (tablets or capsules), suppositories, or intravenous injection). We will include all types of COX inhibitors, non-selective NSAIDS and selective COX-2 inhibitors. We will compare this intervention with other drugs for the treatment of threatened miscarriage, other relevant non-drug treatments, placebo or no intervention.

Types of outcome measures

We will include the following outcomes.

Primary outcomes

1. Miscarriage: We define miscarriage as spontaneous loss of a clinical pregnancy before 20 completed weeks. We will divide miscarriage into early miscarriage and late miscarriage as follows:
   - early miscarriage (miscarriage occurring before 12 weeks' gestation);
   - late miscarriage (miscarriage occurring between 12 and 20 weeks' gestation).

2. Maternal mortality.

Secondary outcomes

1. Women's outcomes

- Cardiac arrest
- Respiratory arrest
- Haemorrhage (antepartum or postpartum)
- Pain
- Depression
- Adverse effects (oedema, hyperkalaemia, hypernatraemia, hypertension)

2. Perinatal/neonatal outcomes

- Stillbirth/neonatal death
- Preterm birth
- Infant with anomaly
- Low birthweight (defined as an infant of less than 2500 g regardless of gestational age)
- Adverse effects (premature closure of fetal ductus arteriosus, oligohydramnios (renal failure)).
- Neonatal morbidity (chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, intraventricular haemorrhage)

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, 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.

Searching other resources

1. Handsearching

We will include a handsearch of miscarriage-related research journals. We will check the reference list of all studies identified by the above methods and examine the bibliographies of any systematic reviews, meta-analyses, or current guidelines. We will handsearch the following journals from first issue.

- African Journal of Health Sciences: from 2005.
- African Journal of Primary Health Care & Family Medicine: from 2009.
- African Journal of Traditional, Complementary and Alternative Medicines: from 2004.
- Clinics in Mother and Child Health: from 2010.
- Expert Review of Obstetrics & Gynecology: from 2006.
- International Journal of Health Research: from 2008
- Journal of African Law: from 1957.
- Journal of Medical Investigation and Practice: from 2000.
- Journal of Medicine and Medical Sciences: from 1999.
- Journal of Psychosomatic Obstetrics & Gynecology: from 1982.
- Obstetrics and Gynaecology Forum: from 2002.
- Open Journal of Obstetrics and Gynecology: from 2011.
- South African Journal of Obstetrics and Gynecology: from 2006.
- The Journal of Obstetrics and Gynecology of India: from 2010.

2. Personal communication

We will contact authors of significant papers and relevant policymakers based in organisations working in miscarriage-related intervention programmes, including the World Health Organization (WHO) to find other relevant published and unpublished studies.

3. Conference proceedings

We will search the following conference proceedings for relevant abstracts.

- American Congress of Obstetricians and Gynecologists (ACOG).
- Asian and Oceanic Congress of Obstetrics and Gynaecology (AOCOG).
- European Society of Human Reproduction and Embryology Annual Meeting (ESHRE).
- Japan Society of Obstetrics & Gynecology Annual Congress (JSOG).
- World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI).

4. Cross-references

We will scrutinise the bibliographies of studies identified by the procedures described above to locate additional studies. The search strategy is iterative, in that bibliographies of the included studies will be searched for additional references.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

At least two review authors (W Wariki, E Ota) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third author (R Mori).

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact the authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:

- low risk of bias (where less than 20% of the randomised population were excluded);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups;'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook*

(Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions Section* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial 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 synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Multiple trial arms

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. For dichotomous outcomes, data from different dosages of the same relevant active intervention arms will be collapsed into a single arm for comparison, or where a study involves two different relevant active intervention arms and a placebo arm, data from a placebo arm will be split equally between comparator arms. For continuous outcomes, means and standard deviations will be combined using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

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 all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either the T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Gestational age: no more than 12 weeks of gestation versus more than 12 weeks of gestation
2. Type of COX inhibitors: non-selective COX inhibitors versus COX-2 selective inhibitor
3. Route of administration of COX inhibitors: a suppository versus oral administration versus an intravenous injection

We will analyse each subgroup in relation to each of the primary outcomes.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will conduct sensitivity analysis based on a) trial quality, excluding trials with unclear/high risk of bias for allocation concealment and sequence generation, and b) published and unpublished studies. We will restrict sensitivity analysis to the review's primary outcomes.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

REFERENCES

Additional references

Andrade 2008
Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D. Use of antidepressant medications during pregnancy: a multisite study. *American Journal of Obstetrics and Gynecology* 2008;**198**(2):194.e1–5.

Arafa 2000
Arafa M, Abdel-Fataah M, Zeid HA, el-Khouly A. Outcomes of pregnancies complicated by early vaginal bleeding. *East Mediterranean Health Journal* 2000;**6**(2-3): 457–64.

Arck 2008
Arck PC, Rucke M, Rose M, Szekeres-Bartho J, Douglas AJ, Pritsch M, et al. Early risk factors for miscarriage: a prospective cohort study in pregnant women. *Reproductive Biomedicine Online* 2008;**17**(1):101–13.

Baba 2011
Baba S, Noda H, Nakayama M, Waguri M, Mitsuda N, Iso H. Risk factors of early spontaneous abortions among Japanese: a matched case-control study. *Human Reproduction* 2011;**26**(2):466–72.

Babay 1998
Babay Z, Lange IR, Amin H. Neonatal and maternal complications after administration of indomethacin for preterm labour between 24 and 30 weeks gestation. *Journal of the Society of Obstetricians and Gynaecologists of Canada* 1998;**20**(5):505–11.

Ban 2012
Ban L, Tata LJ, West J, Fiaschi L, Gibson JE. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. *Plos One* 2012;**7**(8): e43462.

Bartlett 1999
Bartlett SR, Sawdy R, Mann GE. Induction of cyclooxygenase-2 expression in human myometrial smooth muscle cells by interleukin-1beta: involvement of p38 mitogen-activated protein kinase. *Journal of Physiology* 1999;**520 Pt 2**:399–406.

Basama 2004
Basama FM, Crosfill F. The outcome of pregnancies in 182 women with threatened miscarriage. *Archives of Gynecology and Obstetrics* 2004;**270**(2):86–90.

Bloor 2013
Bloor M, Paech M. Nonsteroidal anti-inflammatory drugs during pregnancy and the initiation of lactation. *Anesthesia and Analgesia* 2013;**116**(5):1063–75. [PUBMED: 23558845]

Boomsma 2008
Boomsma CM, Fauser BC, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. *Seminars in Reproductive Medicine* 2008;**26**(1):72–84.

Calleja-Agius 2011
Calleja-Agius J, Schembri-Wismayer P, Calleja N, Brincat M, Spiteri D. Obstetric outcome and cytokine levels in threatened miscarriage. *Gynecological Endocrinology* 2011; **27**(2):121–7.

Chauleur 2010
Chauleur C, Galanaud JP, Alonso S, Cochery-Nouvellon E, Balducchi JP, Mares P, et al. Observational study of pregnant women with a previous spontaneous abortion before the 10th gestation week with and without antiphospholipid antibodies. *Journal of Thrombosis and Haemostasis* 2010;**8**(4):699–706.

Chiodo 2012
Chiodo LM, Bailey BA, Sokol RJ, Janisse J, Delaney-Black V, Hannigan JH. Recognized spontaneous abortion in mid-pregnancy and patterns of pregnancy alcohol use. *Alcohol* 2012;**46**(3):261–7.

Cunningham 2001
Cunningham FG. Section IX. Reproductive success and failure. *Williams Obstetrics*. 21st Edition. New York: McGraw-Hill, 2001.

Das 1996
Das AG, Gopalan S, Dhaliwal LK. Fetal growth and perinatal outcome of pregnancies continuing after threatened abortion. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1996;**36**:135–9.

Dede 2010
Dede FS, Ulucay U, Kose MF, Dede H, Dilbaz S. Fetal loss in threatened abortion after demonstration of fetal cardiac activity in a low socioeconomic population. *Journal of Obstetrics and Gynaecology* 2010;**30**(6):622–5.

Denney 2009
Denney JM, Culhane JF. Bacterial vaginosis: a problematic infection from both a perinatal and neonatal perspective. *Seminars in Fetal & Neonatal Medicine* 2009;**14**(4):200–3.

Dingle 2008
Dingle K, Alati R, Clavarino A, Najman JM, Williams GM. Pregnancy loss and psychiatric disorders in young women: an Australian birth cohort study. *British Journal of Psychiatry* 2008;**193**(6):455–60.

Doret 2002
Doret M, Mellier G, Benchaib M, Piacenza JM, Gharib C, Pasquier JC. In vitro study of tocolytic effect of rofecoxib, a specific cyclo-oxygenase 2 inhibitor. Comparison and combination with other tocolytic agents. *BJOG :an international journal of obstetrics and gynaecology* 2002;**109**(9):983–8. [PUBMED: 12269693]

Dunne 2003
Dunne F, Brydon P, Smith K, Gee H. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. *Diabetic Medicine* 2003;**20**(9):734–8.

Ekici 2013
Ekici AB, Strissel PL, Oppelt PG, Renner SP, Brucker S, Beckmann MW, et al. HOXA10 and HOXA13 sequence variations in human female genital malformations including congenital absence of the uterus and vagina. *Gene* 2013;**518**(2):267–72.

Funk 2001
Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 2001;**294**(5548):1871–5.

Herbert 2009
Herbert D, Lucke J, Dobson A. Pregnancy losses in young Australian women: findings from the Australian Longitudinal Study on Women's Health. *Women Health Issue* 2009;**19**:21–9.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hilton 2010
Hinton AC, Grigsby PL, Pitzer BA, Brockman DE, Ittenbach RF, Hinton RB, et al. Hormonal regulation of prostaglandin E2 receptors: localization and expression in rat cervical tissue. *Reproductive Sciences* 2010;**17**(2):136–46.

Hossain 2007
Hossain R, Harris T, Lohsoonthorn V, Williams MA. Risk of preterm delivery in relation to vaginal bleeding in early pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2007;**135**(2):158–63.

Johns 2006
Johns J, Jauniaux E. Threatened miscarriage as a predictor of obstetric outcome. *Obstetrics and Gynecology* 2006;**107**(4):845–50.

Kaprara 2008
Kaprara A, Krassas GE. Thyroid autoimmunity and miscarriage. *Hormones (Athens)* 2008;**7**(4):294–302.

Khanprakob 2012
Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkamhang US. Cyclo-oxygenase (COX) inhibitors for preventing preterm labour. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD007748.pub2]

Kleinhaus 2006
Kleinhaus K, Perrin M, Friedlander Y, Paltiel O, Malaspina D, Harlap S. Paternal age and spontaneous abortion. *Obstetrics and Gynecology* 2006;**108**(2):369–77.

Klieger-Grossmann 2012
Klieger-Grossmann C, Weitzner B, Panchaud A, Pistelli A, Einarson T, Koren G, et al. Pregnancy outcomes following use of escitalopram: a prospective comparative cohort study. *Journal of Clinical Pharmacology* 2012;**52**(5):766–70.

Lok 2007
Lok IH, Neugebauer R. Psychological morbidity following miscarriage. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2007;**21**(2):229–47.

Loudon 2003
Loudon JA, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labour. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2003;**17**(5):731–44.

Mulik 2004
Mulik V, Bethel J, Bhal K. A retrospective population-based study of primigravid women on the potential effect of threatened miscarriage on obstetric outcome. *Journal of Obstetrics and Gynaecology* 2004;**24**(3):249–53.

Myatt 2004
Myatt L, Lye SJ. Expression, localization and function of prostaglandin receptors in myometrium. *Prostaglandins, Leukotrienes and Esential Fatty Acids* 2004;**70**(2):137–48.

Negro 2011
Negro R, Mestman JH. Thyroid disease in pregnancy. *Best Practice & Research: Clinical Endocrinology & Metabolism* 2011;**25**(6):927–43.

O'Neill 1993
O'Neill GP, Ford-Hutchinson AW. Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues. *FEBS Letters* 1993;**330**(2):156–60.

Ogasawara 2000
Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. *Fertility and Sterility* 2000;**73**(2):300–4.

Pearson 2007
Pearson DW, Kernaghan D, Lee R, Penney GC, Scottish Diabetes in Pregnancy Study Group. The relationship between pre-pregnancy care and early pregnancy loss, major congenital anomaly or perinatal death in type I diabetes mellitus. *BJOG: an international journal of obstetrics and gynaecology* 2007;**114**(1):104–7.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Saraswat 2010
Saraswat L, Bhattacharya S, Maheshwari A, Bhattacharya S. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. *BJOG: an international journal of obstetrics and gynaecology* 2010; **192**(4):245–57.

Scherle 2000
Scherle PA, Ma W, Lim H, Dey SK, Trzaskos JM. Regulation of cyclooxygenase-2 induction in the mouse uterus during decidualization. An event of early pregnancy. *Journal of Biological Chemistry* 2000;**275**(47):37086–92.

Smith 2001
Smith WL, Langenbach R. Why there are two cyclooxygenase isozymes. *Journal of Clinical Investigation* 2001;**107**(12):1491–5.

Sucak 2010
Sucak A, Acar K, Celen S, Danisman N, Sucak GT. Outcome of pregnancies in women with thrombophilic disorders. *Journal of Obstetrics and Gynaecology* 2010;**30**(8): 847–51.

Suzumori 2010
Suzumori N, Sugiura-Ogasawara M. Genetic factors as a cause of miscarriage. *Current Medicinal Chemistry* 2010;**17** (29):3431–7.

Tannirandorn 2003
Tannirandorn Y, Sangsawang S, Manotaya S, Uerpairojkit B, Samritpradit P, Charoenvidhya D. Fetal loss in threatened abortion after embryonic/fetal heart activity. *International Journal of Gynecology and Obstetrics* 2003;**81**:263–6.

Van den Veyver 1993
Van den Veyver IB, Moise KJ. Prostaglandin synthetase inhibitors in pregnancy. *Obstetrical & Gynecological Survey* 1993;**48**(7):493–502.

Warner 2004
Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB Journal* 2004;**18**(7):790–804.

Weiss 2004
Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. *American Journal of Obstetrics and Gynecology* 2004; **190**:745–50.

Wijesiriwardana 2006
Wijesiriwardana A, Bhattacharya S, Shetty A, Smith N, Bhattacharya S. Obstetric outcome in women with threatened miscarriage in the first trimester. *Obstetrics Gynecology* 2006;**107**:557–62.

Wilson 1986
Wilson RD, Kendrick V, Wittmann BK, McGilivray B. Spontaneous abortion and pregnancy outcome after normal first-trimester ultrasound examination. *Obstetrics and Gynecology* 1986;**67**(3):352–5.

Woodcock 2006
Woodcock NA, Taylor CW, Thornton S. Prostaglandin F2alpha increases the sensitivity of the contractile proteins to Ca2+ in human myometrium. *American Journal of Obstetrics and Gynecology* 2006;**195**(5):1404–6.

Zegers-Hochschild 2009
Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertility and Sterility* 2009;**92**(5):1520–4.

Zhao 2012
Zhao ZA, Zhang ZR, Xu X, Deng WB, Li M, Leng JY, et al. Arachidonic acid regulation of the cytosolic phospholipase A 2α/cyclooxygenase-2 pathway in mouse endometrial stromal cells. *Fertility and Sterility* 2012;**97**(5):e1–9.

* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Windy MV Wariki, Erika Ota and Rintaro Mori designed the protocol. Windy MV Wariki conceived and drafted the protocol. Rintaro Mori, Erika Ota and Yoshihito Goto commented on and supervised the protocol. All authors read and approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Ministry of Health, Labour and Welfare, Japan.

Cyclo-oxygenase (COX) inhibitors for threatenedmiscarriage (Protocol)

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