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Nonsteroidal anti-inflammatory drugs (NSAIDs) and spontaneous abortion

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Safety Review

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TGA Health Safety
Regulation

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Executive summary

This issue arose from a pre-market review of the 'Use in pregnancy' section of the Product Information (PI) document for a naproxen-containing medicine. The review identified differences between the PIs of naproxen-containing medicines in regard to information about the potential risk of miscarriage after nonsteroidal anti-inflammatory drug (NSAID) exposure in early pregnancy. This observed discrepancy prompted an evaluation to determine whether this safety issue pertained to all NSAIDs, including aspirin.

The evaluation included comparisons of Australian and international product information documents across the range of NSAIDs; a review of mandated warnings, published literature and therapeutic guidelines; and an analysis of case reports from the TGA Adverse Drug Reactions System (ADRS) database.

NSAIDs are indicated for the treatment of pain, inflammation and fever. Aspirin is also indicated for the treatment of acute coronary syndrome and for the inhibition of platelet aggregation. NSAIDs are available in a variety of doses and formulations for a range of administration routes, including oral, rectal, parenteral, and topical. They are also available in combination products. Under the Poisons Standard February 2016, NSAIDs are classified as unscheduled or schedule 2, 3, or 4 medicines, depending on dose, dosage form and pack size.

A review of Australian and international NSAID product information documents demonstrated that the risk of spontaneous abortion is inconsistently included in Australian PIs across the different non-aspirin NSAIDs. At present, the Australian PIs for only five non-aspirin NSAIDs include a statement warning of the increased risk of miscarriage. The majority of non-aspirin NSAIDs which do not include a warning in their Australian PI have a statement in at least one international product reference document. Australian product information for aspirin alone is not available which is also the situation in the US and New Zealand. Neither the EU Summary of Product Characteristics (SmPC) nor the Canadian Product Monograph for aspirin documents an increased risk of spontaneous abortion.

NSAIDs that are not scheduled as an S4 are required to have various advisory statements on their medicine labels. The following advisory statement is used for NSAIDs in relation to the risk of use in pregnancy:

'Do not use [this product/insert name of product] during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.'

This advisory statement does not address the use in women who have just conceived and are therefore unlikely to be aware that they are pregnant. This is of relevance as the data to support the increased risk of miscarriage with non-aspirin NSAID use suggests that the risk is greatest when the non-aspirin NSAID is taken at the time of conception.

Diclofenac when indicated for children, non-aspirin NSAID preparations for dermal or external use and those which are indicated exclusively for dysmenorrhoea are not required to include this statement. The latter is of concern since treatment guidelines recommend pre-emptive treatment of dysmenorrhoea with non-aspirin NSAIDs and an implantation bleed can mimic the commencement of menstruation, with the potential for women who have conceived but are not yet aware, to self-treat for dysmenorrhoea. Additionally, given the increasing consumer awareness of over-the-counter (OTC) medicine marketing strategies, consumers may realise that NSAIDs indicated exclusively for dysmenorrhoea have the same active ingredient as NSAIDs not indicated exclusively for dysmenorrhoea despite the former being labelled specifically for "period pain". Thus consumers may use non-aspirin NSAIDs that are indicated exclusively for dysmenorrhoea for other indications without being cautioned against the use whilst pregnant.

A review of the medical literature relating to NSAIDs and spontaneous abortion determined that on balance, the epidemiological data supports an association between non-aspirin NSAID use in

pregnancy and the risk of spontaneous abortion, particularly when the non-aspirin NSAID is taken close to the time of conception. The association between non-aspirin NSAID use and increased risk of miscarriage is widely accepted by professional medical organisations. Australian adverse event data was minimal for this association and provides limited support for a causal association. The association is biologically plausible and is supported by animal studies.

In regard to aspirin, there is at present insufficient evidence to support a causal association between aspirin use and an increased risk of miscarriage.

TGA recommendations

1. Harmonise the warnings in the product information for systemic and ophthalmic non-aspirin NSAIDs in regard to the increased risk of spontaneous abortion when NSAIDs are taken around the time of conception.
2. Require all OTC non-aspirin NSAIDs, including those exclusively indicated for dysmenorrhoea, to include an advisory statement on their packaging which appropriately addresses the risk of spontaneous abortion.
3. Communicate the risk to health professionals and consumers.

1 Introduction

This safety issue arose out of the evaluation of a pre-market application for a naproxen-containing combination product.ⁱ The application proposed the inclusion of a statement in the 'Use in Pregnancy' section of the product information (PI) regarding a possible increased risk of miscarriage after the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in early pregnancy. The proposed wording was:

'In humans, data from epidemiological studies suggest that there may be an increased risk of miscarriage after use of NSAIDs in early pregnancy.'

The application included clinical studies to support the inclusion of this statement. However, the innovator product for the non-aspirin NSAID did not include this information and the inconsistency prompted an investigation into whether this issue pertained to all NSAIDs and whether they required a similar warning in their PI.

2 Background

2.1 Mechanism of action

NSAIDs work by inhibiting cyclo-oxygenase (COX) which in turn inhibits prostaglandin synthesis, giving this class of drugs its analgesic, antipyretic and anti-inflammatory properties. NSAIDs can be classified as nonselective (inhibiting both COX-1 and COX-2) or selective COX-2 inhibitors (celecoxib, etoricoxib, meloxicam, and parecoxib). Aspirin is included in the NSAID class of drugs despite having a slightly different mechanism of action to non-aspirin NSAIDs. Non-aspirin NSAIDs reversibly inhibit COX, whereas aspirin's inhibition is irreversible.ⁱⁱ

This review will examine the risk of spontaneous abortion with aspirin and non-aspirin NSAIDs separately.

2.2 Dosage forms

There are 14 non-aspirin NSAID molecules on the ARTG that are registered for use in Australia. These are listed in the table below with information on available dosage forms and corresponding routes of administration.

Table 1: Dosage forms available in Australia for the investigated non-aspirin NSAIDs.

Active Ingredient	Dosage form (route of administration)
<i>Ibuprofen</i>	Tablet (oral), capsule (oral), liquid (oral), gel (topical), granules (oral)
<i>Diclofenac</i>	Tablet (oral), capsule (oral), powder (oral), suppository (rectal), spray (topical), eye drops (ophthalmic), gel (topical)
<i>Indometacin</i>	Capsule (oral), suppository (rectal), solution for aerosol pump (topical), powder for injection (intravenous)
<i>Ketoprofen</i>	Suppository (rectal), capsule (oral)

Active Ingredient	Dosage form (route of administration)
<i>Ketorolac trometamol</i>	Tablet (oral), injection (intramuscular), eye drops (ophthalmic)
<i>Mefenamic acid</i>	Capsule (oral)
<i>Naproxen</i>	Tablet (oral), oral liquid (oral)
<i>Piroxicam</i>	Tablet (oral), capsule (oral), gel (topical)
<i>Sulindac</i>	Tablet (oral)
<i>Celecoxib</i>	Capsule (oral)
<i>Etoricoxib</i>	Tablet (oral)
<i>Meloxicam</i>	Tablet (oral), capsule (oral)
<i>Parecoxib</i>	Powder for injection (intravenous, intramuscular)
<i>Flurbiprofen</i>	Eye drops (ophthalmic), lozenges (oromucosal), granules (oral), solution for throat spray (oromucosal)

2.3 Indications for use

Generally, non-aspirin NSAIDs are indicated for:ⁱⁱ

- Pain due to inflammatory arthropathies, e.g. rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, gout, ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome
- Pain, especially due to inflammation and tissue injury (e.g. dysmenorrhoea, pericarditis, bone metastases, renal colic, headache, migraine, postoperative pain)
- Fever

Indometacin¹ preparations that are intended for intravenous administration are exclusively indicated for the closure of patent ductus arteriosus in premature babies. Given the intended patient population, these products are not relevant to this review.

Aspirin irreversibly inhibits COX, reducing the synthesis of thromboxane A2 and thus inhibiting platelet aggregation for the life of the platelet.² Additionally its effects and mechanisms of action vary with dose as follows:²

- *Low doses:* irreversibly acetylate serine 530 of COX-1 which inhibits platelet generation of thromboxane A12 (i.e. antithrombotic effect)

¹ As of the 6th April 2016, the active ingredient indomethacin was renamed indometacin as part of the TGA's update of medicine ingredient names intended to align Australian medicine names with those used internationally. This review will use the new name (indometacin) unless referring to a clinical study or official document which uses the old name (indomethacin).

- *Intermediate doses:* inhibit COX-1 and COX-2, blocking prostaglandin production (analgesic and antipyretic effects)
- *High doses:* mechanism of action includes both PG-dependant and independent effects (anti-inflammatory effects)

Aspirin is indicated for the following:²

- Inhibition of platelet aggregation
- Acute coronary syndrome
- Relief of pain, inflammation and fever

2.4 Scheduling status

NSAIDs are available in a variety of doses and formulations for a range of administration routes, including oral, rectal, parenteral, and topical. Under the Poisons Standard February 2016, NSAIDs are classified as unscheduled or schedule 2, 3, or 4 medicines, depending on dose, dosage form and pack size.ⁱⁱⁱ

2.5 Specific conditions of use

This safety issue pertains to females of childbearing age who are taking NSAIDs.

2.6 Regulatory and Pharmaceutical Benefit Scheme (PBS) funding status

NSAIDs have been available for supply in Australia for many years. The first non-selective NSAIDs, which were developed in the 1960s and 1970s, were approved for marketing in Australia prior to the establishment of the ARTG in 1991. The selective COX-2 inhibitors have been approved for inclusion on the ARTG from 1999.

Data relating to PBS funding status and usage under the PBS scheme were not considered useful in the context of this evaluation as it would significantly underrepresent the usage of NSAIDs in Australia.

2.7 Related products

There are a number of related products which contain a NSAID in combination with other medication/s including codeine, phenylephrine and pseudoephedrine. Aspirin is also available in combination with clopidogrel and dipyridamole.

3 The safety concern

The safety concern is an increased risk of spontaneous abortion from taking NSAIDs during pregnancy.

The incidence of spontaneous abortion for clinically recognised pregnancies up to 20 weeks gestation is considered to be 8-20%. The incidence of subclinical pregnancy is higher, ranging from 22-26% as found in studies that assessed daily urinary human chorionic gonadotrophin levels.^{iv}

It is recognised in the literature that there is a range of risk factors for spontaneous abortion, including the use of NSAIDs around the time of conception. Other risk factors include:^v

- Advanced maternal age
- Reproductive factors:
 - Previous spontaneous abortion
 - Increasing gravidity
 - Prolonged ovulation to implantation interval
 - Prolonged time to conception
- Medications or substances:
 - Smoking
 - Moderate to high alcohol consumption
 - Cocaine
 - Caffeine
- Other factors:
 - Low folate level
 - Extremes of maternal weight
 - Fever
 - Coeliac disease

The health risks associated with spontaneous abortion include the risk of endometritis, heavy bleeding and risks associated with a general anaesthetic and surgery if a dilatation and curettage is required. Additionally there is often a period of grieving for both the woman and partner after a miscarriage.^{vi}

4 Product Information and Labelling

4.1 Product Information

Australian and international PI documents (including the Food and Drug Administration label, Canadian Product Monograph, European Summary of Product Characteristics and New Zealand Data Sheet) for NSAIDs, were reviewed to determine whether the risk of spontaneous abortion is adequately

documented.^{vii, viii, ix, x, xi, xii, xiii, xiv, xv, xvi, xvii, xviii, xix, xx, xxi, xxii, xxiii, xxiv, xxv, xxvi, xxvii, xxviii, xxix, xxx, xxxi, xxxii, xxxiii, xxxiv, xxxv, xxxvi, xxxvii, xxxviii, xxxix, xl, xli, xlii, xliii, xliv, xlv, xlvi, xlvii, xlviii, xlix, l, li, lii, liii, liv, lv, lvi, lvii, lviii, lix, lx, lxi, lxii, lxiii, lxiv, lxv, lxvi, lxvii, lxviii, lxix}

The review found that the risk of miscarriage is inconsistently included in Australian PI documents across the different non-Aspirin NSAIDs. At present, the Australian PIs for only five non-aspirin NSAIDs (ibuprofen, mefenamic acid, piroxicam, celecoxib and parecoxib) include a statement warning of the increased risk of miscarriage. The majority of non-aspirin NSAIDs which do not include a warning in their Australian PI have a statement in at least one international product reference document. In terms of the adequacy of the warnings, some PIs

include a statement regarding increased pre-implantation and post-implantation losses in animal studies without a link to the clinical effect of an increased risk of spontaneous abortion.

Australian product information for aspirin alone is not available. This situation is the same in the US and New Zealand. Neither the EU SmPC nor the Canadian Product Monograph for aspirin documents an increased risk of spontaneous abortion.^{lxx, lxxi}

Whilst many of the PIs do not specifically document the risk of spontaneous abortion they do note that the product should not be used in pregnancy unless the benefits outweigh the risks. All NSAIDs apart from celecoxib are classified under the 'Australian categorisation system for prescribing medicines in pregnancy' as category C². Celecoxib is classed as category B3³.

4.2 Required Advisory Statements for Medicine Labels (RASML)

NSAIDs that are not scheduled as an S4 are required to have various advisory statements on their medicine labels as per the *Medicines Advisory Statements Specification 2016*. The following advisory statement is used for NSAIDs in relation to the risk in pregnancy. It states:⁷²

'Do not use [this product/insert name of product] during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.'

RASML 2 came into effect on 1 January 2016 and has been consulted to identify the mandatory advisory statements for the different NSAIDs. Tables 2 and 3 summarise the requirements for non-aspirin NSAIDs and aspirin respectively in relation to the above advisory statement.^{lxxii}

Table 2: Required advisory statements relating to pregnancy for different non-aspirin NSAIDs and conditions

Non-aspirin NSAID	Conditions	Statement Required?
Flurbiprofen	In oral preparations that do NOT include indications for use in children under 12 years of age	Yes
	In oral preparations that include indications for use in children under 12 years of age	Yes
Ibuprofen	In preparations for oral use when indicated exclusively for the treatment of dysmenorrhoea	No

² Category C: Drugs which owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

³ Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Non-aspirin NSAID	Conditions	Statement Required?
	For the purpose of exclusion from the schedules to the SUSMP, when the preparation is for oral use and: <ul style="list-style-type: none"> · NOT indicated exclusively for the treatment of dysmenorrhoea; and · NOT indicated for use in children under 12 years of age 	Yes
	When included in a schedule to the SUSMP for oral use, and the preparation is: <ul style="list-style-type: none"> a. NOT indicated exclusively for the treatment of dysmenorrhoea; and NOT indicated for use in children under 12 years of age	Yes
	For the purpose of exclusion from the schedules to the SUSMP, when the preparation is for oral use and: <ul style="list-style-type: none"> b. the preparation includes indications for use in children under 12 years of age 	Yes
	When included in a schedule to the SUSMP for oral use, and: <ul style="list-style-type: none"> a. the preparation includes indications for use in children under 12 years of age 	Yes
	In preparations for dermal use	No
Diclofenac	In preparations for oral use when indicated exclusively for the treatment of dysmenorrhoea	No
	In preparations for oral use in adults and children aged 12 years and over, when NOT indicated exclusively for the treatment of dysmenorrhoea.	Yes
	In preparations indicated for oral use in children under 12 years of age	No
	When the preparation is for dermal use	No
Indomethacin	In preparations for external use	No
Ketoprofen	In preparations for oral use indicated exclusively for the treatment of dysmenorrhoea	No

Non-aspirin NSAID	Conditions	Statement Required?
	When the preparation is for oral use and: <ul style="list-style-type: none"> a. NOT indicated exclusively for the treatment of dysmenorrhoea; and b. NOT indicated for use in children under 12 years of age 	Yes
	When the preparation is for oral use and includes indications for use in children under 12 years of age	Yes
	In preparations for dermal use	No
Mefenamic acid	When indicated exclusively for the treatment of dysmenorrhoea	No
Naproxen	When indicated for oral use exclusively for the treatment of dysmenorrhoea	No
	In preparations for oral use that are: <ul style="list-style-type: none"> c. NOT indicated exclusively for the treatment of dysmenorrhoea; and d. NOT indicated for use in children under 12 years of age 	Yes
	When the preparation includes indications of oral use in children under 12 years of age	Yes

The advisory statement states not to use the product in the first 6 months of pregnancy. The data to support the increased risk of miscarriage with non-aspirin NSAID use suggests that the risk is greatest when the non-aspirin NSAID is taken at the time of conception (discussed below). At this time, it is unlikely that a woman would be aware that she is pregnant. Ideally the warning should encompass women who are planning to become pregnant, such as advisory statement 'Do not use if pregnant or likely to become pregnant'. Another option would be to alter the current statement to include those likely to be pregnant, for example, 'Do not use [this product/insert name of product] if likely to become pregnant or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.'⁷²

From the table above, diclofenac when indicated for children, non-aspirin NSAID preparations for dermal or external use and those which are indicated exclusively for dysmenorrhoea are not required to include this statement. Superficially the exclusion of this statement for products indicated exclusively for dysmenorrhoea seems reasonable as one would not expect a female who is pregnant to be self-treating for dysmenorrhoea. However, according to the Therapeutic Guidelines, NSAIDs are ideally taken 48 hours before menstruation is expected or with onset of pain.^{lxxiii} In these circumstances, it is possible that a woman planning to become pregnant, who has conceived but is not yet aware of the pregnancy, may pre-emptively take non-aspirin NSAIDs indicated exclusively for dysmenorrhoea and not be cautioned about the use during pregnancy. Alternatively, if a woman was not using these products pre-emptively, an implantation bleed could mimic the early signs of menstruation, prompting a consumer to begin non-aspirin NSAID therapy for dysmenorrhoea relief whilst pregnant.

An additional impetus to include warnings on NSAIDs indicated exclusively for dysmenorrhoea relates to increasing consumer knowledge around the marketing strategies of OTC medicines. Consumers may realise that these NSAIDs have the same active ingredient as NSAIDs not indicated exclusively for dysmenorrhoea despite the former being labelled specifically for “period pain”. Thus consumers may use non-aspirin NSAIDs that are indicated exclusively for dysmenorrhoea for other indications without being cautioned against the use in pregnancy.

Aspirin products are not required to include the pregnancy warning statement if they are indicated exclusively for dysmenorrhoea, the prevention of cardiovascular disease, or the inhibition of platelet aggregation, and in sustained release preparations containing 650mg or more of aspirin (see Table 3). Given that there is limited evidence for an association between aspirin and increased risk of spontaneous abortion, this may be appropriate.

Table 3: Required advisory statements relating to pregnancy for the different conditions of aspirin

Aspirin	Conditions	Statement Required?
Aspirin	For the purpose of exclusion from the schedules to the SUSMP when: <ul style="list-style-type: none"> e. Each dosage unit contains MORE than 100 milligrams of aspirin; and f. The preparation is NOT indicated for the prevention of cardiovascular disease or for the inhibition of platelet aggregation 	Yes
	For the purpose of exclusion from the schedules to the SUSMP when: <ul style="list-style-type: none"> g. Each dosage unit contains MORE than 100 milligrams of aspirin; and h. The preparation IS indicated for the prevention of cardiovascular disease or for the inhibition of platelet aggregation 	Yes
	For the purpose of exclusion from the schedules to the SUSMP, when: <ul style="list-style-type: none"> i. Each dosage unit contains 100 milligrams or LESS of aspirin, and: j. The preparation IS indicated for the prevention of cardiovascular disease or for inhibition of platelet aggregation. 	No

Aspirin	Conditions	Statement Required?
	<p>When included in a schedule to the SUSMP and:</p> <ul style="list-style-type: none"> k. The preparation IS indicated for the prevention of cardiovascular disease or for the inhibition of platelet aggregation; or l. In sustained release preparations containing 650 milligrams or more of aspirin. 	No
	<p>When included in a schedule to the SUSMP, and:</p> <ul style="list-style-type: none"> m. The preparation IS indicated exclusively for treatment of dysmenorrhoea; and n. NOT in sustained release preparations containing 650mg or more of aspirin; and o. NOT in combination with other therapeutically active substances (other than effervescent agents) 	No
	<p>When included in a schedule to the SUSMP and:</p> <ul style="list-style-type: none"> p. In combination with other therapeutically active substances (other than effervescent agents); and q. NOT in sustained release preparations containing 650 milligrams or more of aspirin; and r. The preparation is NOT indicated: <ul style="list-style-type: none"> i. For the prevention of cardiovascular disease or for the inhibition of platelet aggregation ii. Exclusively for treatment of dysmenorrhoea 	Yes
	<p>When included in a schedule to the SUSMP and:</p> <ul style="list-style-type: none"> s. NOT in combination with other therapeutically active substances (other than effervescent agents); and t. NOT in sustained release preparations containing 650 milligrams or more of aspirin; and u. The preparation is NOT indicated: <ul style="list-style-type: none"> i. For the prevention of cardiovascular disease or for the inhibition of platelet aggregation; or ii. Exclusively for treatment of dysmenorrhoea 	Yes

5 Literature

5.1 Literature provided with premarket application

Three studies were provided with the premarket application for the naproxen-containing medicine. These are summarised and critiqued below.

Nielsen *et al* (2001)^{lxxiv} published a Danish population based observational study and case-control study examining the risk of adverse birth outcomes in women taking non-aspirin NSAIDs during pregnancy. The observational study specifically examined the risk of congenital abnormality, low birth weight and preterm birth. The case control study examined the association between non-aspirin NSAIDs and miscarriage. The case-control study was based on data from a prescription registry, the Danish birth registry, and one county's hospital discharge registry. Cases were defined as first recorded miscarriages in women who had taken up a prescription for NSAIDs in the 12 weeks before the date of discharge from hospital after the miscarriage. NSAIDs were defined by the international anatomical therapeutical classification code M01A⁴. This classification code does not include aspirin.^{lxxv} Cases included 4268 women who had miscarriages, of whom 63 had taken NSAIDs and controls included 29,750 primiparous women who had live births. The risk estimates were calculated for various time intervals before the day of discharge after miscarriage.

The ORs for miscarriage compared with pregnancies ending in a birth, in women who took up prescriptions for NSAIDs are presented in Table 4 below. The ratio is seen to increase as the time from taking up the prescriptions to discharge from hospital decreases, perhaps reflecting confounding by indication.

⁴ This classification code includes the following medications:⁷⁵

- Butylpyrazolidines (phenylbutazone, mofebutazone, oxyphenbutazone, clofezone, kebuzone)
- Acetic acid derivatives (indometacin, sulindac, tolmetin, zomepirac, diclofenac, alclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, indometacin combinations, diclofenac combinations)
- Oxicams (piroxicam, tenoxicam, droxicam, lornoxicam, meloxicam, meloxicam combinations)
- Propionic acid derivatives (ibuprofen, naproxen, ketoprofen, fenoprofen, fenbufen, benoxaprofen, suprofen, pirofen, flurbiprofen, indoprofen, tiaprofenic acid, oxaprozin, ibuproxam, dexibuprofen, flunoxaprofen, alminoprofen, dexketoprofen, naproxinod, ibuprofen combinations, naproxen and esomeprazole, ketoprofen combinations, naproxen and misoprostol)
- Fenamates (mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid)
- Coxibs (celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib)
- Other inflammatory and antirheumatic agents, non-steroids (nabumetone, niflumic acid, azapropazone, glucosamine, benzydamine, glucosamine polysulfate, proquazone, orgotein, nimesulide, feprazone, diacerein, morniflumate, tenidap, oxaceprol, chondroitin sulfate, avocado and soyabean oil, unsaponifiables, and feprazone combinations).

Table 4: Prescription of NSAIDs among women recorded as having a miscarriage in their 1st pregnancy compared with women who had a live birth**Reproduced from p 268 of Nielsen *et al* (2001)**Table 3** Prescription of NSAIDs among women recorded as having a miscarriage in their first pregnancy compared with women who had a live birth (reference group). Figures are Nos of pregnancies*

Variable	Miscarriage (n=4268)	Live birth (n=29 750)	Adjusted odds ratio (95% CI)
Time from taking up prescriptions for NSAIDs to date of discharge after miscarriage:			
1-12 weeks	63	318	1
1 week	3	9	6.99 (2.75 to 17.74)
2-3 weeks	5	15	3.00 (1.21 to 7.44)
4-6 weeks	14	41	4.38 (2.66 to 7.20)
7-9 weeks	19	92	2.69 (1.81 to 4.00)
10-12 weeks	22	161	1.26 (0.85 to 1.87)
Maternal age:			
<25 years (reference)	1022	8 284	1
25-29 years	1509	12 424	0.99 (0.91 to 1.07)
30-34 years	1128	6 728	1.36 (1.24 to 1.49)
>35 years	609	2 314	2.13 (1.91 to 2.38)
NSAIDs not prescribed during pregnancy	4205	29 432	

NSAIDs=non-steroidal anti-inflammatory drugs.

*Only primigravidas are included in the analysis.

The comparison period used for the reference group was the first trimester.

Several limitations exist in this study including the incomplete ascertainment of miscarriage (clinically unapparent miscarriages and miscarriages that did not require hospital presentation were not included) and non-aspirin NSAID use (the study did not account for OTC use and actual use). Both of these limitations may potentially result in a non-differential misclassification bias, underestimating the strength of the association. Furthermore, gestational age at the time of miscarriage was not available. Therefore an arbitrary 12 week exposure period was chosen from the date of discharge. If the gestational age was < 12 weeks, this period may overestimate exposure in the cases group, potentially overestimating the association. Lastly, there was a lack of information on important confounders (smoking and indication of NSAID use).

Li *et al* (2003)^{lxvii} published a population based cohort study examining exposure to non-aspirin NSAIDs and aspirin during pregnancy and risk of miscarriage. The primary objective of the study was to examine prenatal exposure to magnetic fields. The authors conducted data analyses investigating NSAID use after they learnt of the reported association between NSAID use during pregnancy and miscarriage.

Women were eligible to join the study if they resided in the San Francisco area and had a positive urine pregnancy test between 1996 and 1998 through the Kaiser Permanente Medical Care Program. This Program is a healthcare delivery system whose members are representative of the underlying population in the service area. Of the 2729 eligible women, 1063 (39%) participated and completed an interview conducted soon after each woman's pregnancy was confirmed. Minimal details are provided regarding the form of the interview. During the interview women were asked about drug use since last menstruation (including paracetamol, aspirin and NSAID use), reproductive history, risk factors for miscarriage and sociodemographic characteristics. Of all the non-aspirin NSAIDs, only the use of naproxen and ibuprofen was solicited. Aspirin users were defined as those women who reported using aspirin or preparations containing aspirin.

Pregnancy outcomes up to 20 weeks gestation were ascertained by searching the Kaiser Permanente care programme inpatient and outpatient databases reviewing medical records, and contacting those participants whose outcomes could not be determined.

A Cox proportional hazard regression model allowed the authors to assess whether the effect of non-aspirin NSAID or aspirin use on the risk of miscarriage changed with gestational age. Potential confounders (not stated), known risk factors, and common socioeconomic and demographic variables were included in the model for adjustment. Seven women who reported cramping as the reason for NSAID use were excluded from the study (as cramping may have been an early sign of miscarriage). One further woman was excluded from the study due to missing data on drug use. The final analysis included 1055 women.

Of the 162 women who experienced a miscarriage, 8% (13/162) had used non-aspirin NSAIDs during the pregnancy, compared to 4.6% (40/871) who did not miscarry. For aspirin, the proportion of women who miscarried and took aspirin [3% (5/154)] was closer to the proportion of women who did not miscarry and took aspirin [2% (17/848)]. After adjustment for previous miscarriage, education, maternal age, gravidity, race, use of a Jacuzzi, multivitamin use, and smoking since last menstruation, the HR for NSAID use and miscarriage was 1.8 (95% CI 1.0-3.2). The risk of miscarriage was higher when NSAIDs were taken around the time of conception [adjusted HR 5.6 (95% CI 2.3-13.7)] or were used for longer than 1 week [adjusted HR 8.1 (95% CI 2.8-23.4)] (see Table 5 below). There was weak evidence for an association between aspirin use and miscarriage [HR 1.6 (95% CI: 0.6-4.1)]. The association was stronger when aspirin was first taken at the time of conception [HR 4.3 (95% CI 1.3-14.2)], however this sample was small (n=6). Analysis by duration of use did not identify a statistically significant relationship (see Table 6 below). An additional analysis for paracetamol, which shares many of the indications for use, did not demonstrate an association, suggesting minimal confounding by indication.

Table 5: Prenatal use of NSAIDs by pregnant women and risk of miscarriage*

*Reproduced from p 3 of Li *et al* (2003)

Table 2 Prenatal use of NSAIDs by pregnant women and risk of miscarriage. Values are numbers (percentages) unless stated otherwise

NSAID use	Miscarriage		Hazard ratio (95% CI)*
	Yes (n=162)	No (n=871)	
Non-users (n=980)†	149 (15)	831 (85)	1.0
Users (n=53):	13 (25)	40 (75)	1.8 (1.0 to 3.2)
Gestational age at first use:			
At conception (n=12)‡	6 (50)	6 (50)	5.6 (2.3 to 13.7)
After conception (n=40)	7 (18)	33 (83)	1.2 (0.5 to 2.6)
Duration of use:			
≤1 week (n=47)	9 (19)	38 (81)	1.3 (0.7 to 2.6)
>1 week (n=6)	4 (67)	2 (33)	8.1 (2.8 to 23.4)

*Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables listed in table 1 did not change the results.

†Used neither NSAIDs nor aspirin.

‡At conception: within the first week of gestational age.

Table 6: Prenatal use of aspirin by pregnant women and risk of miscarriage**Reproduced from p 3 of Li *et al* (2003)**Table 3** Prenatal use of aspirin by pregnant women and risk of miscarriage. Values are numbers (percentages) unless stated otherwise

Aspirin use	Miscarriage		Hazard ratio (95% CI)*
	Yes (n=154)	No (n=848)	
Non-users (n=980)†	149 (15)	831 (85)	1.0
Users (n=22):	5 (23)	17 (77)	1.6 (0.6 to 4.1)
Gestational age at first use:			
At conception (n=6)‡	3 (50)	3 (50)	4.3 (1.3 to 14.2)
After conception (n=14)	2 (14)	12 (86)	1.1 (0.3 to 4.5)
Duration of use:			
≤1 week (n=16)	3 (19)	13 (81)	1.4 (0.4 to 4.5)
>1 week (n=5)	2 (40)	3 (60)	3.0 (0.7 to 12.9)

*Adjusted for previous miscarriage, education, maternal age, gravidity, race, use of Jacuzzi or hot tub, multivitamin use, and smoked since last menstruation. Further adjustment for other variables listed in table 1 did not change the results.

†Used neither NSAIDs nor aspirin.

‡Within the first week of gestational age.

Limitations of the study include the low response rate and that the investigation of NSAID use was a non-primary study objective. Strengths of the study include complete ascertainment of miscarriage and better ascertainment of NSAID use which included OTC use and actual use rather than dispensation. However some of the participants who reported no NSAID use at interview may have used NSAIDs after the interview (i.e. whilst still pregnant) resulting in a potential differential misclassification bias. The solicitation of only ibuprofen and naproxen use (rather than all non-aspirin NSAIDs) is likely to have underestimated exposure.

Nakhai-Pour *et al* (2011)^{lxvii} conducted a nested case-control study examining the use of non-aspirin NSAIDs during pregnancy and the risk of spontaneous abortion. Data was obtained from the Quebec Pregnancy Registry (QPR) which is linked to three administration databases, including the RAMQ database (contains information on medical services, filled prescriptions, diagnoses, and hospital admissions), and the Med-Echo database (records data on admissions to acute care hospitals for all residents of Quebec). Cases were defined as a clinically detected miscarriage occurring before 20 weeks' gestation in a first pregnancy. For inclusion, women were required to be insured by the RAMQ drug plan which accounts for 36% of pregnant women in the region.

Data was obtained from the QPR for 4705 women who had a spontaneous abortion. For each case, 10 controls were randomly selected from the remaining women in the registry matched for date of spontaneous abortion and gestational age. The study only considered non-aspirin NSAIDs that were reimbursed by the RAMQ drug plan during the study period. NSAID use and non-use were compared. Analyses also examined different types and dosages of non-aspirin NSAIDs.

Various confounding factors were accounted for in the analysis including sociodemographic characteristics, comorbidities in the year prior to pregnancy, use of medications suspected of increasing the risk of spontaneous abortion, use of NSAIDs before pregnancy, use of health services in the year before pregnancy, and history of planned or spontaneous abortion.

Table 7: Association between the use and the percent maximum daily doses of different non-aspirin NSAIDs and risk of having a spontaneous abortion**Reproduced from p 3 of Nakhai-Pour *et al* (2011)

Table 2: Association between the use and the percent maximum daily doses of different nonaspirin NSAIDs and risk of having a spontaneous abortion				
Variable	Controls n = 47 050	Cases n = 4 705	OR (95% CI)	
			Crude	Adjusted*
Type of NSAID				
None	45 837 (97.4)	4 353 (92.5)	1.00	1.00
Naproxen	435 (0.9)	133 (2.8)	3.22 (2.65–3.92)	2.64 (2.13–3.28)
Ibuprofen	258 (0.6)	61 (1.3)	2.49 (1.88–3.30)	2.19 (1.61–2.96)
Rofecoxib	152 (0.3)	39 (0.8)	2.70 (1.90–3.85)	1.83 (1.24–2.70)
Diclofenac	82 (0.2)	31 (0.7)	3.99 (2.63–6.03)	3.09 (1.96–4.87)
Celocoxib	111 (0.2)	30 (0.6)	2.85 (1.90–4.27)	2.21 (1.42–3.45)
Other	57 (0.1)	32 (0.7)	2.86 (1.93–4.23)	2.65 (1.71–4.12)
Combination	118 (0.2)	26 (0.6)	4.80 (3.02–7.65)	2.64 (1.59–4.39)
Maximum daily dose, %				
None	45 837 (97.4)	4 353 (93.0)	1.00	1.00
1–50	228 (0.5)	59 (1.3)	2.73 (2.05–3.64)	2.61 (1.90–3.59)
51–65	259 (0.6)	56 (1.2)	2.28 (1.70–3.05)	1.90 (1.39–2.61)
66–80	365 (0.8)	120 (2.6)	3.47 (2.81–4.27)	2.55 (2.03–3.21)
≥ 81	304 (0.6)	91 (1.9)	3.16 (2.49–4.00)	2.55 (1.96–3.32)
Unknown	57 (0.1)	26 (0.6)		

Note: CI = confidence interval, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio.
*Odds ratios were adjusted for confounders listed in Methods.

There were 67,160 pregnant women who met the inclusion criteria of which 4705 had a spontaneous abortion and to whom 47,050 controls were matched. Of the women with a spontaneous abortion, 7.5% (352/4705) had filled at least one prescription for non-aspirin NSAIDs during pregnancy compared to 2.6% (1213/47,050) of women who did not have a spontaneous abortion ($p < 0.05$). The use of non-aspirin NSAIDs during pregnancy was significantly associated with a 2.4 fold increase in the risk of spontaneous abortion (adjusted OR 2.43, 95% CI 2.12-2.79). The increased risk was consistent across all types of non-aspirin NSAIDs with the higher risk seen with diclofenac use (see Table 7). No dose-response relationship was seen.

Limitations of the study include incomplete ascertainment of non-aspirin NSAID use (data on OTC use and actual use not included) and miscarriage (only clinically apparent miscarriages were included). Information on important confounding factors (indication for use and smoking) was not available. Strengths of the study include a large sample size, use of prospectively recorded information from databases rather than patient recall, and information on gestational age.

5.2 Literature search

5.2.1 Non-aspirin NSAIDs

A brief literature search for non-aspirin NSAIDs and risk of spontaneous abortion identified two additional articles; a retrospective cohort study by Daniel *et al* (2014)^{iv} and a published letter discussing the analysis of a recent update to the dataset from the original 2001 study by Nielsen *et al*⁷⁸. The search also identified several professional sources/guidelines that referred to the

association between NSAID use in pregnancy and increased risk of miscarriage. These are discussed below.

Daniel *et al* (2014)^{iv} published a retrospective cohort study examining the risk of spontaneous abortion after foetal exposure to non-aspirin NSAIDs. The study included all women aged between 15-45 years registered with Clalit Health Services whose pregnancy was conceived between January 2003 and December 2009 and who were admitted for delivery or spontaneous abortion at Soroka Medical Centre, Israel. Approximately 70% of all women in the southern district of Israel are insured by Clalit Health Services. Soroka Medical Centre is the tertiary hospital in the region.

A computerised database of medication dispensation was linked with computerised databases containing information on births and spontaneous abortions (as per hospital records). Time-varying Cox regression models were constructed and adjusted for maternal age, diabetes mellitus, hypothyroidism, obesity, hypercoagulation or inflammatory conditions, recurrent miscarriage, in vitro fertilisation of the current pregnancy, intrauterine contraceptive devices, ethnic background, tobacco use and year of admission. Two main exposure groups were defined according to the category of non-aspirin NSAIDs used: non-selective COX inhibitors (ibuprofen, diclofenac, naproxen, etodolac, indomethacin, lornoxicam, or nabumetone) or COX-2 selective inhibitors (celecoxib, etoricoxib, or rofecoxib).

There were 66,547 women who conceived between Jan 2003 and Dec 2009 and were admitted to Soroka Medical Centre; 58,949 (88.5%) were admitted for delivery and 7598 (11.4%) due to spontaneous abortion. Of the women with spontaneous abortion, data regarding gestational age was not available for 1090 (14.3%) women and these cases were not included.

The unadjusted and adjusted hazard ratios for spontaneous abortion following exposure to non-aspirin NSAIDs are summarised in Table 8 below. There was a statistically significant association with exposure to non-selective COX inhibitors (crude HR 1.13, 95% CI 1.01-1.25), however when the data was adjusted this association became non-significant (adjusted HR 1.10, 95% CI 0.99-1.22). A similar pattern occurred for selective COX-2 inhibitors however the point estimate and upper limit of the 95% CI was higher (crude HR 1.97, 95% CI 1.12-3.47; adjusted HR 1.43, 95% CI 0.79-2.59). The exposure group was also much smaller (n=71).

A significant association was observed between first trimester exposure to indomethacin and spontaneous abortion. This association was postulated to be secondary to reverse causation bias due to use of indomethacin as a tocolytic agent in preterm labour. This hypothesis is supported by the later median gestational age at exposure (89 days) and an additional analysis that found no association after omission of exposures that occurred during the 4 days before spontaneous abortion.

A dose-response effect was not observed.

Table 8: Risk of spontaneous abortion following exposure to non-aspirin NSAIDs**Reproduced from p 187 of Daniel *et al* (2014)

Exposure	No. of participants	No. of abortions	Median gestational age at exposure, d	Spontaneous abortion hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Not exposed	60 962	6 132			
Nonselective COX inhibitors	4 424	373	31	1.13 (1.01–1.25)	1.10 (0.99–1.22)
Ibuprofen	2 732	215	40	1.13 (0.98–1.30)	1.06 (0.93–1.22)
Diclofenac	919	93	23	1.21 (0.98–1.48)	1.19 (0.97–1.46)
Naproxen	671	53	27	1.87 (0.66–1.17)	0.97 (0.74–1.28)
Etodolac	272	4	20.5	1.26 (0.88–1.80)	1.28 (0.91–1.79)
Indomethacin	132	15	89	3.54 (2.20–5.71)	2.82 (1.70–4.69)
COX-2 selective inhibitors	71	11	25	1.97 (1.12–3.47)	1.43 (0.79–2.59)

Note: CI = confidence interval, COX = cyclooxygenase.
*Adjusted for maternal age, hypothyroidism, diabetes mellitus, obesity, hypercoagulation state, uterine disorders, presence of an intrauterine contraceptive device, history of recurrent abortion, in vitro fertilization used to conceive the current pregnancy, inflammatory diseases and ethnic group (Bedouin v. Jewish).

The limitations of the study include retrospective design, incomplete ascertainment of miscarriage and exclusion of women without data on gestational age. Ascertainment of non-aspirin NSAID use was better compared to previous studies as the databases captured OTC NSAID dispensation at affiliated pharmacies. However the databases did not capture dispensation at private pharmacies and there was no information on compliance. Strengths of the study include the large sample size, and the use of database data (rather than patient recall). Overall this study did not find an association between spontaneous abortion and non-selective NSAID exposure (apart from indomethacin). The findings are inconclusive for COX-2 selective inhibitors, likely due to the small exposure group for these NSAIDs.

Nielsen *et al* (2004)^{lxxviii} published a letter discussing the analysis of a recent update to the dataset from the original 2001 study. The update covered the period 1998-2002 and included data on gestational age (which was not originally accessible). Sampling on the specific gestational age substantially reduced the strength of the previously reported association between use of non-aspirin NSAIDs and risk of miscarriage however the association remained consistently positive in all analysed time periods with a trend towards stronger association for the periods closer to the miscarriage. The results from the re-analysis were not provided in the letter.

Summary of study findings

Overall the data for the association between non-aspirin NSAID use in pregnancy and spontaneous abortion is observational in nature and inconsistent. There are several limitations of the studies presented including incomplete ascertainment of non-aspirin NSAID use and miscarriage. However on balance the data does suggest an association between non-aspirin NSAID use and spontaneous abortion, particularly when the NSAID is taken close to the time of conception.

The evidence also suggests that the observed results are consistent with a class effect. This is supported by a consistently increased risk seen with a number of non-aspirin NSAIDs including naproxen, ibuprofen, diclofenac, celecoxib, and etoricoxib.^{76,77}

Overall a dose-response effect was not supported by the evidence reviewed.^{4,76,77} Studies by Nakhai-Pour *et al* (2011) and Daniel *et al* (2014) did not observe a dose-response effect whilst Li *et al* (2003) suggested a dose-response may be present.^{4,76,77} Nakhai-Pour *et al* (2011) assessed dose-response by measuring the percent maximum daily dose of NSAIDs that women took between the start of pregnancy and the index date.⁷⁷ These doses were subdivided into four categories (1%-50%, 51-65%, 66-80% and > 81%), allowing for the different maximum doses of the different non-aspirin NSAIDs.⁷⁷ Whilst Nakhai-Pour *et al* (2011) only assessed prescription

non-aspirin NSAID use, the dose-response analysis method used in this study is relevant to OTC use as maximum doses are for a specific NSAID and are irrespective of scheduling status.⁷⁷ Daniel *et al* (2014) included prescription and OTC use and assessed dose-response by the number of daily doses, assuming the average maintenance dose per day for a drug.⁴ Li *et al* (2003) suggest that a dose-response effect may be present but this assumption was based on the observation that patients who took NSAIDs for more than one week were at an increased risk of abortion.⁷⁶ Thus, this finding may be more reflective of duration of use or timing rather than dosage per se.

On balance the evidence suggests that the increased risk of spontaneous abortion is a NSAID class effect which is not dose-dependent but may be dependent on duration of use and/or timing and is relevant to prescription and OTC non-aspirin NSAID formulations.

5.2.2 Published guidelines

Australian Medicines Handbook (AMH)

The AMH notes an increased risk of miscarriage with NSAIDs:ⁱⁱ

'Some studies link NSAID use during pregnancy with an increased rate of miscarriage. Risk appears highest when NSAIDs are taken around the time of conception.'

An AMH Senior Editor indicated that the references for these statements were Li *et al* (2003)⁷⁶, Nielsen *et al* (2001)⁷⁴ and Daniel *et al* (2014)^{iv}. Whilst the AMH classifies aspirin as an NSAID, this warning is not included in the AMH aspirin monograph and is included in the monograph for each of the non-aspirin NSAIDs that are the subject of this assessment.²

Therapeutic Guidelines

The Therapeutic Guidelines also discusses an increased risk of miscarriage with NSAIDs:^{lxxix}

'Data have suggested a 5- to 7-fold increased risk of miscarriage in women taking NSAIDs around the time of conception.'

'However, once pregnancy is established, or if pregnancy occurs despite their use, they can be continued into the second trimester (up to 32 weeks) as there are no data suggesting increased fetal malformations.'

References are not provided for these statements. Aspirin is referred to as an NSAID in the Therapeutic Guidelines.

Australian Rheumatology Association

A patient information sheet on NSAIDs can be found on the Australian Rheumatology Association's website. In relation to the risk of miscarriage, the information sheet states the following:^{lxxx}

'NSAIDs are not recommended during pregnancy or during breastfeeding unless specifically advised by your doctor. If you are planning a family or you become pregnant you should discuss this with your doctor as soon as possible.'

'Some studies suggest that if NSAIDs are taken around the time of conception there may be an increased risk of miscarriage.'

This information sheet refers to aspirin and 'NSAIDs' as separate products.

Australian Prescriber

An article titled ‘Analgesics and pain relief in pregnancy and breastfeeding’, published in 2011 summarised the findings from studies by Li *et al* (2003) and Nielsen *et al* (2001). The article also noted a possible mechanism for miscarriage risk as interference with implantation due to effects on the prostaglandin pathway.^{lxxxix}

This article refers to aspirin and ‘NSAIDs’ separately but does explain that aspirin was included in the study by Li *et al* (2003) which found an increased risk of spontaneous abortion with aspirin use.⁷⁶

Overall the association between the use of NSAIDs in early pregnancy and the increased risk of spontaneous abortion is acknowledged by several professional medical groups.

5.2.3 Aspirin

A brief literature search only identified one additional study that examined the risk of miscarriage with aspirin. This study is discussed below. Further to this, several placebo-controlled randomised trials were identified that investigated whether low-dose daily aspirin (with or without low molecular weight heparin) has a protective effect on the risk of miscarriage in women with anti-phospholipid syndrome and women with recurrent miscarriages of unknown cause. At present there is inadequate evidence to support aspirin as an effective therapy for these women.^{lxxxii,lxxxiii,lxxxiv}

Keim and Klebanoff (2006)^{lxxxv} conducted a case-control study to evaluate the association between aspirin use and miscarriage. Data was from the Collaborative Perinatal project which was a cohort study of approximately 54,000 women and their offspring from twelve centres in the United States between 1959 and 1965. Women were enrolled at their 1st prenatal visit with follow-up through to the remainder of the pregnancy.

Exposure was assessed by in-patient interviews at the woman’s first clinic visit and subsequent clinic visits. Exposure was also determined through medical chart review. Products containing aspirin alone or in combination with other medications were included. Non-aspirin NSAIDs were not included in the analysis because they were not commonly available at the time of the study. Dates of drug use were converted to lunar⁵ months of pregnancy. Dosages were not recorded.

Of the 830 women in the cohort study who had experienced a foetal loss, 704 were included in a previous case-control study examining caffeine metabolites and the risk of spontaneous abortion. This study used 2816 matched controls that gave birth to a live-born infant of at least 28 weeks’ gestation. The controls were matched by study site and day of gestation at clinic visit. Only 542 cases and 2587 matched controls from the original study were used in the current study for the following reasons:

- 46 cases were determined to be ectopic pregnancies, maternal deaths, iatrogenic terminations, or induced abortion rather than spontaneous abortions
- Medication use information was not available for 6 controls and 62 cases
- 7 controls and 54 cases delivered or miscarried prior to their first interview
- 216 matched controls were excluded to account for the 162 matched cases that were excluded (for the above reasons).

Time intervals of interest included the lunar month prior to the LNMP and the 1st, 2nd, 3rd and 4th lunar months of pregnancy (in isolation and in combination). Adjusted odds ratios were

⁵ A lunar month in pregnancy is 28 days long. There are 10 lunar months in a pregnancy. The 1st day of the 1st lunar month begins on the first day of the woman’s last normal menstrual period.

calculated from a conditional logistic regression that accounted for maternal age, smoking, education, and race. These factors were determined *a priori*. Aspirin use during the month of miscarriage was not included in the analysis to account for potential confounding by indication and because the pregnancy may not have lasted the whole month (thus shortening the time during which aspirin might have been taken).

Cases were more likely to be older, to be smokers, and have fewer years of education compared to controls. Black women were more likely to be aspirin users compared to white women. The average length of gestation at time of miscarriage was 100 days (14 weeks). A higher proportion of miscarriages occurred in the 4th lunar month (n=224), followed by the 5th (n=184), 3rd (n=130), and lastly the 2nd lunar month (n=4). There was no difference in age, smoking status or education between aspirin users and non-users. More controls (34%, n=159) reported aspirin use at least once from the 1st lunar month of pregnancy to the lunar month before the month of miscarriage compared to cases (29%, n=876).

There was evidence of a protective effect from aspirin on risk of miscarriage in most lunar month and combination analyses (see Table 9 below). Point estimates of the adjusted odds ratios were similar to the corresponding stratum-adjusted OR however most included the null value in their 95% confidence intervals. When aspirin use in the lunar month prior to LNMP was included, a similar result was found (OR 0.72, 95% CI 0.49-1.05). However a regression model examining aspirin use only in the lunar month prior to LNMP produced different results (OR 1.43, 95% CI 0.58-3.59). Only 1% of women reported taking aspirin exclusively at this time. No substantial differences were noted between those cases that were excluded for missing data and those that were included.

Limitations of the study include the exclusion of 23% of cases, lack of an objective measure of exposure, potential incomplete ascertainment of early miscarriages (due to later presentation at first clinic visit at the time of the study), and no information on aspirin dosages or indication for use. Strengths of the study include matched controls, prospectively collected exposure data, and less concern over drug exposure during pregnancy at the time of the study, thus reducing the potential for bias when reporting drug use. Overall this study does not provide evidence to support an association between aspirin use and an increased risk of miscarriage.

Table 9: Association of aspirin use by lunar month with miscarriage*

*Reproduced from p 437 of Keim and Klebanoff (2006)

	Cases No. (%)	Controls No. (%)	Stratum-Adjusted OR (95% CI)	Adjusted OR [†] (95% CI)
Anytime during pregnancy [‡]				
No aspirin	383 (71)	1711 (66)		
Aspirin	159 (29)	876 (34)	0.75 (0.61–0.93)	0.79 (0.62–1.01)
First month				
No aspirin	462 (85)	2120 (82)		
Aspirin	80 (15)	467 (18)	0.74 (0.57–0.97)	0.82 (0.61–1.09)
Second month				
No aspirin	447 (83)	2036 (80)		
Aspirin	91 (17)	519 (20)	0.75 (0.58–0.97)	0.78 (0.59–1.03)
Third month				
No aspirin	308 (75)	1373 (71)		
Aspirin	100 (25)	558 (29)	0.75 (0.58–0.97)	0.73 (0.54–0.97)
Fourth month				
No aspirin	127 (69)	566 (67)		
Aspirin	57 (31)	280 (33)	0.91 (0.64–1.29)	0.92 (0.61–1.38)
First, second, and third month				
No aspirin	293 (85)	1294 (81)		
Aspirin	51 (15)	296 (19)	0.70 (0.49–0.98)	0.70 (0.48–1.02)
First, second, third, and fourth month				
No aspirin	116 (85)	482 (81)		
Aspirin	21 (15)	112 (19)	0.73 (0.42–1.27)	0.64 (0.34–1.22)

*Because of concordance of aspirin use across lunar months, the same women may have been exposed in multiple lunar months.
[†]Adjusted for age, smoking, education, and race.
[‡]Up to the month before miscarriage for cases and equivalent month for matched controls.

6 Adverse Drug Reaction System (ADRS) data

As of 21 January 2016, the TGA had received 3 reports for non-aspirin NSAIDs and spontaneous abortion. Of these, 2 were for ibuprofen and 1 was for naproxen.^{lxxxvi} These cases are summarised in the table below.

Table 10: ADR case details for non-aspirin NSAIDs and spontaneous abortion

Case number	Report entry date	Age (years)	Gender	Medicines reported as being taken	MedDRA reaction terms
189372	11/08/2003	31	Female	Nurofen (Ibuprofen) - Suspected Lyclear (Permethrin) - Suspected	Abortion spontaneous
217903	02/05/2006	-	Female	Advil (Ibuprofen) - Suspected	Abortion spontaneous
281764	20/04/2011	-	Female	Proxen SR (Naproxen) - Suspected	Abortion spontaneous

Important information is missing from these cases including medical history, reproductive history and indication for use which may be confounding factors. Consequently, these three cases provide limited support for a causal association.

As of 21 January 2016, the TGA had received two reports of aspirin and spontaneous abortion.^{6,86} These cases are summarised in the table below.

Table 11: ADR case details for aspirin and spontaneous abortion

Case number	Report entry date	Age (years)	Gender	Medicines reported as being taken	MedDRA reaction terms
227671	18/04/2007	-	Female	Not specified (Aspirin) - Suspected Folic acid - not suspected	Abortion spontaneous
234558	18/10/2007	-	Female	Not specified (Aspirin) - Suspected	Abortion spontaneous

⁶ Preferred terms used: 'abortion spontaneous', 'abortion spontaneous complete', 'abortion spontaneous complete complicated', 'abortion spontaneous complicated', 'abortion spontaneous incomplete' and 'abortion spontaneous incomplete complicated'.

Information on medical history, reproductive history, concomitant medications and indication for use is not included in these reports. Since aspirin may be used to prevent miscarriage in women with anti-phospholipid syndrome or recurrent miscarriages, the association reported in these cases may be confounded by underlying conditions predisposing these women to miscarriage.

7 Discussion

On balance the epidemiological data supports an association between non-aspirin NSAID use in pregnancy and the risk of spontaneous abortion, particularly when the non-aspirin NSAID is taken close to the time of conception. The TGA ADR data is minimal for this association and provides limited support for a causal association. The association is biologically plausible as prostaglandin inhibition is thought to interfere with embryo implantation leading to abnormal implantation that predisposes an embryo to miscarriage.^{76,81} This hypothesis is supported by animal studies that examined selective COX-2 inhibitors and observed increased pre-implantation and post-implantation losses and reduced foetal survival in rats and rabbits.⁷⁶ Additionally it is postulated that non-aspirin NSAID use may impact on placental perfusion and circulation, increasing the risk of foetal demise.⁷⁶ The association between non-aspirin NSAID use and increased risk of miscarriage is widely accepted by professional medical organisations.^{ii,79,80,81}

In regard to aspirin, there is at present insufficient evidence to support a causal association between aspirin use and an increased risk of miscarriage.^{76,85,86}

In the Australian context, several NSAIDs are available over-the-counter and ibuprofen is widely available in supermarkets; consumers are able to purchase these medications with little to no verbal advice or counselling.

At present, the Australian PIs for only five non-aspirin NSAIDs (ibuprofen, mefenamic acid, piroxicam, celecoxib, and parecoxib) include a statement warning of the increased risk of miscarriage. The majority of non-aspirin NSAIDs which do not include a warning in their Australian PI have a statement in at least one international product reference document. Although product information generally states not to use non-aspirin NSAIDs in pregnancy, the increased risk of miscarriage should be specifically included in the product information for all systemic and ophthalmic preparations of non-aspirin NSAIDs, so that:

- The risk can be adequately communicated to patients, allowing a benefit-risk assessment to be made by the consumer based on their specific circumstances and individual evaluation of the risk's significance.
- The Australian product information may be harmonised across the entire class of non-aspirin NSAIDs.

Systemic preparations include formulations intended for oral, rectal or parenteral⁷ administration.^{lxxxvii} Although ophthalmic preparations are intended to be applied topically, excess drug can drain through the tear duct and be systemically absorbed via the nasal mucosa, without first pass through the liver, potentially leading to systemic adverse reactions.^{lxxxviii} Other topical preparations such as gels and spray (which are mostly OTC products) are excluded from the above recommendations as systemic absorption is considered to be significantly less.^{lxxxix} Flurbiprofen lozenges and throat sprays, intended for oromucosal administration, are OTC products (schedule 2) and are required to include the RASML cautioning against use in

⁷ Parenteral preparations include injections, intravenous infusions, powders for injections or intravenous infusions, and concentrates for injections or intravenous infusions.

pregnancy in their labelling. Indometacin products indicated exclusively for use in neonates do not require the recommended PI update.

For OTC non-aspirin NSAIDs (not for dermal or external use), it is recommended that an advisory statement that adequately addresses the risk of spontaneous abortion be mandated so that women who are using these preparations are appropriately cautioned. This recommendation includes those non-aspirin NSAIDs which are exclusively indicated for dysmenorrhoea.

Lastly, to ensure that health professionals (namely doctors and pharmacists) and consumers are aware of the risk of spontaneous abortion with the use of non-aspirin NSAIDs in early pregnancy, a risk communication activity is recommended.

This issue was referred to the Advisory Committee on the Safety of Medicines (ACSOM) for advice.

TGA recommendations

1. Harmonise the warnings in the product information for systemic and ophthalmic non-aspirin NSAIDs in regard to the increased risk of spontaneous abortion when NSAIDs are taken around the time of conception.
2. Require all OTC non-aspirin NSAIDs, including those exclusively indicated for dysmenorrhoea, to include an advisory statement on their packaging which appropriately addresses the risk of spontaneous abortion.
3. Communicate the risk to health professionals and consumers.

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