Medicines Adverse Reactions Committee

Meeting date	9/09/2021	Agenda item	3.2.2
Title	**Non-steroidal anti-inflammatory drug exposure in 2nd trimester and risk of fetal renal impairment and oligohydramnios**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient **Funded brand** **Sponsor**

Active Ingredient(s)	Medicine	Form	Strength	Class	Sponsor
Celecoxib	**Celecoxib Pfizer**	**capsule**	**100 mg** **200 mg**	P P	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
	Celostea	capsule	100 mg	P	Viatris Ltd
	Celebrex	**capsule**	**200 mg**	P	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Diclofenac	**Voltaren**	**solution for injection**	**75mg/3mL**	P	Novartis NZ Ltd
	Voltaren	**suppository**	**12.5 mg** **25 mg** **50 mg** **100 mg**	P P P P	Novartis NZ Ltd
	Voltaren Rapid 25	tablet	25 mg	RM	GlaxoSmithKline Consumer Healthcare NZ ULC
	Voltaren D	**tablet D**	**50 mg**	P	Novartis NZ Ltd
	Diclofenac Sandoz	**tablet EC**	**25 mg** **50 mg**	P P	Novartis NZ Ltd
	Medreich Diclofenac 25	tablet EC	25 mg	RM	Medreich New Zealand Ltd
	Diclofenac 25 Pharmacy Health	tablet EC	25 mg	RM	PSM Healthcare Ltd t/a API Consumer Brands
	Voltaren	tablet EC	50 mg	P	Novartis NZ Ltd
	Diclofenac 25 Dr Reddy's	tablet FC	25 mg	RM	Dr Reddy's NZ Ltd
	Apo-Diclo SR	**tablet MR**	**75 mg** **100 mg**	P	Apotex NZ Ltd
	Voltaren SR	tablet MR	75 mg 100 mg	P P	Novartis NZ Ltd
Etoricoxib	Arcoxia	Tablet FC	60 mg 90 mg 120 mg	P P P	Organon (NZ) Ltd
Ibuprofen	Fenpaed	oral suspension	100 mg/ 5mL	P	AFT Pharmaceuticals Ltd
	Ibuprofen Liquid Capsules Generic Partners	liquid filled capsule	400 mg	RM	Neo Pharma Ltd
	Ibugesic	tablet FC	200 mg	P	REX Medical Ltd

	Ibuprofen Relieve	**tablet FC**	**200 mg**	**P**	**Viatris Ltd**
	Brufen One	tablet FC	400 mg	RM	Viatris Ltd
	Brufen	tablet FC	400 mg	P	Viatris Ltd
	Nurofen 400 Double Strength	tablet FC	400 mg	RM	Reckitt Benckiser (New Zealand) Ltd
	Brufen SR	**tablet MR**	**800 mg**	**P**	**Viatris Ltd**
	Ibuprofen SR BNM	**tablet MR**	**800 mg**	**P**	**Boucher & Muir (NZ) Ltd t/a BNM Group**
Ibuprofen + paracetamol	Maxigesic IV	solution for infusion			AFT Pharmaceuticals Ltd
Ibuprofen + codeine	Neurofen Plus	tablet FC		P	Reckitt Benckiser (New Zealand) Ltd
Ketoprofen	**Oruvail SR**	**capsule MR**	**200 mg**	**P**	**Sanofi-Aventis NZ Ltd**
Ketorolac trometamol	Ketorolac Kabi	solution for injection	30 mg/mL	P	Fresenius Kabi NZ Ltd
Mefenamic acid	**Ponstan**	**capsule**	**250 mg**	**P**	**Pfizer NZ Ltd**
Meloxicam	Melorex	tablet	7.5 mg 15 mg	P P	REX Medical Ltd
	Mobic	tablet	7.5 mg	P	Boehringer Ingelheim (NZ) Ltd
Naproxen	**Naprosyn SR**	**tablet MR**	**750 mg** **1000 mg**	**P** **P**	**Clinect NZ Pty Ltd**
	Noflam	**tablet**	**250 mg** **500 mg**	**P** **P**	**Viatris Ltd**
Parecoxib sodium	Dynastat	powder for injection	40 mg	P	Pfizer NZ Ltd
	Parecoxib JPL	powder for injection (with or without diluent)	40 mg	P	Juno Pharmaceuticals NZ Ltd
	Parecoxib Neo Health	powder for injection (with or without diluent)	40 mg	P	Juno Pharmaceuticals NZ Ltd
Tenoxicam	**Tenoxicam Devatis**	**powder for injection**	**20 mg**	**P**	**Devatis Ltd**
	Tilcotil	**tablet FC**	**20 mg**	**P**	**Viatris Ltd**

D dispersible; EC enteric coated; MR modified release; P Prescription Medicine; RM Restricted Medicine

PHARMAC funding	Shown in bold type above
Previous MARC meetings	170th Meeting (June 2017): NSAIDs and spontaneous abortion 107th Meeting (September 2001): NSAIDs in pregnancy and neonates
International action	The US FDA, Health Canada [redacted] have requested updates to the product information for NSAID medicine to include information on the risk of fetal renal impairment and oligohydramnios with exposure in the second trimester of

	pregnancy. The FDA and Health Canada have issued safety communications about the product information changes.
Prescriber Update	none
Classification	Ranges from general sales (eg, ibuprofen) to prescription
Usage data	Widespread use
Advice sought	**The Committee is asked to advise:** • Whether the information in section *4.6 Fertility, pregnancy and lactation* of the data sheet for all NSAID medicines should be aligned to state that use of the medicine from about 20 weeks gestation may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment • Whether all NSAID medicines should be contraindicated in the third trimester of pregnancy • Whether communication in addition to MARC's Remarks is needed to inform prescribers and consumers about the risk of fetal renal impairment associated with NSAID exposure in pregnancy.

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1 PURPOSE

The purpose of this report is to examine the evidence for an association between non-steroidal anti-inflammatory drug (NSAID) use in the second half of pregnancy and fetal renal dysfunction, leading to oligohydramnios. The New Zealand data sheets for NSAIDs are reviewed to assess whether the information about use in the second and third trimesters reflects the current evidence on this issue.

2 BACKGROUND

2.1 Risk of oligohydramnios following maternal use of NSAIDs at around 20 weeks or later in pregnancy.

On 15 October 2020, the US FDA issued a Drug Safety Communication warning that the use of NSAIDs at around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby, leading to oligohydramnios (low levels of amniotic fluid) and related pregnancy complications [1], (Annex 1). The advice was based on the findings of a literature review and cases reported to the FDA Adverse Event Reporting System (FAERS) database.

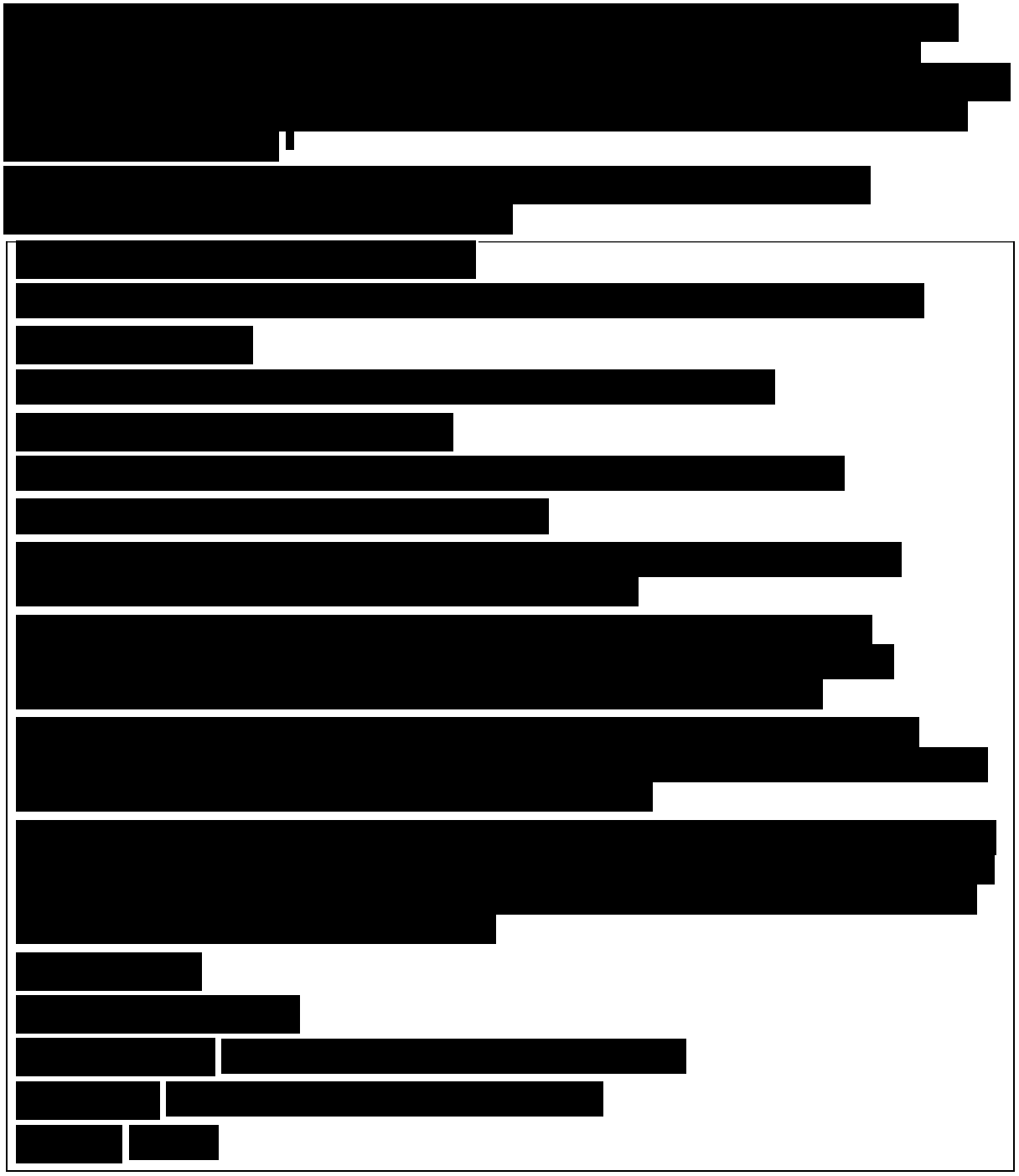
The FDA required the NSAID product labels (prescribing information) to be updated with information about the risk of oligohydramnios and advice to avoid NSAID use in pregnant women from 20 weeks of pregnancy. Prior to the update, the US product labels for NSAIDs recommended that these medicines should not be used from 30 weeks of pregnancy due to the risk of premature closure of the fetal ductus arteriosus.

The FDA issued the following advice to Health Care Professionals:

- *FDA is warning that use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.*
- *These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.*
- *Oligohydramnios is often, but not always, reversible with treatment discontinuation.*
- *Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.*
- *If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. As currently described in the NSAID labels, avoid prescribing NSAIDs at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus.*
- *The above recommendations do not apply to low-dose 81 mg aspirin prescribed for certain conditions in pregnancy.*
- *Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice.*

Health Canada subsequently undertook a safety review of NSAID use in pregnancy [2]. In June 2021, Health Canada issued a safety alert warning that use of NSAIDs beyond 20 weeks of pregnancy may cause serious kidney problems in an unborn baby that can lead to low levels of amniotic fluid and associated pregnancy complications. Health Canada advised women not to use NSAIDs from approximately 20-28 weeks of pregnancy, unless advised to do so by their healthcare professional, and that use of these medicines beyond 28 weeks of pregnancy remains contraindicated. [3]

[redacted]



2.2 Non-steroidal anti-inflammatory drugs and renal function

NSAIDs exhibit their anti-inflammatory effect through inhibition of cyclo-oxygenase (COX), the rate-limiting enzyme in the biosynthesis of prostaglandins from arachidonic acid [4]. (Figure 1)

Oxygenation of arachadonic acid by COX produces prostaglandin H2 (PGH2), which is metabolised by secondary enzymes to bioactive prostanoids – primarily PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane

A_2 (TXA_2). By blocking COX enzymes, NSAIDs inhibit (to varying degrees) the synthesis, and therefore the effects, of prostaglandins, prostacyclin, and thromboxane A_2 [4]

Prostaglandins are found in most mammalian cells and tissues and can promote both the initiation and resolution of inflammation, depending on local concentrations, disease setting, and timing of action [5].

In the kidneys, prostaglandins act as local mediators that regulate a variety of renal functions, such as sodium and water homeostasis [6].

Prostaglandins synthesised by the fetal kidney have a major role in the maintenance of adequate renal perfusion. Inhibition of prostaglandin synthesis by NSAIDs can lead to vasoconstriction resulting in a reduction of renal blood flow, glomerular filtration rate and urine volume. From around 20 weeks gestation, fetal urine output is a significant contributor to amniotic fluid volume. Impaired renal function may therefore lead to oligohydramnios. Pre-natal exposure to NSAIDs can also lead to renal dysfunction in the neonate.

Figure 1. Production and actions of prostaglandins and thromboxane [4]

[redacted]

2.3 Oligohydramnios

The term oligohydramnios is used to describe a lower-than-expected volume of amniotic fluid for gestational age. It may be idiopathic (ie, no identified cause) or due to maternal, fetal or placental causes (Box 2).

Box 2. Causes of oligohydramnios

Maternal

- Medical or obstetric conditions associated with uteroplacental insufficiency (eg, preeclampsia, chronic hypertension, collagen vascular disease, nephropathy, thrombophilia)
- Medications (eg, angiotensin converting enzyme inhibitors, prostaglandin synthetase inhibitors, trastuzumab)

Placental

- Abruption
- Twin to twin transfusion (ie, twin polyhydramnios-oligohydramnios sequence)
- Placental thrombosis or infarction

Fetal

- Chromosomal abnormalities
- Congenital abnormalities, especially those associated with impaired urine production
- Growth restriction
- Demise
- Post-term pregnancy
- Ruptured fetal membranes
- Infection

Idiopathic

Source: *UpToDate* [7]

The fetal prognosis depends on several factors including the underlying cause, the severity (reduced *versus* no amniotic fluid), and the gestational age at which oligohydramnios occurs. Because an adequate volume of amniotic fluid is critical to normal fetal movement and lung development, and for cushioning the fetus and umbilical cord from uterine compression, pregnancies complicated by oligohydramnios from any cause are at risk of fetal deformity, pulmonary hypoplasia, and umbilical cord compression.

Oligohydramnios is associated with an increased risk of fetal or neonatal death, which may be related to the underlying cause of the reduced amniotic fluid volume or due to sequelae of the reduced amniotic fluid volume.

By the beginning of the second trimester, fetal urine begins to enter the amniotic sac, and the fetus begins to swallow amniotic fluid. Therefore, disorders related to the fetal renal/urinary system begin to play a prominent role in the aetiology of oligohydramnios.

2.4 New Zealand data sheets

2.4.1 Prescription and Pharmacist-Only (Restricted) medicines

2.4.1.1 Section 4.6 Fertility, pregnancy and lactation

The information about the risk of fetal renal impairment and oligohydramnios in the New Zealand data sheets for NSAIDs is inconsistent. The relevant information from the data sheets for approved prescription or pharmacist-only (restricted) NSAIDs is detailed in Annex 2 and summarised below in Table 1.

Table 1. NSAID data sheet information (as at 1 September 2021) about risk of fetal renal impairment and oligohydramnios

Information in section 4.6 of the data sheet	**Celecoxib**	**Parecoxib**	**Etoricoxib**	**Naproxen** (Naprosyn)	**Naproxen** (Noflam)	**Ibuprofen** (except Ibugesic)	**Ibuprofen** (Ibugesic)	**Diclofenac**	**Ketoprofen**	**Meloxicam**	**Tenoxicam**	**Ketorolac**	**Mefenamic acid**
Use in the second or third trimester or pregnancy may cause fetal renal dysfunction/oligohydramnios	✓	✓											✓
Use from 20 weeks gestation or later may cause renal dysfunction/oligohydramnios			✓	✓									
Should not be used in first two trimesters of pregnancy unless potential benefit to mother outweighs risk to fetus/clearly necessary					✓	✓		✓	✓				
Use in third trimester may cause renal dysfunction, which may progress to renal failure with oligohydramnios						✓			✓	✓	✓		
Use in latter part of pregnancy may cause … fetal renal impairment							✓	✓				✓	
If necessary to use from 20 weeks, limit to lowest effective dose and shortest duration possible				✓									
Consider ultrasound monitoring of amniotic fluid if use extends beyond 48 hours/ closely monitor amniotic fluid		✓		✓									
Discontinue use if oligohydramnios occurs				✓									
Continuous treatment with NSAIDs in last month of pregnancy should only be given when clearly indicated/on sound indications					✓		✓					✓	
Use in third trimester contraindicated						✓	✓	✓	✓		✓		
Use throughout pregnancy contraindicated										✓		✓	

The data sheets for the COX-2 inhibitors (celecoxib, parecoxib and etoricoxib), naproxen (Naprosyn only) and mefenamic acid state either that fetal renal dysfunction and oligohydramnios may occur with use in the second trimester or with use from 20 weeks gestation.

The data sheets for ibuprofen, diclofenac, ketoprofen, meloxicam and tenoxicam state either that use in the third trimester or use in the latter part of pregnancy may result in fetal renal impairment (and some also mention oligohydramnios). These data sheets do not include information about the risk of fetal renal impairment/oligohydramnios from 20 weeks/2nd trimester.

The data sheets for naproxen (Noflam), ibuprofen (except Ibugesic), diclofenac and ketoprofen state that the medicine should not be used in the first two trimesters unless the benefit outweighs the risk/clearly necessary (ie use in 2nd trimester is not recommended, but risk of fetal renal impairment/oligohydramnios is not specifically mentioned in this context).

The data sheets for Noflam (naproxen), Ibugesic (ibuprofen) and ketorolac state that continuous treatment with NSAIDs in the last month of pregnancy should only be given 'when clearly indicated' or 'on sound indications'. These data sheets do not mention the risk of fetal renal impairment with exposure in either the 2nd or 3rd trimester.

2.4.1.2 Section 4.3 Contraindications

There are also differences in section *4.3 Contraindications* of the NSAID data sheets about whether the medicine is contraindicated in pregnancy (Table 2).

Table 2. NSAID pregnancy contraindications in New Zealand data sheets (as at 27 August 2021)

Medicine	Pregnancy contraindication
Meloxicam Ketorolac	Contraindicated in pregnancy
Diclofenac Ibuprofen Tenoxicam Ketoprofen	Contraindicated in third trimester of pregnancy
Naproxen Celicoxib Parecoxib Etoricoxib Mefenamic acid	Not contraindicated

The data sheets for Ibugesic (ibuprofen) and Ketorolac Kabi (ketorolac) state that *'continuous treatment with non-steroidal anti-inflammatory drugs during the last trimester of pregnancy should be given on sound indications'*, despite being contraindicated in the third trimester and throughout pregnancy, respectively.

2.4.2 Pharmacy Only and General Sale medicines

Pharmacy Only or General Sale medicines are not required to have a data sheet. Over-the-counter (OTC) medicines containing a NSAID (ibuprofen or diclofenac) are required to include the following statement on the product label:

- *Do not use [this product/insert name of the product] if trying 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.*

3 SCIENTIFIC INFORMATION

3.1 US FDA Review

The US FDA reviewed the medical literature, including case reports, randomized controlled studies, and observational studies (published from 1980 to 2016) [1]. The review found that oligohydramnios was mostly observed during the third trimester, but there were multiple reports suggesting an earlier onset at around 20 weeks gestation. Low amniotic fluid levels were detected with use of NSAIDs for varying amounts of time, ranging from 48 hours to multiple weeks. In most cases, oligohydramnios was reversible within 72 hours to 6 days following the discontinuation of the NSAID. Reports were noted in which oligohydramnios was reversed when the NSAID was discontinued (ie, positive dechallenge), and reappeared after restarting treatment with the same NSAID (ie, positive rechallenge). In some reports, oligohydramnios did not reoccur when treatment was restarted with a different NSAID following positive dechallenge.

The review also identified case reports and case series in the medical literature describing the onset of renal failure in neonates exposed to NSAIDs in utero (published from 1989 to 2004) [1]. In total, the reports described 20 neonates with pre-natal exposure durations ranging from 2 days to 11 weeks. The severity of renal dysfunction varied from normalisation at 3 days to persistent anuria requiring dialysis and/or exchange transfusion. Eleven of the 20 cases identified in the literature were fatal. In eight of these cases, the death was reported to be a direct consequence of renal failure or due to complications from dialysis.

In the FDA Adverse Event Reporting System (FAERS) up until to 21 July 2017, there were 35 cases of oligohydramnios or neonatal renal dysfunction associated with intrauterine NSAID exposure. The cases included:

- 32 cases of oligohydramnios (11 with a positive dechallenge), including 8 cases with neonatal renal dysfunction
- 3 cases of neonatal renal dysfunction that did not report oligohydramnios,
- 11 cases where renal dysfunction was reported and the neonate was born pre-term (25 to 36.5 weeks gestation),
- 5 neonatal deaths that were directly or indirectly associated with neonatal renal failure

Oligohydramnios occurred as early as 20 weeks gestation in some cases.

Comment

The US FDA review of the FAERS database included data up to 21 July 2017. The most recent report from the cited literature was published in 2016. The Drug Safety Communication that resulted from this review was published on15 October 2020, but the case numbers had not been updated.

3.2 Scientific Literature

3.2.1 Dathe *et al* (2019)

Risk estimation of fetal adverse effects after short-term second trimester exposure to non-steroidal anti-inflammatory drugs: a literature review [8]

This systematic review was conducted to assess the risk of specific adverse fetal effects (prenatal constriction of the ductus arteriosus, oligohydramnios, neonatal renal failure, and primary pulmonary hypertension) associated with NSAID use in the advanced second trimester. The study authors are associated with the Berlin Embryotox Institute.

The literature search was conducted in PubMed using controlled terms for NSAID medicines, use in pregnancy, and the fetal outcomes of interest (filtered for humans). The search allowed all indications for NSAID use, and initially covered all trimesters to ensure high sensitivity. No limits were placed on publication type, date or language. The search was conducted in December 2015 and repeated in February 2018. Relevant endpoints

were ductus arteriosus constriction/closure, oligo- or anhydramnios, fetal death, neonatal renal insufficiency/failure and primary pulmonary hypertension in the neonate. Filters were added to identify full-text articles, publications containing details on gestational weeks at NSAID exposure, dosage, treatment duration and indication, and fetotoxicity observed exclusively at or before 28 weeks gestation. The relevant exposure and outcome had to be assignable to individual cases or at least to a defined number of cases. Only case reports on adverse effect at ≤ 28 weeks gestation and clearly assignable to NSAID exposure fulfilled the inclusion criteria for further evaluation.

The initial search produced 681 hits. After applying the selection criteria, there were 26 publications reporting cases in which the defined study endpoints were observed after exposure to NSAID at ≤ 28 weeks gestation. Nineteen of the 26 (73%) articles were published between 1986 and 1999, and only 7/26 (27%) were published since 2000.

The majority (22/26) of the case descriptions involved NSAID use for obstetric indications (tocolysis and treatment of polyhydramnios or feto-fetal transfusion syndrome). Three publications reported on NSAIDs used as analgesia, and in one case the NSAID exposure was the result of an intentional overdose.

Most of the descriptions of 2nd trimester fetal adverse effects were related to indomethacin treatment for tocolysis. Only 10 pregnancies with fetotoxic effects concerned other NSAIDs: acetylsalicylic acid, diclofenac, ibuprofen, ketoprofen, nimesulide, and piroxicam. These reports included two affected twin pregnancies and one triplet pregnancy.

Oligo- or anhydramnios was associated with 2nd trimester NSAID exposure in 10 fetuses, including two affected twin pairs, and was observed earliest at 22 weeks gestation.

Postnatal impaired renal function leading to oliguria or anuria was described in 8 infants that were exposed to NSAIDs exclusively in the 2nd trimester, including affected triplets and one affected donor twin in a pregnancy with feto-fetal transfusion syndrome. In all these cases with extremely premature newborns, the exposure-free interval was at most a few days.

In most of the identified publications, 2nd trimester fetal adverse events occurred after NSAID exposure of at least 7 days, and often longer. Not all publications report on the duration of NSAID treatment in detail.

The authors noted that use of indomethacin for tocolysis, which was common prior to the 1990s, has been superseded by medicines with more favourable benefit-risk profiles. The outcomes in cases where indomethacin was used over a longer period for tocolysis may not be applicable to short-term analgesic or antipyretic NSAID use. Furthermore, administration of NSAIDs for tocolysis is more likely to be monitored with ultrasound so oligohydramnios is more likely to be detected, compared to short-term analgesic/antipyretic use. Overrepresentation of indomethacin for tocolysis in the identified literature may be explained by a larger number of exposed pregnancies, stronger toxicity of this NSAID, longer treatment duration for tocolysis than for other indications, or a detrimental effect of the treatment indication, i.e., premature labour.

Oligohydramnios may be the result of NSAID-induced renal damage in the fetus. Long-persisting severe oligohydramnios may lead to limb positioning defects, Potter facies, and lung hypoplasia with respiratory failure after birth. The search identified 10 pregnancies in which oligohydramnios occurred after NSAID exposure at ≤ 28 weeks gestation. The earliest diagnosis of oligohydramnios in NSAID-exposed pregnancies was at 22 weeks gestation and concerned three fetuses: in one report a twin pregnancy had long-term exposure to diclofenac and in another report the fetus was exposed to indomethacin for 1 week. In most cases describing oligohydramnios, amniotic fluid normalized after discontinuation of the NSAID. However, a causal association is difficult to assess.

Prenatal renal damage caused by NSAID may result in renal failure in the newborn presenting with oliguria or anuria. The literature search identified reports of renal impairment in pre-term infants that were exposed to NSAIDs at ≤ 28 weeks gestation, shortly before birth. Such extremely preterm infants present complex clinical problems. Renal impairment in these very pre-term infants may be related to prematurity, and a causal association with NSAID use is difficult to assess.

The authors concluded that, apart from the well-known risk in the 3rd trimester of pregnancy, NSAID use may cause ductus arteriosus constriction and oligohydramnios also in the 2nd trimester. In cases of long-term NSAID use, fetal monitoring is recommended from 20 weeks gestation onward. However, short-term analgesic or antipyretic NSAID treatment not exceeding 1 week does not seem to carry a noteworthy fetal risk of cardiovascular or renal impairment during the 2nd trimester, but further prospective studies focusing on the 2nd trimester are needed.

3.3 CARM data

The Centre for Adverse Reactions Monitoring (CARM) has not received any reports of oligohydramnios associated with NSAID use in pregnancy.

4 DISCUSSION AND CONCLUSIONS

In the United States, the FDA warned that women using pain-relieving and fever-reducing NSAIDs around 20 weeks or later in pregnancy may cause kidney problems in the unborn baby, which can lead to low levels of amniotic fluid and related pregnancy complications. The FDA advised women who are pregnant not to use NSAIDs at 20 weeks or later in pregnancy unless specifically advised to do so by their health care professional.

The FDA recommended that health care professionals should:

- Limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy.
- If NSAID treatment is determined to be necessary, to limit use to the lowest effective dose and shortest duration possible.
- Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found.

Health Canada [redacted] taken similar action.

Information about the risk of fetal renal impairment and oligohydramnios in the New Zealand data sheets for NSAID medicines is inconsistent. Data sheets for the COX-2 inhibitors (celecoxib, parecoxib and etoricoxib), Naprosyn (naproxen) and Ponstan (mefenamic acid) already state that fetal renal dysfunction and oligohydramnios may occur with second trimester use or with use from 20 weeks gestation.

The data sheets for ibuprofen, diclofenac, ketoprofen, meloxicam, tenoxicam and ketorolac currently associate the risk of fetal renal dysfunction and oligohydramnios only with third trimester use. However, the data sheets for ibuprofen (except Ibugesic), naproxen (Noflam only), diclofenac and ketoprofen state that use in the first two trimesters of pregnancy should be avoided if possible (without mention of fetal renal impairment in the second trimester).

Discrepancies in the pregnancy contraindications between NSAID data sheets are noted. The COX-2 inhibitors, naproxen and mefenamic acid are not contraindicated in pregnancy, meloxicam and ketorolac are contraindicated throughout pregnancy, and the remainder are contraindicated only in the third trimester of pregnancy. Furthermore, the data sheets for Noflam (naproxen), Ibugesic (ibuprofen) and Ketorolac Kabi (ketorolac) appear to contradict their respective pregnancy contraindications by stating that continuous treatment with NSAIDs in the last month of pregnancy should only be given when clearly indicated or on sound indications.

The evidence for an association between NSAID use at around 20 weeks gestation or later and fetal renal impairment leading to oligohydramnios is based mainly on case reports and cases series from the literature, many of which were published prior to 2000. The FAERS data identified 35 cases of oligoydramnios and/or neonatal renal dysfunction associated with prenatal NSAID exposure. Although alternative explanations for the renal dysfunction were identified in some of the cases, a positive dechallenge was noted in 11 of the 32 cases of oligohydramnios, including 8 with neonatal renal dysfunction. Also of note was the onset as early as 20 weeks in some of the cases of oligohydramnios.

Little has been published in the scientific literature in recent years on the association between NSAIDs and fetal renal impairment. However, a systematic review published in 2019 by German authors concluded that, in addition to the known risk of fetal renal impairment with third trimester exposure, use of NSAIDs in the second trimester may also cause oligohydramnios. In cases of long-term NSAID use, fetal monitoring is recommended from 20 weeks gestation onward. For short term use (not exceeding one week) the risk was considered to be low, but further studies are needed to be sure.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the information in section *4.6 Fertility, pregnancy and lactation* of the data sheet for all NSAID medicines should be aligned to state that use of the medicine from about 20 weeks gestation may cause neonatal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment
- Whether all NSAID medicines should be contraindicated in the third trimester of pregnancy.
- Whether communication in addition to MARC's Remarks is needed to inform prescribers and consumers about the risk of fetal renal impairment associated with NSAID exposure in pregnancy.

6 ANNEXES

1 US FDA. 2020. *Drug Safety Communication: FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid* 15 October 2020.

2 NSAID data sheet wording about the risk of fetal renal dysfunction and oligohydramnios (section 4.6) and pregnancy contraindication (section 4.3)

7 REFERENCES

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