Medicines Adverse Reactions Committee

Meeting date	10/03/2022	Agenda item	3.2.3
Title	**Safety of non-steroidal anti-inflammatory drug exposure in third trimester of pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

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**	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	187th Meeting (September 2021): Non-steroidal anti-inflammatory drug exposure in the second trimester and the risk of fetal renal impairment and oligohydramnios 170th Meeting (June 2017): NSAIDs and spontaneous abortion 107th Meeting (September 2001): NSAIDs in pregnancy and neonates
International action	Not applicable.
Prescriber Update	none
Classification	Ranges from general sales (eg, ibuprofen) to prescription

Usage data	██ ██ ██ ██ ██ ████████████████████████████
Advice sought	**The Committee is asked to advise:** • Whether all NSAID medicines should be contraindicated in the third trimester of pregnancy • Whether the information in section *4.6 Fertility, pregnancy and lactation* of the data sheet for all NSAID medicines should be aligned • 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

Information in the New Zealand data sheets for non-steroidal anti-inflammatory drugs (NSAIDs) about use in pregnancy is inconsistent. Medicines containing ibuprofen, diclofenac, ketoprofen or tenoxicam are contraindicated in the third trimester, medicines containing meloxicam or ketorolac are contraindicated throughout pregnancy, while naproxen and the COX-2 inhibitors (celecoxib, etoricoxib and parecoxib) are not contraindicated in pregnancy.

The Medicines Adverse Reactions Committee (MARC) reviewed the association between 2nd trimester use of NSAIDs and the risk of fetal renal impairment/oligohydramnios at the 187th meeting in September 2021. The review highlighted inconsistencies across the NSAID data sheets in sections 4.3 Contraindications and 4.6 Fertility, Pregnancy and Lactation (Annex 1). The Committee considered that consistent pregnancy information is desirable to avoid giving the impression that certain NSAIDs are safer than others.

The Committee deferred their recommendation about updating the NSAID data sheet wording on second trimester use until they had reviewed the safety of NSAIDs in the third trimester.

The purpose of this report is to review the available information on the safety of NSAIDs in the third trimester of pregnancy, and to address the data sheet inconsistencies about use of these medicines in pregnancy.

2   BACKGROUND

2.1   Non-steroidal anti-inflammatory drugs and risks in pregnancy

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

COX enzymes (COX1 and COX2) convert arachidonic acid to prostaglandin H2 (PGH2), which is metabolised by specific prostaglandin synthases to produce PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), and thromboxane A_2 (TXA_2) [1, 2].

By blocking COX, NSAIDs inhibit (to varying degrees) the synthesis, and therefore the effects, of prostaglandins, prostacyclin, and thromboxane A_2 [1].(Figure 1)

Maternal use of NSAIDs in the third trimester of pregnancy may have adverse effects for the mother, fetus and neonate such as: [3, 4]

- Maternal effects: prolonged labour, post-partum haemorrhage
- Fetal effects: premature closure of the ductus arteriosus, fetal renal impairment, oligohydramnios, fetal death
- Neonatal effects: respiratory distress syndrome, persistent pulmonary hypertension of the newborn (PPHN), bronchopulmonary dysplasia, renal failure, intraventricular haemorrhage, and necrotizing enterocolitis.
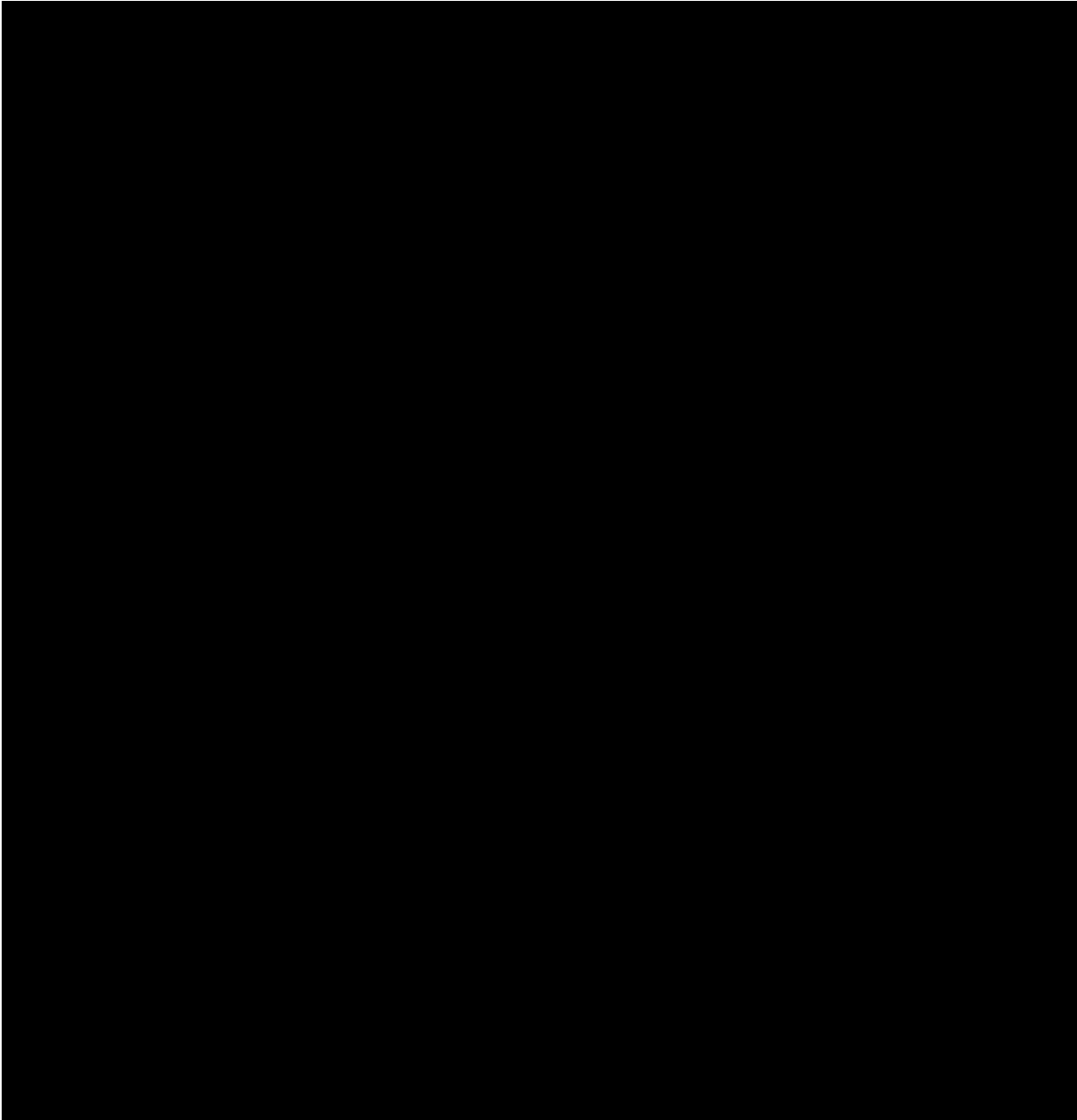
2.1.1   Premature closure of the ductus arteriosus

In the fetal circulation, blood is oxygenated in the placenta instead of the lungs. Oxygenated blood
entering the right side of the heart largely bypasses the high resistance fluid-filled fetal lungs via the
foramen ovale (FO) and ductus arteriosus (DA) to return to the systemic circulation. At birth,
pulmonary vascular resistance falls as the lungs aerate, and the right-to-left DA and FO hemodynamic
shunting ceases. [5, 6]

The DA connects the pulmonary artery to the descending aorta in the fetus, allowing 80–85% of the
right ventricle output to return to the systemic circulation [5]. In healthy term-born infants, the ductus

arteriosus contracts within two days after birth and transforms into the ductus ligamentum over the following weeks[1]. [7]

PGs (especially PGE_2) are important for maintaining the patency of the fetal ductus arteriosus and the autoregulation of blood flow in the brain and the eyes of the growing fetus [2, 5]. With advancing gestation, the DA becomes more sensitive to constricting factors, as it prepares for postnatal closure through a process of histological maturation and remodelling [5].

Inhibition of prostaglandin synthesis by NSAIDs has been associated with premature constriction of the DA [5].

2.1.2   Fetal renal impairment and oligohydromnios

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. The association between NSAIDs and fetal renal impairment leading to oligohydramnios was discussed in the report prepared for the 187th MARC meeting (Annex 1)

2.2   Product information

2.2.1   New Zealand data sheets

2.2.1.1   *Prescription and Pharmacist-Only (Restricted) medicines*

2.2.1.1.1   Section 4.6 Fertility, pregnancy and lactation

Information in the NSAID data sheets about the risks associated with third trimester use 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.

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

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[1] PGI_2 counteracts the vasoconstrictor and platelet aggregation effects of TXA_2. The PGI_2/TXA_2 balance is critical in the regulation of maternal and fetal vascular function during pregnancy and in the newborn. A decrease in PGI_2/TXA_2 ratio in the maternal, fetal, and neonatal circulation may contribute to preeclampsia, intrauterine growth restriction, and persistent pulmonary hypertension of the newborn (PPHN), respectively. Conversely, increased PGI_2 activity may contribute to patent ductus arteriosus (PDA) and intraventricular haemorrhage in premature newborns. The NSAIDs indomethacin and ibuprofen are used to close patent DA in the premature newborn. 2. Majed BH and Khalil RA. 2012. Molecular mechanisms regulating the vascular prostacyclin pathways and their adaptation during pregnancy and in the newborn. *Pharmacol Rev* 64(3): 540-82. 10.1124/pr.111.004770

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.

2.2.1.1.2   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 1)

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.

2.2.1.2   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.*

Information in section 4.6 of the data sheet	Celecoxib	Parecoxib	Etoricoxib	Ibuprofen		Naproxen		Diclofenac	Ketoprofen	Meloxicam	Tenoxicam	Ketorolac	Mefenamic acid
	Celecoxib Pfizer Celebrex	Dynastat	Arcoxia	All except Ibugesic	Ibugesic	Naprosyn	Noflam	All except Voltaren Rapid/ Diclofenac Dr Reddys	Oruvail	Mobic	Tilcotil Tenoxicam Devatis	Ketorolac Kabi	Ponstan
Pregnancy category	B3	C	C	(C)	C	C	C						C
There is no information on the use of [NSAID] in pregnant women	✓												
Effects on **labour and delivery** not known	✓												
Not recommended in pregnancy (± unless clinically essential/ benefit outweighs risk)	✓	✓											✓
Use in the **second or third trimester** should be avoided	✓								✓				
Use in the **third trimester** should be avoided/not recommended		✓	✓										✓
Avoid use on **late pregnancy** – may cause **premature closure of DA**			✓			✓	✓	✓					
Avoid use in **last few days** before expected birth					✓	✓							✓
If used in **second or third trimester**, use lowest dose and shortest duration possible						✓	✓						
If necessary to use **from 20 weeks**, limit to lowest effective dose and shortest duration possible				✓	✓								
Continuous treatment with NSAIDs in **last month** of pregnancy should only be given when clearly indicated/on sound indications					✓		✓					✓	

Statement	1	2	3	4	5	6	7	8	9	10	11	12	13
Should not be used in **first and second trimesters** unless benefit justifies/outweighs risk/clearly necessary	✓			✓	✓	✓	✓	✓	✓			✓	
Use in **first 20 weeks** only if benefits justify/outweigh risks			✓										
Increased risk of spontaneous abortion after use of PG synthesis inhibitors in **early pregnancy**	✓												✓
Increased risk of miscarriage/congenital malformation in **first trimester**				✓								✓	
Use in the **second or third trimester** of pregnancy (or from 20 weeks gestation) may cause **fetal renal dysfunction/oligohydramnios**	✓	✓	✓				✓						✓
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					✓				✓				✓
Pregnant women on [NSAID] should be closely **monitored for amniotic fluid volume**	✓												✓
Consider **ultrasound monitoring** of amniotic fluid if use extends **beyond 48 hours**		✓					✓						
Discontinue use if oligohydramnios occurs		✓					✓						
Use in **third trimester** contraindicated				✓	✓				✓	✓		✓	
Use **throughout pregnancy** contraindicated											✓		✓

Table 1. Key data sheet wording about use in pregnancy (section 4.6) and pregnancy contraindication (section 4.3) for NSAIDs (current on 23 February 2022)

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3   SCIENTIFIC INFORMATION

3.1   Scientific Literature

3.1.1   Nielsen et al (2001)

Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study [8]

Objective: To estimate the risk of adverse birth outcome in women who take non-steroidal anti-inflammatory drugs during pregnancy.

Methods: The risk of adverse birth outcome (congenital abnormality, low birth weight, and preterm birth) was examined in a cohort analysis and the risk of miscarriage in a case-control analysis. The studies were conducted in the Danish county of North Jutland (population 490,000). All women who had a live birth or stillbirth after 28 weeks gestation or who had a miscarriage during the period 1991-1998 were included in the cohort. Data was obtained from the Danish birth registry and the county's hospital discharge registry. The Danish birth registry contains information on all births in Denmark since 1 January 1973 and includes information on maternal age, self-reported smoking status, order of birth, gestational age, length and weight of neonate at birth, and personal identifiers for both mother and child.

Exposure: NSAID exposure data was obtained from the pharmaco-epidemiological prescription database of North Jutland, which holds key data on all reimbursed prescribed drugs sold at pharmacies in the county since 1 January 1991. During the period studied, indomethacin was the drug-of-choice to delay premature delivery. To assess confounding by indication, analyses were performed both with and without data on women who were dispensed indomethacin during pregnancy.

Outcome: Cases of congenital abnormality and miscarriage were identified from the regional hospital discharge registry, from which data are transferred to the national Danish hospital discharge registry, which comprises data on 99.4% of all discharges from Danish hospitals. Personal identifiers were used to link prescription records with both registries.

Cohort analysis: Women who had a live birth or a stillbirth after the 28th week of gestation were divided into two groups based on NSAID exposure: the early pregnancy group (prescriptions from 30 days before conception to the end of the first trimester) was used to estimate the risk of congenital abnormality, and later pregnancy group (prescriptions in the second or third trimesters) was used to estimate the risk of preterm birth and low birth weight (full term births only). The reference group was all pregnant women who were not prescribed any kind of reimbursed medicine in the study period. Logistic regression analyses were performed to estimate the risk of congenial abnormality, low birth weight and preterm birth associated with NSAIDs, adjusted for maternal age, birth order and smoking status.

Case control analysis: Cases were defined as first recorded miscarriages in women who were dispensed a NSAID in the 12 weeks before the date of discharge from hospital after the miscarriage. The control group was primiparous women who had live births. The first trimester was used as the exposure period in the control group. Logistic regression analyses were performed to estimate the risk of miscarriage associated with NSAIDs. Variables included the period from the date the NSAID was dispensed to the date of discharge following miscarriage, adjusting for maternal age.

Results: In the cohort study, 1462 women who had a live birth or stillbirth after GW28 were dispensed 1742 prescriptions for NSAIDs: 1106 women were dispensed a NSAID in early pregnancy and 997 in later pregnancy. Among the 1106 pregnancies that were exposed to a NSAID in early pregnancy, 46 had a congenital abnormality compared to 564 of the 17259 pregnancies in the reference cohort.

The logistic regression analysis shows that smoking was associated with low birthweight and preterm delivery, but there was no association between 'late pregnancy' NSAID exposure and congenital abnormalities, low birth weight or preterm delivery. (Table 3)

In the case-control analysis, the ORs for miscarriage vs birth in women exposed to NSAIDs decreases as the time from dispensing to discharge from hospital increases. (Table 4)

Limitations of the study included no information on whether the pregnant woman took the dispensed medicine. Over the counter use of low-dose non-prescription NSAIDs was not captured in the data. There was no information about gestational age at the time of miscarriage. There is a possibility that the association between NSAID use in early pregnancy and miscarriage is due to confounding by indication (NSAID prescribed to treat pain that may be a precursor to miscarriage).

Table 3. Logistic regression analyses of birth outcome in women dispensed an NSAID during pregnancy and in women who were not prescribed any drug during pregnancy.

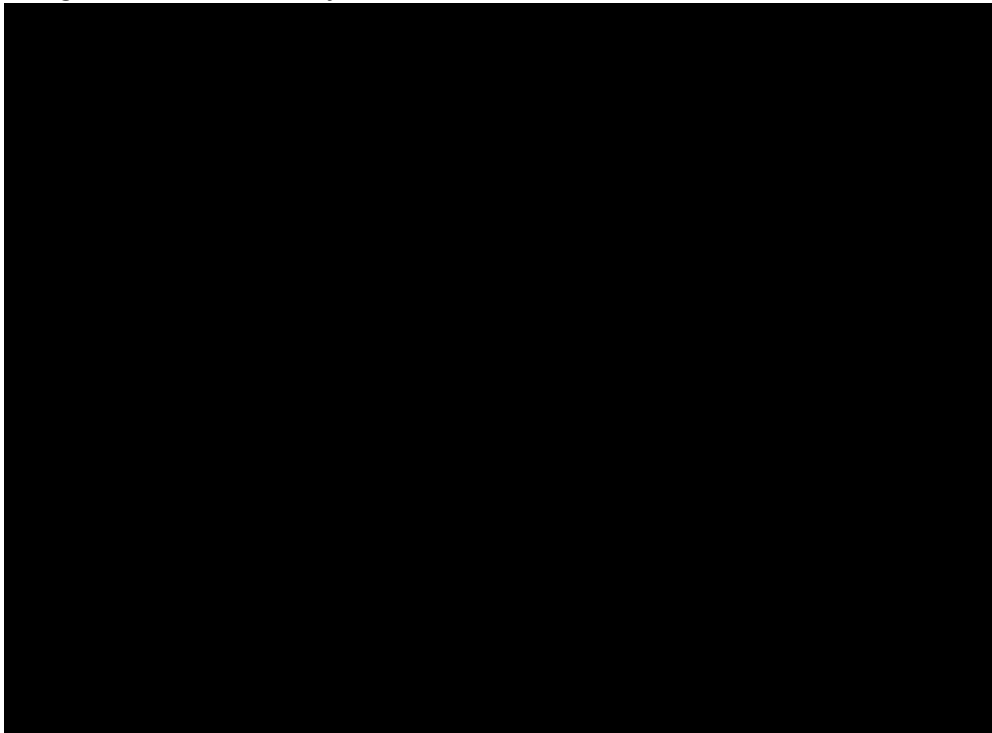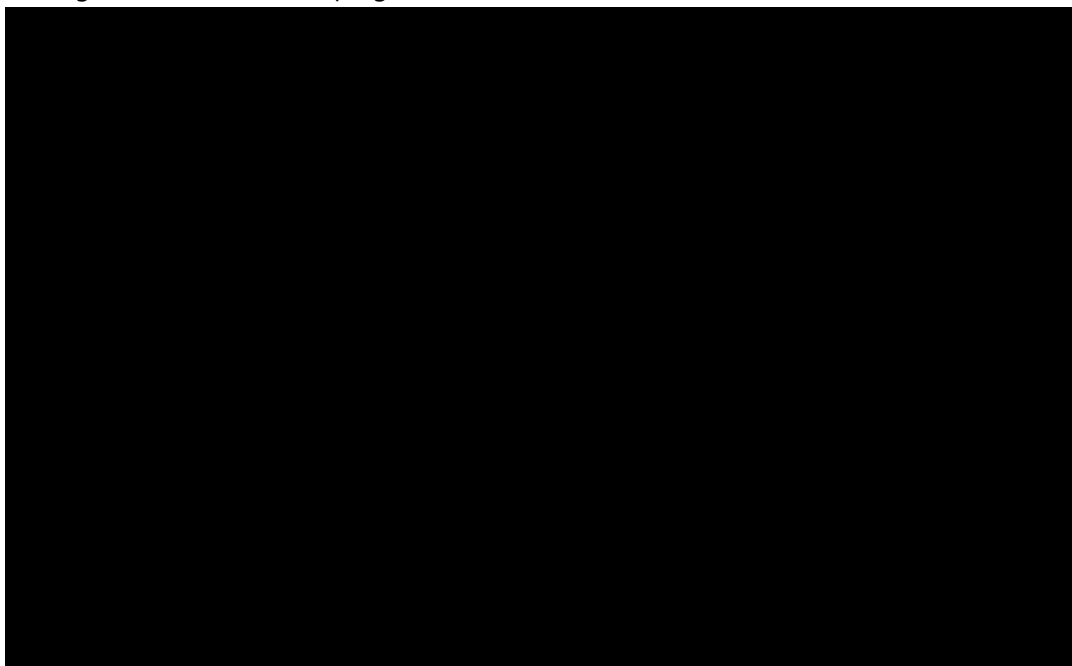Figures are crude and adjusted odds ratios (95% confidence intervals)

Table 4. 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 numbers of pregnancies *

Conclusions: The authors concluded that the risk of adverse outcome at birth (congenital abnormality, low birth weight, or preterm birth) was not associated with NSAID use during pregnancy. However, based on the case-control analysis, use of NSAIDs in the first trimester was associated with an increased risk of miscarriage.

Comment

This study looks at whether there is a link between NSAID use in late pregnancy and the adverse pregnancy outcomes of low birth weight and pre-term delivery, neither of which were found to be associated.

The case-control analysis showed an increased risk of miscarriage associated with NSAID use in the first trimester. The increase in the OR for miscarriage as the interval between NSAID dispensing and hospital discharge decreases may reflect protopathic bias/confounding by indication (ie, the NSAID may have been prescribed for pain associated with an early miscarriage or an undiagnosed miscarriage may have been mistaken for menstrual pain and treated with an NSAID).

3.1.2 Koren et al (2006)

Nonsteroidal anti-inflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis [4]

Objective: to conduct a systematic review of all published trials to determine whether the use of NSAIDs during the third trimester of pregnancy is associated with an increased risk of premature closure of ductus arteriosus.

Methods: The authors searched Medline, Embase and the Cochrane Database of Systematic Reviews up to spring 2004 for randomised controlled trials in humans using the key words 'NSAIDs' and 'pregnancy'. Studies that examined maternal exposure to NSAIDs during the third trimester of pregnancy and reported constriction of the ductus arteriosus as a fetal outcome were included. Studies were excluded if the abstract was not available in English. Data extracted from each study using structured data collection forms included: population characteristics, NSAID exposure (dose, duration), assessment of ductal constriction, exposure to other drugs, outcome measures (ductal closure). Analyses included comparison of indomethacin with placebo,
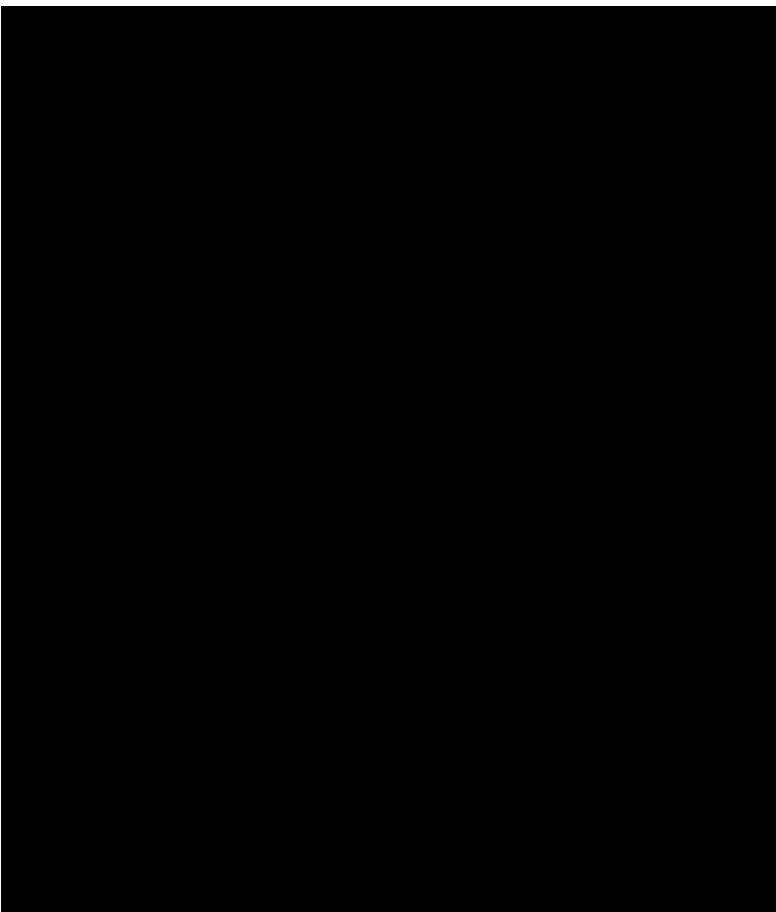
comparison of intravenous indomethacin with other NSAIDs, a meta-analysis of rate differences between oral indomethacin and control groups, and a funnel plot to detect publication bias.

Results: 12 studies met the inclusion criteria (Table 5). A total of 553 patients (272 in the exposed group, 281 in the comparison arm) were enrolled in these studies. Seven studies were conducted in the US, two in Finland, one each in Israel, the UK, and Canada.

Closure of the DA was determined by either a systolic velocity greater than 140 cm/sec or a diastolic velocity greater than 35 cm/sec. Two studies evaluated ductal closure based on a pulsatility index of 1.9 or less; one study defined ductal closure based on a pulsatility index less than 1.75. Three studies did not describe their criteria for assessing closure.

Four studies compared NSAIDs with placebo, four compared NSAIDs with a non-NSAID agent, and four assessed oral indomethacin versus another NSAID.

Table 5. Characteristics of Eligible Trials [4]

The NSAID most commonly used in these studies was indomethacin. The other drugs assessed were sulindac, celecoxib and nimesulide. Study duration ranged from 24 hours to 42 days.

In the first sub-analysis, comparison of NSAIDs versus placebo or another non-NSAID showed that the rates of ductal closure for women exposed to NSAIDs in the third trimester were significantly higher than for women exposed to placebo or another non-NSAID (pooled OR = 15.04; 95% CI 3.29 to 68.68), (Figure 2).
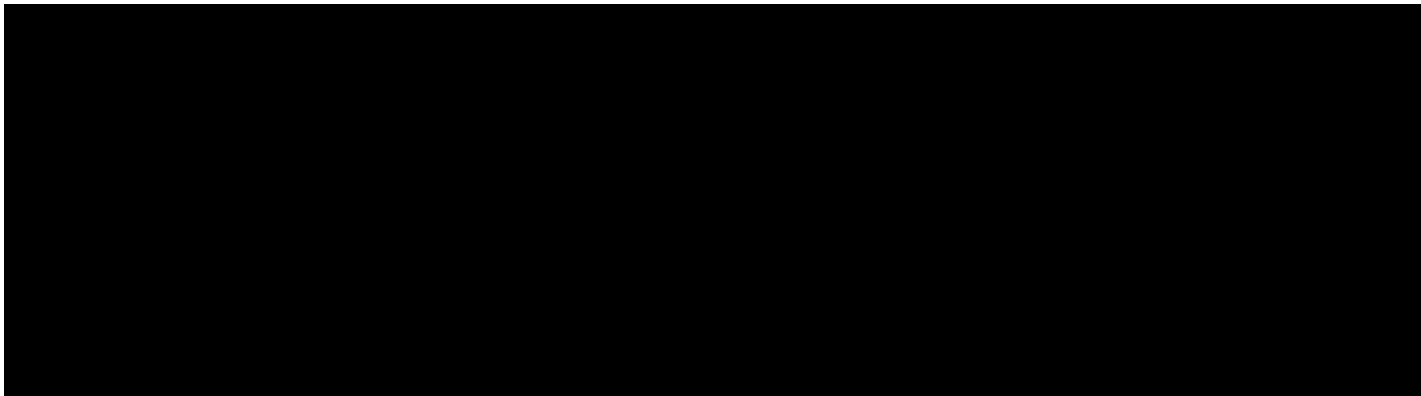
Figure 2. Forrest plot indicating odds ratios for each of the 8 studies describing the risk of fetal ductal closure in women exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) in the third trimester of pregnancy compared with those given placebo or another non-NSAID.

The overall rate difference reflected the same finding, with a significant rate difference (0.11; 95% CI 0.01 to 0.21)

In the second sub-analysis, comparison of oral indomethacin with another NSAID (Figure 3) indicated a nonsignificant risk of ductal closure for the indomethacin-exposed group compared with another NSAID (OR = 2.12; 95% CI 0.48 to 9.25). The overall rate difference reflected a nonsignificant difference (0.17; 95% CI –0.08 to 0.41).
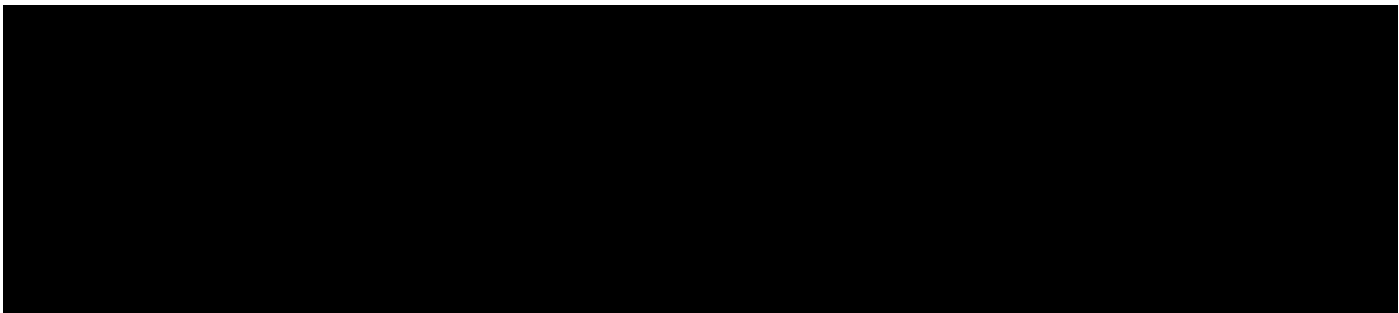
Figure 3. Forrest plot indicating odds ratios for each of the 4 studies describing the risk of fetal ductal closure in women exposed to oral indomethacin in the third trimester of pregnancy compared with those given another NSAID.

Conclusion: Based on 217 patients exposed to indomethacin and 221 to placebo, the risk of ductal closure was 15-fold higher in the group of women exposed to NSAIDs compared with those receiving either placebo or other NSAIDs (8 studies; OR = 15.04, 95% CI 3.29 to 68.68).

Comment

The first sub-analysis showed a significant difference between the NSAID group and the 'placebo or non-NSAID' group, although the confidence intervals are wide. Of the 8 studies included in the first sub-analysis, the OR was not estimable in four of the studies (due to there being no relevant cases in the treatment or control groups) and was not significant in two studies. The OR for the remaining two studies had very wide confidence intervals, with the lower bound only just above 1.

The second sub-analysis showed no significant difference between the indomethacin group and the 'other NSAID' group. The number of individuals in each of the four studies was small with a pooled total of 55 in the treatment group (14 events) and 65 in the control group (10 events).

In addition to comparisons of the odds ratio (OR) for each of the sub-analyses, the analysis included a comparison of the 'rate difference', which is not defined.

3.1.3 Van Marter et al (2013)

Nonsteroidal Antiinflammatory Drugs in Late Pregnancy and Persistent Pulmonary Hypertension of the Newborn [6]

Objective: To test the hypothesis that late pregnancy exposure to NSAIDs is associated with an increased risk of persistent pulmonary Hypertension of the Newborn (PPHN).

Methods: North American case-control study of risk factors for PPHN among infants identified through the Slone Epidemiology Centre's Birth Defects Study (BDS)[2]. Study subjects were drawn from 97 institutions in 4 metropolitan areas (Boston, Philadelphia, San Diego, and Toronto) between 1998 and 2003. They were identified through review of admissions and discharges at major referral hospitals and clinics, logbooks in NICUs and through weekly telephone contact with collaborators at newborn nurseries in community hospitals. Healthy newborns from the same centres were also enrolled.

Cases: Medical records of infants with respiratory signs or diagnoses were screened to determine whether they met the criteria for PPHN. Infants with major congenital malformations, including congenital heart disease or pulmonary hypoplasia, were excluded. PPHN cases were defined as: gestational age > 34 weeks, severe respiratory failure (requiring intubation and mechanical ventilation) presenting shortly after birth, and evidence of pulmonary hypertension based on echocardiographic evidence. Potential cases were excluded if he or she had any congenital cardiothoracic abnormality except for patent DA, patent FO, atrial septal defect, or a small ventricular septal defect. Due to incomplete information from some centres, cases were classified as confirmed, probable, possible or not a case. Only confirmed and probable cases were included in the main analysis.

Controls: The control group included infants born after 34 weeks gestation without a congenital abnormality or respiratory problem who were matched to cases by birth hospital and date of birth (± 30 days). Four potential controls were selected for each case and an average of 2.2 controls were interviewed per case. After final classification of PPHN cases and completion of interviews, controls who were matched to confirmed and probable cases and those who had completed interviews were selected for the analyses.

NSAID exposure: Mothers were interviewed within 6 months of delivery. The structured telephone interview included questions on demographic characteristics, mother's medical and obstetric history, parents habits and occupations, medication history (Rx and OTC) from 2 months before conception and throughout the entire pregnancy. Late pregnancy exposure was defined as use of NSAIDs anytime in the third trimester. Aspirin and non-aspirin NSAIDs were included.

Because the third trimester is shorter among infants born preterm, the authors considered the use of NSAIDs during the month preceding the delivery (time-varying exposure) and repeated the analysis among infants born at full-term gestation (≥37 weeks postmenstrual age). To assess whether first trimester exposure increased the risk of PPHN, the authors evaluated the effect of NSAID use for each trimester. As low-dose aspirin is used to treat some pregnancy-related conditions and NSAID treatment is used to arrest preterm labour, the authors also evaluated the potential effect of these indications for treatment.

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[2] The Birth Defects Study (BDS) / Pregnancy Health Interview Study (PHIS) was a multicentre case-control study conducted in North America. Data collection ceased in November 2015, after 39 years of activity that involved approximately 52,000 mothers of infants with and without major birth defects. Infants with birth defects and a sample of healthy infants without birth defects were identified through special arrangements with either state birth defect registries or through regular contact with approximately 28 participating institutions. Mothers of these infants were invited to take part in a telephone interview conducted by trained nurse-interviewers. The interview included questions on medical history, previous pregnancies, nutrition, occupation, health behaviours, and smoking, as well as detailed questions on medication use and vaccines received in the period prior to conception through the entire pregnancy

Analyses: Matched ORs and their 95% CIs were estimated for PPHN by using multivariate conditional logistic regression with separate terms for 3 medication exposures (aspirin, ibuprofen, acetaminophen), race/ethnicity (ie, black, Hispanic, Asian, others, and white as referent), diabetes mellitus, pre-pregnancy BMI (ie, 20–27, >27, unknown, and <20 as referent), hypertension, and multiple birth. Analyses were performed by using SAS for Windows.

Results: Of 843 term or near-term newborn infants identified with diagnoses of asphyxia, cyanotic congenital heart disease, respiratory distress syndrome, pneumonia, meconium aspiration, transient tachypnoea of the newborn, persistent fetal circulation, or pulmonary hypertension, 377 were classified as having confirmed or probable PPHN. They were matched to 836 controls. The participation rate was 69% for mothers of PPHN subjects and 68% for mothers of controls.

In a previous study, the authors had identified risk factors for PPHN, including caesarean delivery, late preterm or post-term birth, being large for gestational age, and maternal black or Asian race, overweight, diabetes, and asthma [9]. Analysis of demographic factors in this study showed a significant imbalance between cases and controls in maternal race, with a higher proportion of women identifying as White in the control group than the PPHN group (72.5% vs 57.6%, respectively) and a lower proportion of women identifying as Black (9.0% vs 18.6%) or Asian (5.0% vs 8.5%) in the control group compared to the PPHN group, respectively. The groups were well matched for the other PPHN risk factors.

In the logistic regression analysis, the crude third trimester estimates were 1.82 for aspirin, 0.65 for ibuprofen and 0.8 for acetaminophen; all the 95% CI bounds included the null (ie, not significant). ORs remained largely unchanged for ibuprofen and acetaminophen but decreased for aspirin to 1.19 (0.50–2.87) when adjusted for potential confounders, late preterm birth (GW 34-37) and caesarean delivery.

Conclusion: The study did not support the hypothesis that antenatal NSAID exposure increases the risk of PPHN. Multivariable analysis of third-trimester exposures adjusting for other risk factors revealed an increase in risk of PPHN associated with antenatal exposure to aspirin intake, and an unexpected reduction in PPHN associated with third-trimester maternal intake of ibuprofen.

Comment

The accuracy of exposure data in this study is limited by recall as women were interviewed up to 6 months after delivery.

The study is poorly reported with information missing on the number of women in each group that were exposed to NSAIDs of any type during pregnancy, and specifically in the third trimester. The study reports the proportion of matched control subjects that were exposed at any stage during pregnancy as 71.7% for acetaminophen, 28.3% for ibuprofen, 6.9% for aspirin, and 5.4% for other NSAIDs. It also provides data on the proportion of controls who took an analgesic at each month of pregnancy. The proportion of women in the control group using a NSAID in each of the gestation months (GM) 7, 8, 9 and10 ranges from 1.4-1.9% for aspirin, 5.9-6.7% for ibuprofen, and 0.3-0.5% for other NSAIDs. The overall number of women in the control group was 836, of which the participation rate was 68% (ie, 568 women). Based on the reported monthly exposure proportions for the control group the actual number of women exposed to any NSAID appears to be quite low. (Eg, in GM 9, ibuprofen exposure in the control group was 5.9% = 33 women; aspirin exposure 1.6% = 9 women). The overall number of women in the cases group was 377 of which 69% participated (ie, 260 women). Assuming the same proportion of women were exposed in the cases group as in the control group, based on the non-significant OR, the actual number of cases exposed to a NSAID is also very small. (Eg, in GM 9, ibuprofen exposure in the case group ≈5.9% ≈ 15 women; aspirin exposure 1.6% = 4 women). These numbers are too low to draw any meaningful conclusions.

3.1.4   Nezvalová-Henriksen *et al* (2013)

Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study [10]

Objective: To investigate individual effects of ibuprofen, naproxen and piroxicam on pregnancy outcome using a cohort study in a Norwegian population.

Methods: The study used data from the Norwegian Mother and Child Cohort Study (NMCCS) data set (version 6, released autumn 2011, consisting of quality assured files for 108 863 subjects) and the Medical Birth Registry of Norway (MBRN) records. The NMCCS is a nationwide, prospective cohort study conducted by the Norwegian Institute of Public Health to evaluate the effect of various exposures on pregnancy and maternal and fetal outcomes. The participation rate was 38.5%. MBRN comprises all births in Norway since 1967.

NMCCS information used in this study was acquired from four self-administered questionnaires answered by pregnant women who participated in the study between 1999-2006. The questionnaires covered socio-demographic and lifestyle characteristics, maternal medical history, maternal health during pregnancy, drug use, and neonatal and infant health during the first 6 and 18 months of age. The questionnaires covered four distinct periods of time: 6 months prior to pregnancy up to GW 18, GWs 19-29, GW 30-delivery and first 6 months postpartum, and 6-18 months postpartum, respectively.

The MBRN contains detailed medical information about the newborn and all information reported during pregnancy in the woman's maternity record, including maternal socio-demographic and lifestyle characteristics, maternal health prior to and during pregnancy, and information on the course of delivery, and postpartum complications and interventions.

Data from the NMCCS and MBRN were linked via the woman's unique personal identification number (allocated to all legal residents in Norway).

A total of 94,290 pregnant women with records from the first and second questionnaires were eligible for inclusion in our study (86.6% of the population in the initial quality-assured data file). Multiple pregnancies (n = 3054) were excluded.

Exposure: Pregnant women reporting any intake of one or several of four oral NSAIDs: ibuprofen, diclofenac, naproxen, or piroxicam. Women who used other NSAIDs (i.e. acetylsalicylic acid, indomethacin, celecoxib, ketoprofen, tolfenamic acid, meloxicam, and nabumetone; n = 819) were excluded from the study. The final study population therefore consisted of 90 417 women: 6511 in the exposed group and 83 906 in the non-exposed group.

Variables: information on the type and timing of NSAID use was available from the study questionnaires. Dose information was not available. Data on duration of treatment was incomplete and therefore not used.

The effect of each NSAIDs was analysed according to the timing of therapy: any use during pregnancy, GW 1-12, GW 13-28 and GW 29-delivery.

Outcomes: all diagnoses based on ICD-10. Outcomes from MBRN included: infant survival, congenital malformations, major congenital malformations, patent DA, BW<2500g, gestational age < 37 weeks, Apgar score <7 at 5 mins, neonatal respiratory depression, intracranial haemorrhage, intraventricular haemorrhage, vaginal bleeding during pregnancy (including bleeding during the first, second, and/or third trimesters), and postpartum haemorrhage > 500 ml.

Confounding factors adjusted for in the analysis: socio-demographic, lifestyle, and medical characteristics, concomitant drug use, factors related to delivery and postpartum lifestyle and medical characteristics.

Analyses: Significant associations between each of the four individual NSAIDs and pregnancy complications and outcome were measured using logistic regression. Risk ratio estimates are given as adjusted odds ratios (ORs) with 95% CIs. For ORs significant at the 5% level, 99% CIs are also presented because of the large number of comparisons made.

<u>Results</u>: 6611 (7.2%) of the 90417 pregnant women included in the study reported using at least one of the four NSAIDs, and 93906 (92.8%) did not use any NSAID during pregnancy (unexposed group). (Table 6)

Table 6. Frequency of use of NSAIDs by trimester in the study population (n=90,417)

More NSAID users were overweight (body mass index > 25.0 kg/m2) prior to pregnancy, were on sick leave during pregnancy, smoked throughout pregnancy, and consumed alcohol once a week or more during pregnancy. women using NSAIDs were also more likely to suffer from various conditions and medical complications prior to and during pregnancy. Musculoskeletal pain, headache or migraine, and fever were particularly common in the exposed group, and may be suggestive of the indication for NSAID use. Consequently, concomitant drug use was also more frequent in the exposed group.

No significant difference in the survival, overall congenital malformation, major congenital malformation, or structural heart defect rates were found when comparing first-trimester use with the unexposed group. There was a borderline association between ibuprofen use during the first trimester and structural heart defects detected in the infant during the first 18 months of life (adjusted OR 1.2, 95% CI 1.0–1.6).

An increased likelihood of vaginal bleeding in the second and/or third trimesters and postpartum haemorrhage was found to be associated with diclofenac use towards the end of pregnancy compared to the unexposed group: second trimester 13.1% vs 7.1% (adjusted OR 1.8, 95% CI 1.1–3.0); third trimester 27.8 vs 15.3% (adjusted OR 1.9, 95% CI 1.2–2.9), respectively.

An increased risk of low birthweight (<2500 g) after ibuprofen exposure in the second trimester (4.1 versus 2.5%; adjusted OR 1.7, 95% CI 1.3–2.3) was detected, but was within the normal baseline risk range. This association remained significant at the 1% level (adjusted OR 1.7, 99% CI 1.2–2.5). Diclofenac use during the second trimester was also associated with low birthweight (6.5 versus 2.5%; adjusted OR 3.1, 95% CI 1.1–9.0) but this association did not remain significant at the 1% level (adjusted OR 3.1,b99% CI 0.8–12.5). No significant associations with patent ductus arteriosus or intraventricular haemorrhage were found when logistic regression analyses were performed.

There were three cases of patent ductus arteriosus when diclofenac was used during the third trimester (1.3 versus 0.3%). Similarly, there was one case of intraventricular haemorrhage when diclofenac had been used during the third trimester (4.8 versus 0.0%).

An association between ibuprofen use during the second and third trimesters and an increased risk of asthma detected in the infant at 18 months of age was found [4.0 and 4.5%, respectively, versus 1.2%; adjusted OR 1.5 (95% CI 1.2–1.9) and 1.5 (95% CI 1.1–2.1), respectively]. The association with use in the second trimester remained significant at the 1% level (adjusted OR 1.5, 99% CI 1.2–2.0), but not with use in the third trimester (adjusted OR 1.5, 99% CI 1.0–2.3). Stratified analyses found no effect modification from underlying medical conditions commonly associated with NSAID use (musculoskeletal pain, headache, and/or migraine).

Study limitations: Low participation rate in the NMCCS (38.5%) may have led to selection bias. Furthermore, the 13% of women who were excluded from the study because they did not complete wither or both of the

first and second questionnaires may have affected prevalence of NSAID use but is unlikely to have affected the associations between NSAID exposure and pregnancy outcomes. The study was unable to assess dose or duration of treatment.

Conclusion: The authors concluded that the lack of associations with congenital malformations is reassuring. The significant association between diclofenac and ibuprofen use late in pregnancy, and maternal bleeding and asthma in the child, respectively, is consistent with their pharmacological effects. The increased risk of low birthweight may partly have been caused by underlying inflammatory conditions and was similar to the expected baseline risk of low birthweight.

Comment

Of the 90417 pregnant women in the study, 6511 (7.2%) reported use of NSAIDs, including 1140 (1.3%) who reported 3rd trimester use. No association was found between the use of ibuprofen, diclofenac, naproxen or piroxicam and infant survival or congenital malformation.

Ibuprofen:

- first trimester use borderline associated with structural heart defects in the infant during the first 18 months after birth (adjusted OR 1.2, 95% CI 1.0–1.6).
- second trimester use associated with low birth weight
- second and third trimester use associated with asthma at 18 months.

Diclofenac:

- second and third trimester use associated with maternal vaginal bleeding in the second and/or third trimesters, and with postpartum haemorrhage.
- Second trimester use associated with low birth weight

No significant associations with patent ductus arteriosus or intraventricular haemorrhage were found.

The study relies on maternal recall for NSAID exposure information, although the interval between the period of interest and completing the questionnaire was less than in the study by van Marter et al [6], described in section 0 above.

The study was reviewed in BMJ Evidence-Based Medicine by Damase-Michel and Hurault-Delarue (2014). [11], who noted that *'the results concerning ibuprofen on global malformation risk are convincing due to the large population, but those for other NSAIDs must be interpreted with more caution since exposure to these drugs is at least 10 times lower. Furthermore, four times more participants would have been necessary to show a significant 0.3% increase in the absolute risk of cardiac defect.'*

The authors did not quantify the risk of premature closure of the DA or renal dysfunction in this study.

3.1.5   Nezvalová-Henriksen et al (2016)

Association of prenatal ibuprofen exposure with birth weight and gestational age: a population-based sibling study [12]

Objective: To evaluate the association of prenatal ibuprofen with birth weight and gestational age at birth, using a sibling design to adjust for the possibility of familial confounding.

Methods: The study used data from the Norwegian Mother and Child Cohort Study (NMCCS) data set (version 8, released 2014, consisting of quality assured files for 114,275 subjects) and the Medical Birth Registry of Norway (MBRN) records. All pregnant women living in Norway who gave birth between 1999 and 2008 were invited to participate in the NMCCS with no exclusion criteria. The participation rate was 40.6%.

Of the initial population of 114 275 pregnant women, 32 946 participated more than once. After excluding multiple pregnancies, pregnancies lacking information in any of the two study questionnaires and siblings exposed to other NSAIDs than ibuprofen, a total of 27 904 siblings were included in the final study population. The final study sample included 1080 siblings (3.9%) exposed to ibuprofen during pregnancy; of these 996 belonged to a sibling pair and 84 were in clusters of three or more. The remaining 26 824 siblings (96.1%) were unexposed to any NSAID.

Information on ibuprofen exposure was available from the two questionnaires answered during pregnancy (Qw17 and Qw30).

Birth weight in grams and gestational age in days were derived from the MBRN. Birth weights outside 3.5 standard deviations from the gender specific mean at each pregnancy week (0.5%) and gestational ages exceeding 44 weeks (0.9%) were recoded as missing.

Random and fixed effects models with propensity score adjustment were used to evaluate the effects of ibuprofen exposure on birth weight and gestational age.

Results:

Of the 1080 (3.9%) siblings that were prenatally exposed to ibuprofen, 798 were exposed during the first trimester and 481 were not exposed to any other trimester; 249 were exposed during the second and/or third trimesters but not in the first, and 33 were exposed anytime during pregnancy without the particular trimester being specified. 740 siblings were exposed to ibuprofen during any one trimester and 340 siblings exposed to ibuprofen during two or more trimesters.

The mean gestational age (39.2 weeks) was the same for all infants whether they were exposed to ibuprofen anytime during pregnancy, during the first trimester only and during the second and/ or third trimesters or not exposed at all. 54 infants (5.0%) were exposed to ibuprofen during pregnancy that were born before the 37th gestational week, in contrast to 1034 infants (3.8%) who were not exposed to any NSAIDs during pregnancy.

In the propensity score adjusted random effects model, infants exposed to ibuprofen during the first trimester on average weighed 50 grams less than infants whose mothers did not use any NSAIDs during pregnancy (β: -50 grams; 95%CI -94 grams to -7 grams).

In the fixed effects model, allowing for adjustment for familial factors, infants exposed to ibuprofen during the first trimester on average weighed 79 grams less than infants whose mothers did not use any NSAIDs during pregnancy (β: -79 grams; 95%CI -133 grams to -25 grams). There was no effect on birth weight of ibuprofen exposure in the second and/or third trimesters only.

Conclusion: Exposure to ibuprofen during the first trimester is associated with a slight decrease in birth weight.

Comment

The key findings from this study were:

- Ibuprofen exposure during the first trimester was associated with a decrease in birth weight of 79 grams (95% CI: -133 to -25 grams), but exposure in the second and/or third trimester exposure had no impact on birth weight.
- Ibuprofen exposure had no association with gestational age at birth.

3.1.6   Hjorth et al (2021)

Prenatal exposure to non-steroidal anti-inflammatory drugs and risk of attention-deficit/hyperactivity disorder: A follow-up study in the Norwegian mother, father and child cohort [13]

Objective: To estimate the association between Attention-Deficit/Hyperactivity Disorder (ADHD) in children in preschool and primary school, and prenatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) by timing and duration.

Methods: This study was based on the Norwegian Mother, Father and Child Cohort Study linked to the Medical Birth Registry of Norway, the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NSAID exposure was identified by maternal self-report in pregnancy. Child diagnosis of ADHD was obtained from NPR and NorPD. Symptoms of ADHD at age 5 years were measured using Conners' Parent Rating Scale-Revised, where higher scores correspond to more symptoms.

Results: The analyses on ADHD diagnosis and ADHD symptoms included 56 340 and 34 961 children respectively. Children exposed to NSAIDs prenatally had no increased risk of ADHD diagnosis (first trimester: HR 1.12, 95% CI 0.86;1.45, second trimester: HR 0.98, 95% CI 0.69;1.38, third trimester: HR 0.68, 95% CI 0.31; 1.46) or ADHD symptoms (first trimester: standardized mean difference 0.03, 95% CI −0.03;0.09, second trimester: standardized mean difference 0.03, 95% CI −0.04;0.11, third trimester: standardized mean difference 0.11, 95% CI −0.03; 0.25). There was no duration-response relationship for either outcome.

Conclusion: These findings suggest no substantially increased risk of ADHD diagnosis or symptoms in children prenatally exposed to NSAIDs, regardless of timing or duration.

Comment

Prenatal exposure to NSAIDs was investigated as a possible risk factor for ADHD because both COX1 and COX2 are expressed in the brain and NSAID might therefore influence child neurodevelopment. Prior to this study, only two studies had follow-up beyond 3 years of age, and one found slightly poorer executive function in exposed children.

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3.4 CARM data

As of 1 November 2021, the Centre for Adverse Reactions Monitoring (CARM) had not received any reports of adverse fetal/neonatal and/or maternal events associated with NSAID use in the third trimester of pregnancy.

The CARM database search, which included all NSAIDs, identified nine reports of exposure during pregnancy. Four of these reports concerned exposure to topical NSAIDs: Cataflam (1 report), Voltaren Emulgel (3 reports, all submitted by pharmaceutical company in 2009). Only one of the nine pregnancy reports involved exposure during the 3rd trimester. The report concerned exposure to Voltaren Emulgel at 38 weeks gestation, but no adverse event was reported.

All the other pregnancy cases concerned first trimester exposure. CARM has not received any reports of fetal or neonatal adverse effects associated with pregnancy exposure to a NSAID since 2001.

3.5 VigiBase data

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4 DISCUSSION AND CONCLUSIONS

The current data sheets for NSAID medicines contain inconsistent wording around use in pregnancy. In section 4.3 Contraindications, the data sheets for diclofenac, ibuprofen, tenoxicam and ketoprofen state that the medicine is contraindicated in the third trimester of pregnancy, and the data sheets for meloxicam and ketorolac state that the medicine is contraindicated throughout pregnancy. In contrast, the data sheets for naproxen, mefenamic acid and the COX-2 inhibitors (celecoxib, etoricoxib and parecoxib) do not include a pregnancy contraindication. (Table 1)

The NSAID data sheet wording on pregnancy varies in relation to:

- Use in pregnancy: not recommended (celecoxib, parecoxib, naproxen, and mefenamic acid) vs contraindication at least in the third trimester (ibuprofen, diclofenac, ketoprofen, meloxicam, tenoxicam and ketorolac)
- Use in first trimester
- Use in second and third trimester due to risk of fetal renal dysfunction/oligohydramnios (however, only the Noflam data sheet is silent on this issue)
- The need for ultrasound monitoring of amniotic fluid
- Use of the Australian pregnancy category (the assigned category varies between the COX-2 inhibitors: celecoxib is category B3, while etoricoxib and parecoxib are both category C)

At the 187th MARC meeting, the Committee asked Medsafe to review the information on the safety of NSAIDs in the third trimester, to facilitate discussion on the necessary wording changes concerning the risk of fetal renal impairment and oligohydramnios in the second trimester (as discussed at the 187th MARC meeting).

The literature review identified several large cohort studies using Scandinavian population-based data [8, 10, 12, 13] that have looked at pregnancy outcomes following NSAID exposure in the third trimester.

- Nielsen et al (2001) [8] found no association between second or third trimester use and low birth weight or pre-term delivery.

- Nezvalová-Henriksen et al (2013) [10] found a significant association for second trimester exposure to ibuprofen or diclofenac and low birth weight, second and third trimester exposure to ibuprofen and asthma at 18 months, and second or third trimester exposure to diclofenac and maternal bleeding.

- Nezvalová-Henriksen et al (2016) [12] found a significant association for first trimester exposure to ibuprofen and a decrease in birth weight, but exposure in second and third trimesters had no impact on birth weight.

- Hjorth et al (2021) [13] found no association between prenatal NSAID exposure and ADHD

In a large case-control study based on interview data in the North American Birth Defects Study/Pregnancy Health Interview Study, Van Marter et al (2013) [6] found no association between antenatal exposure to NSAIDs and an increased risk of PPHN. However, the exposure data in this study is based on maternal recall up to 6 months after delivery and may be incomplete and subject to bias.

The meta-analysis by Koren et al (2006) [4] is poorly documented. It shows a statistically significant risk of premature closure of the DA with third trimester NSAID exposure. However, the studies included in the analysis are small, dated and have wide confidence intervals (due to the small number of relevant cases) or no estimate (due to the absence of cases in either the treatment or control groups).

CARM has not received any reports of fetal or neonatal adverse effects associated with third trimester NSAID exposure. The most recent report concerning NSAID exposure during pregnancy was received in 2001. The lack of reports suggests that adverse effects associated third trimester NSAID exposure are well-known.

In summary, few studies have been conducted in the past 20 years to examine the association between 3rd trimester NSAID use and adverse fetal and neonatal outcomes. This review identified six studies that examined NSAID exposure in the third trimester and adverse fetal or neonatal outcomes. Among these studies, the positive associations identified with NSAID exposure in the latter half of pregnancy were: an increased risk of low birth weight with second trimester exposure to ibuprofen or diclofenac, an increased risk of asthma at 18 months with second or third trimester exposure to ibuprofen, and an increased risk of maternal bleeding with second or third trimester exposure to diclofenac. The paucity of studies on third trimester NSAID exposure and adverse fetal and neonatal outcomes is likely to reflect the conventional wisdom that NSAIDs are not recommended in late pregnancy.

5   ADVICE SOUGHT

The Committee is asked to advise:

- Whether all NSAID medicines should be contraindicated in the third trimester of pregnancy

- Whether the information in section *4.6 Fertility, pregnancy and lactation* of the data sheet for all NSAID medicines should be aligned
- 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   MARC Report: *Non-steroidal anti-inflammatory drug exposure in 2nd trimester and risk of fetal renal impairment and oligohydramnios.* 187th MARC meeting (9 September 2021).
2   Key data sheet wording about use in pregnancy (section 4.6) and pregnancy contraindication (section 4.3) for NSAIDs, (current on 23 February 2022).

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