FOLIA MEDICA CRACOVIENSIA
Vol. LXV, 4, 2025: 199–214
PL ISSN 0015-5616 eISSN 2957-0557
DOI: 10.24425/fmc.2025.156709

Population developmental hazard of over-the-counter NSAIDs

Franciszek Burdan[1,2], Maciej Burdan[2], Maja Potępa[1], Przemysław Kucharski[1]

[1] Experimental Teratology Unit, Department of Human Anatomy, Medical University of Lublin, Lublin, Poland
[2] St. John's Cancer Centre, Lublin, Poland

Corresponding author: Prof. Franciszek Burdan, M.D., Ph.D., E.R.T.
Experimental Teratology Unit, Department of Human Anatomy, Medical University of Lublin
ul. Jaczewskiego 4, 20-090 Lublin, Poland
Phone: +48 603 767 649; E-mail: fb3@wp.pl

Abstract: Introduction: Over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs, i.e., aspirin, diclofenac, dipyrone, ibuprofen, naproxen) and paracetamol are commonly ingested medications during pregnancy that for a long time were classified as relatively safe for mothers and fetuses.
Areas covered: The review focuses on developmental toxicity of OTC NSAIDs.
Expert opinion: Same epidemiological studies show that OTC antipyretics and painkillers may increase risk of spontaneous abortion, intrauterine growth retardation, preterm constriction of ductus arteriosus with secondary persistent pulmonary hypertension, reduced fetal renal perfusion that leads to oligohydramion, prolonged pregnancy, as well as selected congenital anomalies, including orofacial cleft, cardiovascular (i.e. ventricular septal defect, pulmonary valve stenosis) and neural tube defects (i.e., anophthalmia/microphthalmia, encephalocele, spina bifida), amniotic bands/limb body wall defects, and transverse limb deficiencies. However, other reports prove high prenatal tolerability or even beneficial effect in case of selected maternal sicknesses, especially influenza or disease with fever and thrombotic complications. The best advice for pregnant women is to avoid any xenobiotic, especially multidrug therapy, but in case OTC NSAIDs are needed they should be ingested in lowest effective dose under physician consultation. After gestational week 20, NSAIDs could be ingested with caution and withdrawn at gestational week 32, since they may induce constriction of the ductus arteriosus and affect renal function. The only exception is low-dose of aspirin, ingestion of which should be stopped one week before delivery with epidural anesthesia or could be prolonged until the end of pregnancy in patients with antiphospholipid syndrome.

Keywords: non-steroidal anti-inflammatory drugs, spontaneous abortion, over-the-counter medication, cyclooxygenase inhibitor, congenital defects, developmental abnormalities.

Submitted: 23-Oct-2025; **Accepted in the final form:** 30-Nov-2025; **Published:** 31-Dec-2025.

Introduction

Pregnancy is a physiological condition that may be complicated by a number of discomforts, secondary to gestational adaptation changes. Usually the initial ones are nausea and fatigue but due to increasing uterinal size heartburn, congestion, constipation and backache may also be reported. Kamysheva *et al.* [1] stress that 76% of pregnant women suffer from various forms of pain, including headache, back and groin ones, while gastrointestinal complications are only slightly rarer (75%). Similar symptoms are also typical for various disorders that may destroy welfare of both mother and embryo/fetus. It is especially important for infectious diseases since their pathogens may have teratologial potential (e.g., rubella and measles virus) and may induce fever and stress that are responsible for abnormal development themselves. Despite the increased knowledge of a potential drug's harmful effects; in such situations, many women ingest various substances, often without any consultation with their physician. It is especially important for the so-called over-the-counter (OTC) medications that are available without prescription from a healthcare professional (drugstores) and, depends on the country, also in general stores, supermarkets, gas stations, self-operator dispenser machines, etc. [2]. Most of them are used to lower the intensity of abnormal symptoms, not to treat the disease itself. From among all the OTC products the most commonly consumed ones are nonsteroidal anti-inflammatory drugs (NSAIDs). They usually provide dose-related antipyretic, analgesic and anti-inflammatory activity, secondary to non-selective inhibition of inducible isoform of cyclooxygenase (COX-2). Due to interference with constitutive isoform (COX-1) and transcriptional nuclear factor kappa B (NF-κB) they also provide antithrombotic, chemoprotective, neuroprotective and tocolytic activity as well as various well-known side effects including gastrointestinal-, hepato-, nephron-, neuro- and hematotoxicity [3–6]. Depending on the country, from among all NSAIDs in the OTC market acetylsalicylic acid (ASA), diclofenac, ibuprofen, metamizole and naproxen are available. It is worth pointing out that ASA — unlike other OTC NSAIDs — in low doses (<40–60 mg) is a selective COX-1 inhibitor, while in greater ones becomes a non-selective compound that inhibits both COX-1 and COX-2 activity. However, there are two other COX inhibitors like paracetamol and propyphenazone, that belong to the OTC list but do not have any anti-inflammatory effect in therapeutic doses. All of the listed substances easily pass through the placenta and reach similar or even higher concentrations in fetal blood than in maternal blood [5–8].

Usage of over-the-counter NSAIDs during pregnancy

According to Czeizel and Racz [9] only 9.1% of women do not take any drugs during pregnancy. Such incidence increased (26.8%) when diet supplementation products (i.e., vitamins, micro- and macro-elements) were excluded. The remaining women took usually two different medications and in the evaluated Hungarian population the most common ones were antibiotics (42%), anxiolytics (40%), hormones (40%), as well as NSAIDs (26%). However, newer epidemiological data published by Olesen *et al.* [10, 11] and Olsen *et al.* [12] stress that COX inhibitors, including NSAIDs, are the most commonly consumed xenobiotics during pregnancy. Glover *et al.* [13] indicates that 92.6% of women take OTC preparations while pregnant with more than 20% self-medicating with at least five different drugs. Furthermore, US National Birth Defect Prevention Study and the Boston University Slone Epidemiology Center Birth Defects Study, stresses that acetaminophen is the most commonly administered painkiller (65.5% out of 23000). Much lower

consumption was reported for remaining COX inhibitors, e.g., ibuprofen (15%), ASA (4%). However, using the same database Hernandez *et al.* [14] state that among 3173 pregnant women who frequently ingested NSAIDs during the first trimester ASA was used in 22%, while ibuprofen, naproxen and other ones in 77, 15 and 1.2%, respectively. The data was different in a group that ingested drugs sporadically (n =1452) — "as needed": ASA (15%), ibuprofen (85%), naproxen (17%) and other NSAID (34%). Interestingly only 15% responders used one type of the drug. The data was partially confirmed in currently published study by Lupatelli *et al.* [15] which reports high usage of prescribed and non-prescribed drugs (81.2%) or OTC medication (66.9%) among pregnant women (n = 9459). Interestingly, 68.4 and 17% of responders ingested at least one OTC product for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. Similar to previous reports paracetamol was the most commonly ingested analgesic (47.7%) while remaining compounds like ASA (0.6%), metamizole/dipyrone (0.5%) and other OTC NSAIDs were rarely revealed (4.5%). Data confirmed that drug ingestion has a strong geographical implication. In case of NSAIDs the highest usage was reported in South America (17.1%) and the lowest in Western Europe (2.2%). The highest OTC drug ingestion for chronic/long-term disorders was typical for older women, lower educational level, housewives, non-immigrants and women with an unplanned pregnancy. Current Norwegian study performed among 90,417 pregnant women showed that 7.2% of them (n = 6511) ingested NSAIDs, mainly ibuprofen, diclofenac, naproxen or piroxicam, or their combination [16]. Musculoskeletal pain, fever, headache or migraine were the most common indications for treatment. Furthermore, women frequently ingested other drugs, including paracetamol (75.1%), followed by opioid analgesics (7.1%), antidepressants (2.4%), anxiolytics (1.4%), hypnotics (1.0%) and systemic corticosteroids (1.3%). Similar drug distribution was reported in a US study [17] but slightly higher was in France where 13.5% of pregnant women ingested prescription drugs while 2% OTC NSAIDs [18, 19]. On the other hand, most of the reported studies are based on questionnaires and are related to data presented by mothers, dependent on their memory and cooperativeness, which highly influences results. In this place it is worth to mention that Alano *et al.* [19] confirmed metabolites or NSAIDs themselves in meconium of 49.5% out of 101 examined newborns: 22.8% were positive for ibuprofen, 18.8% for naproxen, 7.9% for indomethacin and 43.6% for ASA. However, there was a low association between maternal history of NSAID use and their detection in meconium (odds ratio [OR:] = 21.47; 95% confidence interval [95%CI:] = 7.12–64.71). Such data indicates that ingestion of OTC NSAIDs may be even higher than in the presented above cited epidemiological studies.

Developmental toxicity of over-the-counter NSAIDs

For a long time NSAIDs have been considered as relatively safe for human offspring, with exception to high dose of ASA (> 325 mg) that may increase prevalence of intracranial bleeding in newborns during labor [2, 7]. However, in-utero exposure may be complicated by intrauterine growth retardation (IUGR), ductus arteriosus constriction with secondary persistent pulmonary hypertension, reduced fetal renal perfusion that leads to oligohydramion, prolonged pregnancy, high risk of spontaneous abortion, stillbirth and birth defects [7]. With exception of preterm constriction of ductus arteriosus proved for most NSAIDs and intracranial newborn bleeding, typical for ASA; the remaining complications were reported mostly for the group of drugs not for particular compound or usually in single clinical studies. Due to insufficient human clinical and epidemiological data most of OTC NSAIDs, similar to other drugs, belong to group B according

to the risk classification by Food and Drug Administration (FDA) [7]. Only aspirin is classified to group C. However, developmental toxicity data is not well-known by physicians, pharmacists and pregnant women. Such a strange situation was already pointed by US National Institute of Child Health and Human Development [20] that together with FDA [21] and Teratology Society are responsible for evaluation of the human risk assessment. Based on their recommendations since 2008 FDA suggests to omit lettering A-X classification instead of full narrative information on potential risks that has to be presented for each woman who is or may become pregnant or a breastfeeding one.

Due to low numbers of exposed patients, most of the clinical studies explain developmental effects of all the NSAIDs as a group, not a selective compound, and majority of them were performed for both prescribed and OTC COX inhibitors. The only exception is aspirin and paracetamol which were more commonly ingested due to high worldwide consumption. However, newer data was also selected for ibuprofen and naproxen. Due to insufficient space, the review presented below will concentrate mostly on human, not animal findings.

Infertility and premature termination of pregnancy

Animal and human studies suggest that NSAIDs, as potent COX inhibitors, may affect both ovulation by delaying follicular release and implantation, since both processes are related to overexpression of COX-2. However, none of the evaluated NSAIDs provide sufficient contraception. NSAIDs may also be responsible for preterm termination of pregnancy in a later stage. Death of the conceptus before the 20th week of gestation, defined as spontaneous abortion (miscarriage), is a common complication [22]. Its incidence is estimated at 15% but it is probably higher (22–30%) based on the decrease of the daily urinal level of human chorionic gonadotropin [23]. Most of them (80%) occur before the 12^{th} week and are associated with parental genetic abnormalities, advanced maternal age, uterine anatomical abnormalities, endocrine diseases (i.e., diabetes mellitus, hypothyroidism, polycystic ovary syndrome), hypercoagulability diseases, obesity, smoking and increased consumption of alcohol and caffeine. On the other hand, fetal death after 20 weeks of gestation is defined as stillbirth and occurs in 8 per 1000 [24]. However, half of them are classified as asphyxia or are associated with maternal illnesses, mostly hypertension and infections. Moreover, congenital anomalies were seen in 20% of such cases.

Velez Edwards *et al.* [17] presents probably the only study undertaken to establish the risk of spontaneous abortion among women (n = 2780) treated exclusively with OTC NSAIDs during pregnancy (n = 1185). However, the risk estimated as hazard ratio was low (HR: 1.01, 95%CI: 0.82–1.24), including models adjusted for maternal age (HR: 1.00, 95%CI: 0.81–1.23). The recent analysis performed by the same statistics showed protection of OTC drugs from miscarriage among African Americans (HR: 0.84; 95%CI: 0.73–0.96) but no effect in Caucasians (HR: 1.01; 95%CI: 0.88–1.16) [25]. Li *et al.* [26] established 80% increased risk of spontaneous abortion among 1055 US women treated with NSAIDs (HR: 1.8l, 95%CI: 1.0–3.2). Higher risk was reported for ingestion around conception (HR: 5.6, 95%CI: 2.3–13.7) or when drugs were used for longer than a week (HR: 8.1, 95%CI: 2.8–23.4). Such data was confirmed for ASA and hazard risk for all three groups was estimated at 1.6 (95%CI: 0.6–4.1), 4.3 (95%CI: 1.3–14.2) and 3.0 (95%CI: 0.7–12.9), respectively. However, insignificant elevation was revealed for paracetamol — 1.2 (95%CI: 0.8–1.8), 0.8 (95%CI: 0.2–3.3), 0.7 95%CI: (0.2–2.9). Interestingly, unlike NSAIDs and ASA slightly higher risk was noted among women who ingested paracetamol after conception

(2.2, 95%CI: 0.8–2.0) and for shorter than one week (1.3, 95%CI: 0.8–2.1). Similar data was found in a Danish study [27] in which the risk of spontaneous abortion among women who took any prescribed NSAIDs was 1.05 as calculated adjusted odds ratio (95%CI: 0.80–1.39). Odds ratios (OR) ranged from 2.69 (95%CI: 1.81–4.00) to 6.99 (95%CI: 2.75–17.74) for drug usage 7–9 weeks and one week before miscarriage, respectively. However, there were no stillbirths related to the treatment. Such results are partially supported by Canadian observations. From among 67 160 pregnancies, Nakhai-Pour *et al.* [28] selected 4705 terminated by spontaneous abortion. In this group naproxen was the most common non-aspirin ingested NSAID (2.8%), followed by ibuprofen (1.3%), diclofenac (0.7%). The treatment was significantly associated with a 2.4-fold increase of risk of spontaneous abortion (OR: 2.43, 95%CI: 2.12–2.79). It was higher (OR: 3.47, 95% CI 2.01–6.00) in case exposure took place in the two weeks immediately before abortion. One of the most important findings of the study is a fact that all non-aspirin NSAIDs significantly increased the risk of spontaneous abortion but without any dose-relations. From among OTC available drugs, the highest risk was found for diclofenac (OR: 3.09, 95%CI: 1.96–4.87), followed by naproxen (OR: 2.64, 5%CI: 2.13–3.28) and ibuprofen (OR: 2.19, 95%CI: 1.61–2.96). Interestingly, lower risk was reported for selective COX-2 inhibitors. Opposite results are presented in the recently published Israel study involved data of 66 547 pregnancies, including 7598 (11.4%) terminated by spontaneous abortion [29]. Moreover, 4495 out of 65 457 (6.9%) mothers were exposed to NSAIDs during gestation. Like in the Canadian study, the highest exposure was noted for OTC available compounds, including ibuprofen (4.25%), diclofenac (1.4%) and naproxen (1.0%). It is also important that 259 women were treated with 2, 26 with 3 while 2 with 4 different NSAID medications. The adjusted hazard ratios for spontaneous abortion for non-selective COX inhibitors was 1.1 (95%CI: 0.99–1.22) for the whole group and 1.06 (95%CI: 0.93–1.22) for ibuprofen, 1.19 (95%CI: 0.97–1.46) for diclofenac, 0.97 (95%CI: 0.74–1.28) for naproxen. The significantly increased risk was found only for indomethacin (OR: 2.82, 95%CI:1.70–4.69) which is a strong non-selective COX inhibitor, available only on prescription.

There is a number of studies dedicated exclusively to ASA, mostly for low doses, used in prevention of venous thromboembolism, antiphospholipid syndrome and preeclampsia but their findings were meta-analyzed by Henderson *et al.* [30]. Based on data from 21 studies involving 50529 women, authors state that in utero exposure to ASA reduced the risk of preeclampsia and has beneficial effects on perinatal health outcomes. Incidence of preterm birth was reduced by 14%. Pooling of perinatal mortality findings suggested a tendency toward a reduced risk of perinatal mortality (rate ratio [RR]: 0.92; 95%CI: 0.76–1.96), particularly when analyses were limited to women with increased risk of preeclampsia (RR: 0.81; 95%CI: 0.65–1.01). Such data was confirmed in another meta-analysis by Roberge *et al.* [31]. Authors analyzed 42 studies, involving 27 222 women, stated that low-dose aspirin (50–150 mg/day) started before the 16th week of gestation compared with low-dose aspirin started after the 16th week of gestation is associated with a significant reduction of perinatal death (RR: 0.41, 95%CI: 0.19–0.92) vs (RR: 0.93, 95%CI: 0.73–1.19) also pre-eclampsia (RR: 0.47, 95% CI 0.36–0.62; vs RR: 0.78, 95%CI: 0.61–0.99), severe pre-eclampsia (RR: = 0.18, 95%CI:, 0.08–0.41; vs RR: 0.65, 95%CI: 0.40–1.07), and preterm birth (RR: 0.35, 95%CI: 0.22–0.57; vs RR: 0.90, 95%CI: 0.83–0.97). Interestingly, all the evaluated pregnancy outcomes were not related to the dose of ASA, since similar results were found among women treated with doses of ≤80 and ≥100 mg daily. Similar observations were also reported by Kozer *et al.* [32]. However, in that meta-analysis, observations undertaken among women exposed to higher doses of ASA were also included. The risk of miscarriage was insignificantly

affected (RR: 0.92, 95%CI: 0.71–119) but similar to above presented data, women who ingested ASA had a lower risk of preterm delivery (RR: 0.92, 95%CI: 0.86–0.98). Insignificant differences of perinatal mortality were also revealed (RR: 0.92, 95%CI: 0.81–1.05).

Unlike the number of studies dedicated for spontaneous abortion, there is limited data regarding stillbirth. Pastore *et al.* [33] evaluated the incidence of fetal death after 20 weeks of gestation and for infants within 24 hours after birth. Among 332 positive cases and 357 control ones, the highest drug exposure was found for acetaminophen (44.9 vs 53.8%), followed by antihistamines (5.7 vs 8.4%), non-specified pain medication (6.9 vs 4.2%) and ASA (5.7 vs 8.4%). None of the presented drugs increased the risk, however positive influence was found for combining the non-specified migraine and prescription pain medications for the first (RR: 1.3, 95%CI: 1.0–1.8), second (RR: 1.4, 95%CI: 1.1–1.8) but not for the third trimester (RR: 1.0, 95%CI: 0.8–1.2). However, higher risk was proved for stillbirths due to congenital malformations in groups exposed to prescribed painkillers during the first or second trimester (OR: 7.5, 95%CI: 2.3–23.1). Adjusted RR for acetaminophen in the first and second trimester was 0.9 (95%CI: 0.8–1.0) and 0.8 (95%CI: 0.8–0.9) for the third trimester. Similar insignificant data was found for the first (RR: 0.9, 95%CI: 0.7–1.1) and second trimester (RR: 0.8, 95%CI: 0.6–1.2) for ASA. Lack of increased risk of a preterm birth was also revealed among women (n = 98,140) who ingested paracetamol during the third trimester of pregnancy (OR: 1.14, 95%CI: 1.03–1.26) [34]. However, the risk was higher for mothers with preeclampsia (OR: 1.55, 95%CI: 1.16–2.07) but an insignificant increase was also noted for patients with normal blood pressure (OR: 1.08, 95%CI: 0.97–1.20).

Intrauterine growth retardation/restriction

Growth impairment is typical for fetuses with congenital malformation(s) but such complications may be also visible within well-formed offspring. Incidence of IUGR (defined as birth weight below the 10th percentile) is estimated to be 15.5% worldwide, but its number is greatly underestimated [35]. In about 25% cases various chromosomal abnormalities were evaluated but the most common risk factors were maternal malnutrition, mostly alimentary deficiency, cigarette smoking, ethanol and drug abuse. Dose-related IUGR was described in most of the experimental studies in which developmental toxicity of NSAIDs was examined. However, human data does not fully support such findings. Most of the studies with lower doses of ASA even stress beneficial effect of the treatment, especially in patients with various thromboembolism complications [30, 31]. Meta-analysis by Henderson *et al.* [30] reported that incidence of IUGR was reduced by 20% among offspring delivered by women prenatally treated with low doses of ASA. Moreover, higher newborn birth weight (130 g) was also found in this group. Similar data is presented by Roberge *et al.* [31] who revealed lower risk of fetal growth restriction among children in-utero exposed to low-doses of aspirin before (RR: 0.46, 95%CI: 0.33–0.64) and after the 16th gestational week (RR: 0.98, 95%CI: 0.88–1.08). Similar but insignificant data (RR: 0.96, 95%CI: 0.87–1.07) was presented in an older meta-analysis [32]. Good tolerability was also proved for other prescribed NSAIDs in above cited paper by Nielsen et al [27] in which the odds ratio for IUGR was low 0.79 (95%CI: 0.45–1.38). However, the risk significantly increased (OR: 3.09; 95%CI: 0.91–10.52) among offspring in-utero after exposure to more than one NSAID. On the other hand, positive risk was also presented by Nezvalová-Henriksen *et al.* [16] based on data from the Norwegian Mother and Child Cohort Study and Medical Birth Registry of Norway Datasets (90 417 completed pregnancies, 6511 women exposed to NSAIDs) for the second trimester ingestion of ibuprofen (OR:1.7, 95%CI: 1.3–2.3) and diclofenac (OR: 3.1, 95%CI: 1.1–9.0).

Structural congenital abnormalities

Congenital malformations (birth defects) are defined as all persistent structural, functional and biochemical abnormalities developed during the prenatal period, involving single or multiple organs, systems or the whole body, which expend phenotype changes modulated by epigenetic factors for the proper population. Usually they are recognizable at birth or during the neonatal period. Their worldwide incidence is an estimated 1 in 33 infants and result in approximately 3.2 million birth defect-related disabilities every year. An estimated 270 000 newborns die during the first 28 days of life every year from congenital anomalies [36]. Such developmental anomalies may complicate obstetrical therapy, but were sporadically observed in laboratory animals and humans exposed to NSAIDs.

The initial study by Richards [37], Nelson and Forfar [38] and Saxen [39] indicated that ASA may have teratogenic potential, promoting mostly oral cleft. Later, higher risk of cardiovascular abnormalities, in particular abnormal septation of the truncus arteriosus (transposition of great arteries, tetralogy of Fallot) was found among 80 out 390 offspring in-utero exposed to the drug. Cardiac developmental toxicity was later confirmed by Zierler and Rothman [40] but negated by Werler *et al.* [41] who established low, no dose-related relative risk of any heart anomalies (RR: 0.9; 95%CI: 0.8–1.1). It was similar for aortic stenosis (RR: 1.2; 95%CI: 0.6–2.3), coarctation of the aorta (RR: 1.0; 95%CI: 0.6–1.4), hypoplastic left ventricle (RR: 0.9, 95%CI: 0.6–1.4), transposition of the great arteries (RR: 0.9; 95%CI: 0.6–1.2) and cono-truncal defects (RR: 1.0; 95%CI: 0.8–1.2). It is worth to stress that results came from a large database involving 1381 infants with cardiovascular abnormalities and 6966 children with other developmental abnormalities used as a control group. Similar data was found based on 5015 cases with congenital cardiovascular defects out of 57 730 children born in Sweden in 1995–2001 [42]. The risk was similar for both ASA (OR: 1.1, 95%CI: 0.76–1.33), ibuprofen (OR: 1.08, 95%CI: 0.78–1.50), diclofenac (OR: 1.3, 95%CI: 0.78–2.16), and all NSAIDs (OR: 1.2; 95%CI: 0.99–1.55) but higher for naproxen (OR: 1.7, 95%CI: 1.14–2.54). Comparable results are presented by van Gelder *et al.* [43] based on Medical Birth Registry of Norway (see below). However, much higher risk of cardiovascular defects was found in a previous Scandinavian study (OR: 1.86, 95%CI: 1.32–2.62) [44] but the evaluated group was smaller (n = 2557 completed pregnancy). Greater risk was also reported for the orofacial cleft (OR: 2.61, 95%CI: 1.01–6.78) while for any structural abnormalities was relatively low (OR: 1.04, 95%: 0.84–1.29). An increased tendency for congenital cardiac defect was also revealed in a Canadian study among offspring of 36 387 pregnant women exposed in utero to NSAID inhibitors [45]. It is the first large human study in which high risk was found for ventricular septal defects (OR: 3.34; 95%CI: 1.87–5.98) and similarly to same above presented articles for all the congenital structural anomalies (OR: 2.21; 95%CI: 1.72–2.85). It should also be pointed out that higher risk of gastroschisis was reported for ASA by Kozer *et al.* [46] (OR: 2.37, 95%CI: 1.44–3.88) and Martinez-Frias *et al.* [47] (OR: 3.33, 95%CI: 1.05–9.80). Torfs *et al.* [48] established it for both ASA (OR: 4.7, 95%CI: 1.2–18.1) and ibuprofen (OR: 4.0, 95%CI: 1.0–16.0). Similar data was pointed out in the most recently published meta-analysis [49], that included 751,954 pregnancies. Pooled RRs showed significant association between aspirin (RR 1.66, 95%CI 1.16–2.38) and ibuprofen (RR 1.42, 95%CI: 1.26–1.60), while lack of association was found for paracetamol (RR 1.16, 95%CI: 0.96–1.41).

However, good prenatal tolerability without increased risk of teratogenicity was also confirmed for ASA in both above presented meta-analyses by Henderson *et al.* [30] and Roberge *et al.* [31] as well as preliminary results of the US Collaborative Perinatal Project [50] which covers data of 50,282 completed pregnancies. In that group 14,864 women were treated with ASA in the first

trimester while 32,164 in different periods of pregnancy. Similar data was found in the first large multicenter study that evaluated developmental effects of ASA and other NSAIDs, performed in the US between 1985–1992. It involves 229,101 completed pregnancies, but only in some cases prenatal exposure to over-the-counter COX inhibitors and developmental abnormalities were revealed [7]. The incidence of all the evaluated major congenital malformations (i.e., oral clefts, spina bifida, polydactyly, limb reduction, cardiovascular defects) was similar between OTC drugs and reached 4.9% for ASA, 4.8% for naproxen,4.6% for acetaminophen and 4.5% for ibuprofen. Opposite data, related especially to neural tube defects, is presented but newer analysis based on Slone Epidemiology Center Birth Defects Study and the US National Birth Defects Prevention Study [14]. The higher risk for anophthalmia/microphthalmia was proved for all NSAIDs (OR: 2.1, 95%CI: 1.3–3.5), as well as ASA (OR:3.0, 95%CI: 1.3–7.3), ibuprofen (OR: 1.9, 95%CI: 1.1–3.3) and naproxen alone (OR: 2.8, 95%CI: 1.1–7.3). All three compounds increase risk of neural tube defects, in particular: anencephaly/craniorachischisis in case of ASA (OR 2.0, 95%CI: 1.0–3.9), spina bifida in case of ibuprofen (OR:1.6, 95%CI: 1.2–2.1) and encephalocele in case of naproxen (OR: 2.5, 95%CI: 0.89–7.3). Similar data was found for cleft defects, including cleft palate whose risk was higher for ASA (OR: 1.8, 95%CI: 1.1–2.9) followed by ibuprofen (OR: 1.3, 95%CI: 0.99–1.7) and naproxen (OR: 1.4, 95%CI: 0.84–2.5) However, in the case of concomitant palate and lip cleft the risk for the drug was as follow ASA (OR: 1.1; 95%CI: 0.72–1.7) ibuprofen (OR: 1.3, 95%CI: 1.1–1.6) and naproxen (OR: 1.7, 95%CI: 1.1–2.5). Higher risk was also found for transverse limb deficiency in case of naproxen (OR: 2.0, 95%CI: 1.0–4.4), amniotic bands/limb body wall for ASA (OR 2.5, 95%CI: 1.1–5.9) and ibuprofen (OR: 2.2, 95%CI: 1.4–3.5), while isolated pulmonary valve stenosis was reported only for naproxen (OR: 2.4, 95%CI: 1.3–4.5). Based on the same database, an increased risk of hemifacial microsomia was previously reported in children prenatally exposed to ibuprofen (OR: 1.7; 95%CI: 0.9–3.0) [51]. However, no association of muscular ventricular septal defects and prenatal exposure to NSAIDs (OR: 1.0; 95%CI: 0.64–1.6) during the first trimester or month before pregnancy was found (OR: 0.99; 95%CI: 0.67–1.5) [52]. Such data was partially confirmed in a new analysis among 267 infants with spina bifida and 6,233 controls, that mothers report periconceptional intake of evaluated drugs in 20% (16% ibuprofen, 4% aspirin, 3% naproxen, and <1% COX-2 inhibitors) [53]. For any NSAID use, the ORs among low and high folic acid consumption by women were 1.70 (95%CI 1.13–2.57) and 1.09 (95%CI: 0.69–1.71), respectively.

On the other hand, a lack of teratogenicity of NSAIDs was revealed in Israeli observations taken among 109,544 completed pregnancies [54]. In-utero exposure to entire groups of NSAIDs (n = 5153) in the first trimester, was not associated with an increased risk of major congenital malformations (OR: 1.07, 95%CI: 0.96–1.21). Similar data was found for selected compounds, including those from the OTC list. Insignificantly increased risk of congenital abnormalities was also reported by Nielsen *et al.* [27] who reported 46 malformed offspring delivered by 1106 women treated during early pregnancy with prescribed NSAIDs (OR: 1.27, 95%CI: 0.93–1.75). Similar data is presented by van Gelder *et al.* [43] based on Medical Birth Registry of Norway, involving 69,929 women including 3023 treated with NSAIDs in gestational weeks 0–12. Women who used NSAIDs during early pregnancy were more commonly married, well-educated, obese and had a previous miscarriage, stillbirth, or induced abortion. The prevalence of all major birth defects was 2.7% (80 affected NSAID-exposed and 1,730 non-exposed infants), while selected birth defects were diagnosed in 638 children (1.0%). A total of 18 offspring had a neural tube defect (including 2 with anencephaly, 2 with encephalocele, and 15 with spina bifida), 435 congenital

heart defects (including 38 with cono-truncal defect, 289 with ventricular septal defect, 156 with atrial septal defect, and 7 with atrioventricular septal defect), 134 an orofacial cleft (including 44 with cleft palate and 90 with cleft lip with or without cleft palate), 20 an esophageal defect, 16 an anorectal malformation, 11 a diaphragmatic defect, and 21 an abdominal wall defect (including 6 with omphalocele and 15 with gastroschisis). In 42 cases (6.6%) multiple defects were noted. The risk of congenital malformation for NSAIDs — as a group of drugs — was low (OR: 0.7, 95%CI 0.4–1.1) for any of the most commonly observed birth defects, including all congenital heart malformations (OR: 0.9 (95% CI 0.5–1.4), any septal defects (OR: 0.8 (95%CI: 0.5–1.4), including ventricular (OR: 0.7, 95%CI: 0.4–1.4) and atrial septal defects (OR: 1.1, 95%CI: 0.5–2.3). Slightly increased risk for atrial septal defects after NSAID exposure in gestational weeks 5–8 was found (OR: 1.6, 95%CI: 0.7–3.9). No associations were observed between the selected birth defects as a group and exposure to diclofenac and other acetic acid derivatives, including diclofenac (only 1 exposed case), propionic acid derivatives including ibuprofen and naproxen (OR: 0.7, 95%CI: 0.4–1.2), ASA (OR: 1.1, 95%CI: 0.4–3.5) or multiple NSAIDs exposure (OR: 2.5, 95%CI: 0.6–10.1). Increased risk of congenital heart defects (OR: 3.7, 95%CI: 0.9–14.9), especially septal defects (OR 3.9, (95%CI: 0.9–15.7) was found only for multiple NSAIDs during gestational weeks 0–12 but data was obtained using only 2 positive cases. Marginal association (OR: 1.2, 95%CI: 1.0–1.6) between ibuprofen exposure during the first trimester and structural heart anomalies detected during the first 18 months of life was revealed in the currently published Norwegian study but a lack of significant effect was reported for all other structural abnormalities [16].

In the available literature there are only epidemiological studies that evaluate the fetal outcome of dipirone (metamizole), that in some countries belong to the OTC list as well [55]. The Hungarian database (22 843 neonates with and 38 151 without congenital anomalies) was able to detect 74 malformed and 1911 healthy infants in-utero exposed to dipyrone. In such a group higher risk was found for diaphragmatic (prevalence OR: 2.7; 95%CI: 1.0–6.8) and cardiovascular defects (OR: 1.3; 95%CI: 1.0–1.7) and other isolated congenital abnormalities (OR: 1.8; 95%CI: 1.1–2.9). However, evaluation of only medically recorded drug use did not confirm these possible associations. The comparison of dipyrone treatment between 25 congenital abnormality groups and malformation controls as the referent group also did not confirm any difference in the dipyrone use during the second and third months of gestation.

As it was presented above, paracetamol is the most commonly ingested OTC antipyretic and painkiller. It does not belong to NSAIDs, but its developmental toxicity should be pointed out due to high usage among pregnant women (see above). Feldkamp *et al.* [56] reported that drug intake — among women reporting infection and fever in the first trimester of gestation (n = 11,610) — was associated with a significantly decreased risk for anencephaly or craniorachischisis (OR: 0.35, 95%CI: 0.08–0.80), encephalocoele (OR: 0.17, 95%CI: 0.03–0.87), anotia or microtia (OR: 0.25, 95%CI: 0.07–0.86), cleft lip with or without cleft palate (OR: 0.44, 95%CI: 0.26–0.75), and gastroschisis (OR: 0.41, 95%CI: 0.18–0.94). On the other hand, exposure to paracetamol during the first and second trimesters was also associated with an increased incidence of cryptorchidism (OR: 1.33, 95%CI: 1.00–1.77) [57]. Such data is important since it was found in a large, well-established Danish National Birth Cohort among 47,400 live-born boys in which 980 were diagnosed with the urethral defect. A higher occurrence (OR: 1.38, 95%CI: 1.05–1.83) was found when the drug was ingested for more than four weeks during testicular descending that takes place during the 8–14th gestational week. However, an exposure to ibuprofen and ASA was not associated with this anomaly. Such findings are especially important since ASA

blocks the androgen response to human chorionic gonadotropin, which stimulates androgen synthesis and plays a core role in the organ's descent to the scrotum [58]. However, the data was not confirmed by Rebordosa *et al.* [59]. in offspring exposed to acetaminophen during the first trimester (n = 26,424). The risk of any congenital abnormalities was insignificant (HR: 1.01, 95%CI: 0.93–1.08), with exception for complex abnormalities of the ear, face and neck, known as medial cysts (HR: 2.15, 96%CI: 1.17–3.95).

Preterm closure of the ductus arteriosus

The ductus arteriosus is a short artery that directly connects the pulmonary trunk and the terminal part of arch of aorta during the fetal period. It is responsible for shunting 90% of the right ventricular blood volume from the lesser and greater circulation. Prenatally its proper drainage is stimulated mainly by a low local partial oxygen pressure and endothelially synthesized vasodilator compounds such as nitric oxide and prostaglandins, in particular PGE2. Premature closure leads to an acute increase of right ventricular afterload and pressure, which may be complicated by tricuspid valve regurgitation with right ventricular-atrial shunt. In severe stages, right to left transatrial shunt and increased pulmonary blood flow are responsible for the dilatation of the left ventricle, but the most common hemodynamic complication is prenatal pulmonary hypertension [5–7, 60, 61].

Preterm closure of the ductus arteriosus is the most typical prenatal complication of COX inhibitors, especially when ingested in late gestation (>30th week). However, it may also occur together with other cardiovascular anomalies (e.g., restrictive foramen ovale, transposition of the great arteries) as well as spontaneously, whose incidence is estimated around 0.3–1.3% of pregnancies [62]. In case of NSAIDs, the mechanism of closure is partially similar to physiological closure that take place within 10–15 hours after birth. The evaluated compounds decrease synthesis of vasodilatation eicosanoids (PGE2, PGI2) and stimulate initially functional constriction or occlusion, but later secondary to endothelial adhesion and proliferation as well as migration of smooth muscle cells from the media to intima layer of arterial wall, the permanent closure occurs [6, 62].

The complication was also reported in various clinical and epidemiological studies. Meta-analysis presented by Koren *et al.* [63] showed that the highest risk was seen among infants prenatally exposed to indomethacin (OR: 15.04, 95%CI: 3.29–68.68) when compared with offspring delivered by untreated mothers. However, effect was insignificantly higher (OR: 2.12, 95%CI: 0.48 to 9.25) when data was compared with other drugs. Furthermore, insignificant risk (OR: 0.8; 95%CI: 0.5–1.3) was also found in a US multicenter-study, among children born with persistent pulmonary hypertension (n = 377) [64]. In such a group only 33 infants were in-utero exposed to NSAIDs during the third trimester of gestation. Such findings were proven for ASA, ingested at any time during pregnancy, as well as ibuprofen (OR: 0.65; 95%CI: 0.38–1.12), ASA (OR: 1.82, 95%CI: 0.92–3.62), paracetamol (OR: 0.80, 95%CI: 0.643–1.03) and other NSAIDs used during the third trimester. Similar data was established when the analyses were restricted to infants born at or beyond 37 weeks of gestation.

Bleeding complications

Bleeding complications are the most typical for ASA due to its high antithrombotic activity. In low doses (60–150 mg/day), the drug irreversibly blocks a platelet COX which results in a greater inhibitor thromboxane B2 synthesis than prostacyclin production by endothelial cells. This

beneficial effect seems to be limited to the maternal body since ASA administered for three weeks before labor affected only maternal and not fetal activity of platelet COX [7]. The data was confirmed by Benigni *et al.* [65] who found that the drug (60 mg) selectively suppressed maternal platelet thromboxane B_2 while sparing vascular prostacyclin, and only partially suppressed neonatal platelet function (69%), allowing hemostatic competence in the fetus and newborn without any developmental abnormalities. This safety was recently confirmed by meta-analysis [30]. The drug did not increase risk of intracranial fetal/neonatal bleeding (RR: 0.84; 95% CI 0.61–1.16) or postpartum maternal hemorrhage but the risk of abruption was not eliminated. However, Sasidharan [66] reported fetal intracranial hemorrhage due to antenatal low dose aspirin intake. In-utero exposure to ASA in doses over 325 mg, especially before labor, may affect clotting and lead to hemorrhagic complications such as petechiae over the presenting part, hematuria, cephalohematoma, subconjunctival hemorrhage and prolonged bleeding from circumcision. On the other hand, intracranial hemorrhage commonly coexists with IUGR [67].

Nezvalová-Henriksen *et al.* [16] based on a large Norwegian database also found significant association between maternal vaginal bleeding (OR 1.8, 95% CI 1.1 to 3.0) and diclofenac exposure during the third trimester.

Other functional complications

Functional impairments include various organ-system dysfunctions that are difficult to evaluate, since they may occur years after birth [36]. The most common ones are related to the central nervous system. Such complications were also reported in case of NSAIDs. The initial data collected in the seventies among 4-year old children prenatally exposed to alcohol (n = 1529) and ASA (n =192) indicated an adverse effect on intelligence quotient (IQ), in particular among girls [68]. Such data was not confirmed in a later study, involving 19226 babies, including 10 1559 in-utero exposed to ASA [69]. The mean IQ scores for positive and control population differed insignificantly and reached levels of 98.2 and 96.1 points, respectively.

Another example of a functional complication is schizophrenia, which according to epidemiological data is associated with prenatal COX inhibitor exposure [70] as well as maternal influenza [71]. The strongest effect was found in a population exposed to analgesics during the second trimester (OR: 4.75, 95%CI: 1.9–12.0) but the risk was higher in females (OR: 4.94, 95% CI: 1.6–16.4) than males (OR: 3.77, 95% CI: 1.5–9.6).

Nowadays, the most commonly discussed functional prenatal outcome is asthma. Based on the Danish National Birth Cohort, Rebordosa *et al.* [72] was able to state that prenatal exposure to acetaminophen significantly increased occurrence of bronchial asthma or bronchitis among children of 18 months (RR: 1.17, 95%CI: 1.13–1.23) and 7 years (RR: 1.15, 95%CI: 1.02–1.29) as well as hospitalizations due to asthma up to 18 months (HR: 1.24, 95%CI: 1.11–1.38). The highest risk was reported for the first trimester exposure and persistent wheezing (RR: 1.45, 95%CI: 1.13–1.85). The prenatal etiology and risk of bronchopulmonary complications of paracetamol are not directly related to the current paper. Furthermore, they were explained in detail in current papers published by Scialli *et al.* [73, 74]. Similar data for asthma for 18 month old children was proved in Norwegian studies for NSAIDs, but positive association was found only for ibuprofen ingested during the second (OR: 1.5, 95%CI: 1.2–1.9) and third gestational trimester (OR 1.5, 95%CI: 1.1–2.1) [16].

Since NSAIDs cross the placenta, the drugs may inhibit fetal renal COX activity and reduce fetal renal perfusion that lead to organ insufficiency, complicated by oligohydramion [2, 3, 7].

Such side effects are well known, but similar to prenatal construction of ductus arteriosus, are not-well documented in large clinical and epidemiological studies. Hennessy *et al.* [75] did not observe such complications among 52 women who were exposed to high anti-inflammatory doses of ibuprofen as a tocolytic agent up to the 32nd gestational week. Only in 3 cases slightly lower volume of fluid was observed, but it normalized after drug discontinuation. Positive association (OR: 2.346, 95%CI: 1.168 to 4.710) between prenatal exposure to NSAIDs and acute renal failure was presented by Cataldi *et al.* [76], who analysed 172 preterm infants at 38 weeks of gestation, including 71 affected ones. The highest risk was proved for very low birth weight and other factors, including postnatal pharmacotherapy exposure, including ibuprofen.

Conclusion

Over-the-counter NSAIDs are commonly ingested medications during pregnancy. For the longest time they were classified as relatively safe for pregnant women and their offspring. However, some new data stresses that popular non-prescribed antipyretics and painkillers may also induce a higher risk of selected congenital anomalies (i.e., oral cleft, cardiovascular and neural tube defect) and functional and growth impairments. For such reason, any drug administration, especially prolonged one, has to be monitored by professionals. The best advice is to omit any harmful factors from maternal environment but in most cases it is not possible, since the majority of the ingested xenobiotics are taken to reduce the symptoms or to treat various diseases that are more dangerous for both mother and fetus than the applied therapy. The best of this example is above pointed schizophrenia. Moreover, Oster *et al.* [77] revealed significant associations of maternal fever and influenza with congenital heart anomalies such as right sided obstruction (fever OR: 2.04, 95% CI: 1.27–3.27; influenza OR: 1.75, 95% CI: 1.16–2.62) and atrioventricular septal defects in infants with Down syndrome (fever OR: 1.92, 95% CI: 1.10–3.38; influenza OR: 1.66, 95% CI: 1.04–2.63). On the other hand, ASA, paracetamol and OTC NSAIDs decrease these associations. As always, pharmacotherapy should be preceded by safer procedures (e.g., compresses, hypnosis) but in case of their ineffectiveness proper drugs should be applied. It is important to ingest the lowest effective dose to reduce potential maternal toxicity, since animal data point out that such mechanism usually leads to IUGR and skeletal developmental variations. To reduce the risk of developmental toxicity any mixed formula drugs that contain more than one active ingredient should be contraindicated during pregnancy or administered under a doctor's control. It is especially important for products with propyphenzone (isopropylantipyrine), which does not have any human data. In case an antipyretic or a mild analgesic is needed, paracetamol should be taken. However, due to its hepatotoxicity the drug is not recommended for patients with liver insufficiency, especially with decreased hepatic glutathione content observed in advanced fasting, prolonged fever, anorexia, cachexia and chronic alcohol or isoniazid intake. In such cases ibuprofen seems to be more suitable.

From my point of view, the best recommendation for NSAID administration during pregnancy was prepared by Minika Østensen in concomitant with the international multidisciplinary expert group [78]. Even though the report focused on rheumatic disorders, the data could be applied for OTC compounds. The recommendations are as follows:

1. NSAIDs can prevent or retard ovulation but frequency of ovulation inhibition is unknown
2. after gestational week 20, all non-selective COX inhibitors (except ASA at doses less than 100 mg/day) can cause constriction of the ductus arteriosus and impair fetal renal function

3. all NSAIDs except low-doses of ASA (less than 325 mg/day) should be withdrawn at gestational week 32
4. the ASA treatment should be stopped one week before delivery with epidural anesthesia or could be prolonged until the end of pregnancy in patients with antiphospholipid syndrome.

The only exception of original recommendation is the lack of teratogenic effect of NSAIDs, which in light of the newer study (see above) has to be revised, and in my opinion replaced with low potency to induce congenital malformation, especially in incidental treatment that is suggested for OTC medication. However, larger epidemiological studies, especially multi-center ones are desirable to fully establish the developmental tolerability of the evaluated medication. In any controversial cases an Organization of Teratology Information Services should be contacted (http://www.otispregnancy.org).

References

1. *Kmysheva E., Wertheim E.H., Skouteris H., et al.*: Frequency, severity, and effect on life of physical symptoms experienced during pregnancy. J Midwifery Womens Health. 2009; 54: 43–49.
2. *Cabbage L.A., Neal J.L.*: Over-the-counter medications and pregnancy: An integrative review. Nurse Pract. 2011; 36: 22–28.
3. *Murdoch I., Carver A.L., Sultan P., et al.*: Comparison of different nonsteroidal anti-inflammatory drugs for cesarean section: a systematic review and network meta-analysis. Korean J Anesthesiol. 2023; 76: 597–616.
4. *Zafeiri A., Mitchell R.T., Hay D.C., Fowler P.A.*: Over-the-counter analgesics during pregnancy: a comprehensive review of global prevalence and offspring safety. Hum Reprod Update. 2021; 27: 67–95.
5. *Gonzalez-Luis G.E., Borges-Lujan M., Villamor E.*: Association between endotypes of prematurity and pharmacological closure of patent ductus arteriosus: A systematic review and meta-analysis. Front Pediatr. 2023; 11: 1078506.
6. *Wilson A., Hodgetts-Morton V.A., Marson E.J., et al.*: Tocolytics for delaying preterm birth: a network meta-analysis (0924). Cochrane Database Syst Rev. 2022; 8: CD014978.
7. *Briggs G.G., Freeman R.K., Yaffe S.J.*: Drugs in pregnancy and lactation. A reference guide to fetal and neonatal risk. 7th edn. Philadelphia: Lippincott Williams & Wilkins, 2005.
8. *Levy G., Procknal J.A., Garettson L.K.*: Distribution of salicytes between neonatal and maternal serum at diffusion equilibrium. Clin Pharmacol Ther. 1975; 18: 210–214.
9. *Czeizel A., Rácz J.*: Evaluation of drug intake during pregnancy in the Hungarian Case-Control Surveillance of Congenital Anomalies. Teratology. 1990; 42 (5): 505–512.
10. *Olesen C., Sørensen H.T., de Jong-van den Berg L., et al.*: Prescribing during pregnancy and lactation with reference to the Swedish classification system. A population-based study among Danish women. The Euromap Group. Acta Obstet Gynecol Scand. 1999; 78: 686–692.
11. *Olesen C., Steffensen F.H., Nielsen G.L., et al.*: Drug use in first pregnancy and lactation: a population-based survey among Danish women. The EUROMAP group. Eur J Clin Pharmacol. 1999; 55: 139–144.
12. *Olsen J., Czeizel A., Sørensen H.T., et al.*: How do we best detect toxic effects of drugs taken during pregnancy? A EuroMap paper. Drug Saf. 2002; 25: 21–22.
13. *Glover D.D., Amonkar M., Rybeck B.F., Tracy T.S.*: Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. Am J Obstet Gynecol. 2003; 188: 1039–1045.
14. *Hernandez R.K., Werler M.M., Romitti P., et al.*: Nonsteroidal antiinflammatory drug use among women and the risk of birth defects. Am J Obstet Gynecol. 2012; 206: 228.e1–8.
15. *Lupattelli A., Spigset O., Twigg M.J., et al.*: Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014; 4: e004365.

16. *Nezvalová-Henriksen K., Spigset O., Nordeng H.*: Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. BJOG 2013; 120: 948–959.
17. *Velez Edwards D.R., Baird D.D., Hasan R., et al.*: First-trimester bleeding characteristics associate with increased risk of preterm birth: data from a prospective pregnancy cohort. Hum Reprod. 2012; 27: 54–60.
18. *Crespin S., Bourrel R., Hurault-Delarue C., et al.*: Drug prescribing before and during pregnancy in south west France: a retrolective study. Drug Saf. 2011; 34: 595–604.
19. *Alano M.A., Ngougmna E., Ostrea E.M. Jr., Konduri G.G.*: Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics. 2001; 107: 519–523.
20. US National Institute of Child Health and Human Development. NICHD Pregnancy & Perinatology Branch: A Strategic Plan 2005–2010. Available at: http://www.nichd.nih.gov/publications/pubs/ppb_strategicplan_2010/Documents/ppb_strategicplan_2010_full.pdf [Last accessed 2 July 2024].
21. Food and Drug Administration. HHS: Labelling and effectiveness testing: sunscreen drug products for over-the-counter human use. Final rule. Fed Regist. 2011; 76: 35620–35665.
22. *Lim H., Paria B.C., Das S.K., et al.*: Multiple female reproductive failures in cyclooxygenase 2-deficient mice. Cell. 1997; 91: 197–208.
23. *Wang X., Chen C., Wang L., et al.*: Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril. 2003; 79: 577–584.
24. *Lammer E.J., Brown L.E., Anderka M.T., Guyer B.*: Classification and analysis of fetal deaths in Massachusetts. JAMA. 1989; 261: 1757–1762.
25. *Velez Edwards D.R., Hartmann K.E.*: Racial differences in risk of spontaneous abortions associated with periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure. Ann Epidemiol. 2014; 24: 111–115.e1.
26. *Li D.K., Liu L., Odouli R.*: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ. 2003; 327: 368.
27. *Nielsen G.L., Sørensen H.T., Larsen H., Pedersen L.*: Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. BMJ. 2001; 322: 266–270.
28. *Nakhai-Pour H.R., Broy P., Sheehy O., Bérard A.*: Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011; 183: 1713–1720.
29. *Daniel S., Koren G., Lunenfeld E., et al.*: Fetal exposure to nonsteroidal anti-inflammatory drugs and spontaneous abortions. CMAJ. 2014; 186: E177–182.
30. *Henderson J.T., Whitlock E.P., O'Conner E., et al.*: Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Available at: http://www.ncbi.nlm.nih.gov/books/NBK196392/ [Last accessed 2 July 2024].
31. *Roberge S., Nicolaides K.H., Demers S., et al.*: Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. Ultrasound Obstet Gynecol. 2013; 41: 491–499.
32. *Kozer E., Costei A.M., Boskovic R., et al.*: Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis. Birth Defects Res B Dev Reprod Toxicol. 2003; 68: 70–84.
33. *Pastore L.M., Hertz-Picciotto I., Beaumont J.J.*: Risk of stillbirth from medications, illnesses and medical procedures. Paediatr Perinat Epidemiol. 1999; 13: 421–430.
34. *Rebordosa C., Kogevinas M., Bech B.H., et al.*: Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. Int J Epidemiol. 2009; 38: 706–714.
35. *Lopez A.D., Mathers C.D., Ezzati M., et al.*: Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006; 367: 1747–1457.
36. WHO. Congenital anomalies. Available at: http://www.who.int/mediacentre/factsheets/fs370/en/ [Last accessed 2 July 2024].

37. *Richards I.D.*: Congenital malformations and environmental influences in pregnancy. Br J Prev Soc Med. 1969; 23: 218–225.
38. *Nelson M.M., Forfar J.O.*: Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. Br Med J. 1971; 1: 523–527.
39. *Saxén I.*: Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol. 1975; 4: 37–44.
40. *Zierler S., Rothman K.J.*: Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. N Engl J Med. 1985; 313: 347–352.
41. *Werler M.M., Mitchell A.A., Shapiro S.*: The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. N Engl J Med. 1989; 321: 1639–1642.
42. *Källén B.A., Otterblad-Olausson P.*: Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol. 2003; 17: 255–261.
43. *van Gelder M.M., Roeleveld N., Nordeng H.*: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and the risk of selected birth defects: a prospective cohort study. PLoS One. 2011; 6: e22174.
44. *Ericson A., Källén B.A.*: Nonsteroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol. 2001; 15: 371–375.
45. *Ofori B., Oraichi D., Blais L., et al.*: Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs, A nested case-control study. Birth Defects Res B Dev Reprod Toxicol. 2006; 77: 268–279.
46. *Kozer E., Nikfar S., Costei A., et al.*: Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. Am J Obstet Gynecol. 2002; 187: 1623–1630.
47. *Martínez-Frías M.L., Rodríguez-Pinilla E., Prieto L.*: Prenatal exposure to salicylates and gastroschisis, a case-control study. Teratology. 1997; 56: 241–243.
48. *Torfs C.P., Katz E.A., Bateson T.F., et al.*: Maternal medications and environmental exposure as risk for gastroschisis. Teratology. 1996; 54: 84–92.
49. *Baldacci S., Santoro M., Mezzasalma L., et al.*: Medication use during pregnancy and the risk of gastroschisis: a systematic review and meta-analysis of observational studies. Orphanet J Rare Dis. 2024; 19 (1): 31.
50. *Slone D., Siskind V., Heinonen O.P., et al.*: Aspirin and congenital malformations. Lancet. 1976; 1: 1373–1375.
51. *Werler M.M., Sheehan J.E., Hayes C., et al.*: Vasoactive exposures, vascular events, and hemifacial microsomia. Birth Defects Res A Clin Mol Teratol. 2004; 70: 389–395.
52. *Cleves M.A., Savell V.H. Jr., Raj S., et al.*: Maternal use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and muscular ventricular septal defects. Birth Defects Res A Clin Mol Teratol. 2004; 70: 107–113.
53. *Esposito D.B., Parker S.E., Mitchell A.A., et al.*: Periconceptional nonsteroidal anti-inflammatory drug use, folic acid intake, and the risk of spina bifida. Birth Defects Res. 2021; 113: 1257–1266.
54. *Daniel S., Matok I., Gorodischer R., et al.*: Major malformations following exposure to nonsteroidal anti-inflammatory drugs during the first trimester of pregnancy. J Rheumatol. 2012; 39: 2163–2169.
55. *Bánhidy F., Acs N., Puhó E., Czeizel A.E.*: A population-based case-control teratologic study of oral dipyrone treatment during pregnancy. Drug Saf. 2007; 30: 59–70.
56. *Feldkamp M.L., Meyer R.E., Krikov S., Botto L.D.*: Acetaminophen use in pregnancy and risk of birth defects, findings from the National Birth Defects Prevention Study. Obstet Gynecol. 2010; 115: 109–115.
57. *Jensen M.S., Rebordosa C., Thulstrup A.M., et al.*: Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology. 2010; 21: 779–785.
58. *Conte D., Romanelli F., Fillo S., et al.*: Aspirin inhibits androgen response to chorionic gonadotropin in humans. Am J Physiol. 1999; 277: e1032–1037.
59. *Rebordosa C., Kogevinas M., Horváth-Puhó E., et al.*: Acetaminophen use during pregnancy, effects on risk for congenital abnormalities. Am J Obstet Gynecol. 2008; 198: 178.e1–7.
60. *Almoslem M., Shah S.D., Vozmediano V., Guzy S., Kim S., Hudak M.L., Schmidt S.*: Pharmacokinetic and Pharmacodynamic Analysis of Acetaminophen and Ibuprofen Dual Therapy for Patent Ductus

Arteriosus Closure in Preterm Neonates at Less Than 29 Weeks of Gestation. J Clin Pharmacol. 2024 Mar; 64 (3): 312–322.
61. *Kaur S., Manerkar S., Mondkar J., Kalamdani P., Patra S., Kalathingal T.*: The dilemma of feeding during the treatment of patent ductus arteriosus with oral ibuprofen in preterm infants ≤30 weeks of gestation-a randomized controlled trial. J Perinatol. 2023 Feb; 43 (2): 203–208.
62. *Al-Naami G.H., Al-Mesned A.A.*: Transposition of great arteries with constrictive ductus arteriosus revisited. Pediatr Cardiol. 2008; 29: 827–829.
63. *Koren G., Florescu A., Costei A.M., et al.*: Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. Ann Pharmacother. 2006; 40: 824–829.
64. *Van Marter L.J., Hernandez-Diaz S., Werler M.M., et al.*: Nonsteroidal antiinflammatory drugs in late pregnancy and persistent pulmonary hypertension of the newborn. Pediatrics. 2013; 131: 79–87.
65. *Benigni A., Gregorini G., Frusca T., et al.*: Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. N Engl J Med. 1989; 321: 357–362.
66. *Sasidharan C.K., Kutty P.M., Ajithkumar, Sajith N.*: Fetal intracranial hemorrhage due to antenatal low dose aspirin intake. Indian J Pediatr. 2001; 68: 1071–1072.
67. *Rumack C.M., Guggenheim M.A., Rumack B.H., et al.*: Neonatal intracranial hemorrhage and maternal use of aspirin. Obstet Gynecol. 1981; 58 (5 Suppl): 52S–6S.
68. *Streissguth A.P., Treder R.P., Barr H.M., et al.*: Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. Teratology. 1987; 35: 211–219.
69. *Klebanoff M.A., Berendes H.W.*: Aspirin exposure during the first 20 weeks of gestation and IQ at four years of age. Teratology. 1988; 37: 249–255.
70. *Sørensen H.J., Mortensen E.L., Reinisch J.M., Mednick S.A.*: Association between prenatal exposure to analgesics and risk of schizophrenia. Br J Psychiatry. 2004; 185: 366–371.
71. *Brown A.S., Begg M.D., Gravenstein S., et al.*: Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry. 2004; 61: 774–780.
72. *Rebordosa C., Kogevinas M., Sørensen H.T., Olsen J.*: Prenatal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. Int J Epidemiol. 2008; 37: 583–590.
73. *Scialli A.R., Ang R., Breitmeyer J., Royal M.A.*: A review of the literature on the effects of acetaminophen on pregnancy outcome. Reprod Toxicol. 2010; 30: 495–507.
74. *Scialli A.R., Ang R., Breitmeyer J., Royal M.A.*: Childhood asthma and use during pregnancy of acetaminophen. A critical review. Reprod Toxicol. 2010; 30: 508–519.
75. *Hennessy M.D., Livingston E.C., Papagianos J., Killam A.O.*: The influence of ductal constriction and oligohydramions during tocolytic therapy with ibuprofen. Am J Obstet Gynecol. 1992; 166: 234.
76. *Cataldi L., Leone R., Moretti U., De Mitri B., et al.*: Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. Arch Dis Child Fetal Neonatal Ed. 2005; 90: F514–519.
77. *Oster M.E., Riehle-Colarusso T., Alverson C.J., Correa A.*: Associations between maternal fever and influenza and congenital heart defects. J Pediatr. 2011; 158: 990–995.
78. *Østensen M., Khamashta M., Lockshin M., et al.*: Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006; 8: 209.