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**Review**

# Prenatal tolerability of acetaminophen and other over-the-counter non-selective cyclooxygenase inhibitors

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**Abstract:**
Over-the-counter cyclooxygenase inhibitors are used to relief fever and various types of acute pain like headache, toothache, earache, sore throat, as well as postoperative and menstrual ones. They are also major ingredients in cold and flu mixtures. Unlike well-known organ toxicological profile, their prenatal toxicity was not fully established. For a long time, acetaminophen was considered as a relatively safe antipyretic and analgesic drug during pregnancy. However, a new data indicate that it may increase the risk of cryptorchidism and asthma during childhood as well as preeclampsia, preterm birth, maternal phlebothrombosis and pulmonary embolism. Contrary to acetaminophen, non-selective cyclooxygenase inhibitors (non-steroidal anti-inflammatory drugs – NSAID; i.e., diclofenac, ibuprofen, naproxen) may induce intrauterine growth retardation, ductus arteriosus constriction with secondary persistent pulmonary hypertension, reduced fetal renal perfusion that led to oligohydramion, prolonged pregnancy as well as increase prevalence of intracranial bleeding in newborns. Furthermore, a higher risk of miscarriage, stillbirth and some congenital malformations (cardiac and diaphragmatic defects, celosomy – gastroschisis and umbilical hernia) was reported for non-selective inhibitors, in particular high doses of acetylsalicylic acid (aspirin).

**Key words:**
analgesic, antipyretic, drug safety, over-the-counter medication, pregnancy, NSAID

**Abbreviations:** COX – cyclooxygenase, COX-1 – constitutive isoform of cyclooxygenase, COX-2 – inducible isoform of cyclooxygenase, FDA – Food and Drug Administration, OR – odds ratio, OTC – over-the-counter, NF-κB – transcriptional nuclear factor κB, NSAID – non-steroidal anti-inflammatory drug, 95% CI – 95% confidence interval

## Introduction

Over-the-counter (OTC) drugs is a growing market of the medications available without any prescription that can be found in drugstore as well as grocery store,

refilling station, press kiosk, etc. They are used to treat various common discomforts, including pregnancy-related ones i.e., nausea, heartburn, congestion, constipation, pain and fever [10, 48, 49, 55]. Among all such pharmaceutical products, the most commonly purchased are antipyretic and analectic ones. Most of them contain at least one non-selective cyclooxygenase (COX) inhibitors, previously known as non-steroidal anti-inflammatory drugs (NSAID) [5, 10, 17, 48, 49]. Such drugs have also antithrombotic, chemoprotective, neuroprotective and tocolytic activity [5, 11, 24, 53] but they are not free of side-effects [12, 14, 35, 46, 49, 50].

According to Glover et al. [18] as much as 92.6% of pregnant woman consume OTC medication but 20% of them ingested at least five different products. In 76% cases such drugs are used to treat headache, backache and groin pain [22]. Based on US National Birth Defect Prevention Study and the Boston University Slone Epidemiology Center Birth Defects Study, acetaminophen is the most commonly administered OTC analgesic during pregnancy [18]. Approximately 65.5% of the interviewed mothers (out of 23.000) took the drugs at least ones during pregnancy, while ibuprofen and aspirin were consumed infrequently (15 and 4%, respectively).

Acetaminophen, unlike other drugs from that group, is a selective COX-3 inhibitor, without anti-inflammatory activity in therapeutic doses [5, 19]. With exception to high dose of aspirin (325 mg), prenatal toxicity of COX inhibitors is low and they have been considered as relatively safe for embryo and fetus [2, 10, 33]. However, in-utero exposure may be complicated by the intrauterine growth retardation, ductus arteriosus constriction with secondary persistent pulmonary hypertension, reduced fetal renal perfusion that led to oligohydramion, prolonged pregnancy as well as increase prevalence of intracranial bleeding in newborns [10, 24, 33]. A high risk of miscarriage, stillbirth and some congenital malformations (celosomy, cardiac and diaphragmatic defects) was also reported [33]. Most of adverse reactions are secondary to disturbance of the local cellular physiology by inhibition of eicosanoid synthesis and influence activity of transcriptional nuclear factor κB (NF-κB). Genotoxicity and mutagenicity are less likely since they were not observed after therapeutic doses of the drugs [2, 33, 49]. However, according to the general teratological principles, some other mechanisms of prenatal toxicity of COX inhibitors should be also discussed.

## Is a maternal fever and pain a big problem for embryo and fetus?

One of the mechanisms that led to the congenital abnormalities is so-called maternal toxicity [25, 43]. According to the experimental and clinical observations, any serious and/or chronic disturbance of maternal physiology may influence fetal development [6, 8, 25, 43]. Such data were also collected for symptoms that are treated with COX inhibitors as well as side-effects seen during drugs administration [6, 8, 25, 32, 45]. It is especially important for various upper respiratory tract infections complicated by prolonged fever and pain [1, 3, 27, 45]. Unlike previous data [15, 26, 28], Li et al. [27] reported that neural tube defects are strongly associated with maternal flu and fever (OR[1]: 3.93; 95% CI[2]: 2.48–6.23). Moreover, the incidence of anomalies in children delivered by mothers with both syndromes who also ingested antipyretics showed a significantly higher adjusted odds ratio for anencephaly (14.75 *vs.* 4.52), spina bifida (16.30 *vs.* 3.85) and all the neuronal defects (13.91 *vs.* 4.04) than offspring of women with flu or fever who did not use any COX inhibitors. Schizophrenia is associated with prenatal maternal influenza [3] and prenatal use of COX inhibitors as well [47]. The strongest effect was found in population exposed to analgesics during second trimester (OR: 4.75, 95% CI: 1.9–12.0) but the risk was higher in female (OR: 4.94, 95% CI: 1.6–16.4) than male (OR: 3.77, 95% CI: 1.5–9.6). In recently published paper, Oster et al. [32] 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). It is worth to mention that aspirin, acetaminophen and other COX inhibitors decrease these associations.

1 odds ratio
2 95% confidence interval

## Developmental toxicity of COX inhibitors – new and same old data

Feldkamp et al. [16] indicate that acetaminophen intake – among women reporting infection and fever in the first trimester of gestation – 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 acetaminophen during the first and second trimesters was also associated with an increased incidence of cryptorchidism (OR: 1.33, 95% CI: 1.00–1.77) [20]. 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 the gestational weeks 8–14, in which testicular descent occurs. However, an exposure to ibuprofen and acetylsalicylic acid was not associated with cryptorchidism. Such finding is especially important since aspirin directly blocks the androgen response to human chorionic gonadotropin – the hormone that in-utero stimulates androgen production and plays a crucial role in physiological descending of the testis [13]. Moreover, Rebordosa et al. [41] indicate that exposure to acetaminophen during the third trimester of pregnancy increased risk of preeclampsia (OR: 1.40, 95% CI: 1.24–1.58), particularly before the 32nd gestational week (OR: 1.47, 95% CI: 1.12–1.93), severe preeclampsia (OR: 1.51, 95% CI: 1.15–2.00) or chronic hypertension (OR: 1.44, 95% CI: 1.13–1.83). The drug administration during the second and third trimester was associated with an increased risk of maternal pulmonary embolism (OR: 3.02, 95% CI: 1.28–7.15) and phlebothrombosis (OR: 2.15, 95% CI: 1.06–4.37). In a simultaneously performed study an increased risk of the preterm birth (OR: 1.14, 95% CI: 1.03–1.26) in population ingested the drug during the third trimester of pregnancy was revealed [38]. The risk was higher for mothers with preeclampsia (OR: 1.55, 95% CI: 1.16–2.07) but insignificant increase was also found for patients with a normal blood pressure (OR: 1.08, 95% CI: 0.97–1.20). However, in offspring exposed to acetaminophen during the first trimester an increased prevalence of congenital abnormalities (OR: 1.01, 95% CI: 0.93–1.08) was not found, except for complex abnormalities of the ear, face and neck, known as medial cysts (OR: 2.15, 96% CI: 1.17–3.95) [39]. Based on data bank of Danish National Birth Cohort, it was possible to state that prenatal exposure to acetaminophen significantly increased occurrence of bronchial asthma or bronchitis among children at 18 months (OR: 1.17, 95% CI: 1.13–1.23) and 7 years (OR: 1.15, 95% CI: 1.02–1.29) [40]. The highest risk was reported for the first trimester exposure and persistent wheezing (OR: 1.45, 95% CI: 1.13–1.85). On the other hand, COX inhibitors, in particular aspirin, may induce asthma in adult persons [50].

Because of dualistic role of antipyretics and analgesics, in case of maternal low-intensive pain and fever, a traditional, less invasive methods should be recommended e.g., rest, cold or worm compress, drinking of herbal or fruit infusions etc. However, when expected therapeutic effect is not achieved, a proper drug has to be ordered. It is the general rule that all the medications should be ingested in the lowest therapeutic doses to decrease potential risk for the embryo and fetus [2, 34, 42]. It is especially important for acetaminophen, that is one of the most common causes of poisoning worldwide [36]. The drug can not be administered for a long period, especially for patients with a low amount of the hepatic glutathione. The hepatotoxicity results from the drug metabolite, i.e., *N*-acetyl-*p*-benzoquinoneimine, that depletes the liver antioxidant glutathione and directly damages hepatocytes. The highest risk of the liver failure is reported in advanced fasting, prolonged fever, anorexia, cachexy and chronic alcohol or isoniazid intake. The drug has to be prescribed with caution also for emotionally instable patients since its interval between the therapeutic and toxic doses is low [12, 23, 36]. There are number of reports on fatal complication of acetaminophen overdose for both mother and fetus [29, 36, 54, 56]. However, an early treatment with *N*-acetylcysteine may significantly improve pregnancy outcome [29, 36]. Because of potential acetaminophen hepatotoxicity in prolonged fever, ibuprofen seems to be better choice. The drug tolerability especially in low doses is high. Beside, it has anti-inflammatory activity that is not present in therapeutic dose of acetaminophen [19, 36, 37]. Diclofenac and naproxen are not recommended since both drugs do not present high antipyretic activity [2, 42].

Unlike acetaminophen [36, 44], prenatal toxicity of ibuprofen and other COX inhibitors has not been extensively studied. Most data came from studies that

**Tab. 1.** Incidence of total and major six congenital malformations among offsprings in-utero exposed to over-the-counter available cyclooxygenase inhibitors in a surveillance study of Michigan Medicaid [2]

| | RF[1] | No. of exposures | Number of anomalies (observed/expected) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Total | Cardiovascular | Oral clefts | Spina bifida | Polydactyly | Limb reduction | Hypospadiasis |
| Acetaminophen | B | 9146 | 423/416 | 87/91 | 16/16 | 4/7 | 30/27 | 14/16 | 16/22 |
| Aspirin | C | 1709 | 83/73 | 19/17 | 2/3 | 0/1 | 3/5 | 1/3 | 6/4 |
| Diclofenac | B | 51 | 1/2 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| Ibuprofen | B | 3178 | 143/129 | 33/30 | 7/5 | 3/2 | 11/9 | 5/5 | 4/8 |
| Naproxen | B | 1448 | 70/62 | 14/14 | 2/2 | 0/1 | 3/4 | 2/2 | 3/3 |

[1]RF – risk factors according to FDA classifications of medications in pregnancy [2]. Category A – Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote. Category B – Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). Category C – Either animal studies have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Category D – There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Category X – Animals or human studies have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. Category A according to Congenital Abnormalities Sub-committee of the Australian Drug Evaluation Committee (the group contains drugs which have been taken by a large number of pregnant women and women of childbearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed). Cathegory D if used in 3rd trimester or near delivery

evaluate common, simultaneous effects of various NSAIDs, ingested in high anti-inflammatory doses [2, 33, 42]. The final results vary on the size of examined populations, different socio-economics factors and applied procedures. The first important results came from US observations involving 229,101 completed pregnancies, but only in some cases prenatal exposure to over-the-counter COX inhibitors and developmental abnormalities were found (Tab. 1) [2]. Major congenital malformations were revealed in offspring delivered by mothers treated with aspirin (4.9%), naproxen (4.8%), acetaminophen (4.6%) and ibuprofen (4.5%). Among 1462 pregnant Danish women who ingested COX inhibitors thirty days before the conception and during pregnancy as well as 17,259 untreated ones, an increase prevalence of all malformations was reported (OR: 1.27, 95% CI: 30.93–1.73) [30]. A prevalence to preterm delivery (OR: 1.05, 95% CI: 0.8–1.39) and intrauterine growth retardation was also observed (OR: 0.79, 95% CI: 0.45–1.38). A similar data – without specific to any COX inhibitor – was found for all structural abnormalities (OR: 1.04, 95% CI: 0.84–1.29) among offspring delivered by 2557 Swedish women [15]. However, higher risk was reported for the orofacial cleft (OR: 2.61, 95% CI: 1.01–6.78) and cardiac malformations (OR: 1.86, 95% CI: 1.32–2.62). As a continuations of that study, a higher incidence of cardiac defects was found in newborns exposed in-utero to naproxen (OR: 1.7, 95% CI: 1.14–2.54) [21]. An insignificant increase was established for ibuprofen (OR: 1.08, 95% CI: 0.78–1.50), diclofenac (OR: 1.3, 95% CI: 0.78–2.16), aspirin (OR: 1.01, 95% CI: 0.76–1.33), as well as all the examined COX inhibitors (OR: 1.24, 95% CI: 0.99–1.55). A higher risk for all the congenital anomalies (OR: 2.21; 95% CI: 1.72–2.85) was also noted in a Canadian study involving 36,387 pregnant women exposed to various COX inhibitors [31]. Similarly to previous experimental [7, 14] and epidemiological observations [21, 27, 33, 37], an increase prevalence was revealed for the cardiac septal defects (OR: 3.34; 95% CI: 1.87–5.98). It should be also pointed that higher risk of gastroschisis (OR: 2.37, 95% CI: 1.44–3.88) was observed exclusively for aspirin by Kozer et al. [26] and for the aspirin (OR: 4.7, 95% CI: 1.2–18.1) and ibuprofen (OR: 4.0, 95% CI: 1.0–16.0) by Torfs et al. [51]. The aspirin data were partially confirmed by Martinez-Frias et al. [28] (OR:

3.33, 95% CI: 1.05–9.80) but in all studies results were highly dependent on maternal age and smoking.

It is well-known that COX inhibitors are contraindicated in the last trimester of pregnancy, especially near delivery due to the tocolytic activity as well as increased risk of prenatal closure of the ductus arteriosus. However, continuous drug administration may also result in higher incidence of prolonged bleeding during labor [2, 33, 42]. It is especially important for high dose of aspirin that may be complicated with an intracerebral bleeding.

The second mechanism that should be also pointed in this paper is so-called placental toxicity [43]. Based on rodent studies with various COX inhibitors, it is hypothesized that local placental disturbance of eicosanoids synthesis may led to decrease of the vascular labyrinth and injury the placental barrier in an ischemic-reperfusion mechanism [9]. However, until now such data are not fully proved in clinical and epidemiological observations.

Most of the presented data were collected for the single xenobiotic, not for mixed formula medications that are also available over-the-counter. It seems reasonable that all mixtures with two or more COX inhibitors (e.g., acetaminophen + aspirin + caffeine) should be contraindicated and replaced by single drug treatment to reduce the potential risk of toxicity for both fetus and mother. It is especially important for products with propyphenazone (isopropylantipyrine), which does not has any human data and animals observations are sparse [4].

## Conclusion

Acetaminophen is (or rather was) elected as the safest antipyretic and analgesic drug for pregnant women. We all have believed in such dogma until the various Danish, above presented observations were published [20, 38–41]. Nowadays, it is probably true only for short administration period (as all the over-the-counter pharmaceuticals should be ingested) and for mothers without any additional risk of the liver injury and hypertension. In case of high and prolonged fever or any other serious symptoms of infection, low doses of ibuprofen should be taken but the medical consultation is strongly suggested. However, an additional epidemiological study regarding prenatal tolerability of low doses of ibuprofen will be desirable. One of the best recommendations for COX inhibitors administration during pregnancy was prepared by Monika Østensen in concomitant with the international multidisciplinary expert group [33]. Even that the rapport focuses on rheumatic disorders, the data should be simply applied for over-the-counter antipyretic and analgesic medications, especially since it was prepared in a new narrative style that is presently preferred by FDA and replaced the old Risk Factor (A, B, C, D, X) [52]. The conclusions and recommendations are as follows [33]:

1) non-selective and selective COX inhibitors can prevent or retard ovulation but frequency of ovulation inhibition is unknown;
2) non-selective COX inhibitors are not teratogenic and can be continued during the first and second trimester of pregnancy;
3) after gestational week 20, all non-selective COX inhibitors (except aspirin at doses less than 100 mg/day) can cause constriction of the ductus arteriosus and impair fetal renal function;
4) all non-selective COX inhibitors except low-dose of aspirin (less than 325 mg/day) should be withdrawn at gestational week 32;
5) the aspirin 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.

Based on presented data it is not easy to answer question from the title. Yes, the acetaminophen is relatively safe when administered as a single ingredient for short period. However, as all the xenobiotics, it is not free of the adverse reactions, including developmental and reproductive toxicity. The drug administration has to be monitored and in same cases, replaced with other COX inhibitors. From among the non-selective compounds available also as over-the counter medicines, application of ibuprofen should be considered. In any controversial cases, an Organization of Teratology Information Services (http://www. otispregnancy.org) could be contacted.

### References:

1. Abe K, Honein MA, Moore CA: Maternal febrile illnesses, medication use, and the risk of congenital renal anomalies. Birth Defects Res A Clin Mol Teratol, 2003, 67, 911–918.

2. Briggs GG, Freeman RK, Yaffe SJ: Drugs in pregnancy and lactation. A reference guide to fetal and neonatal risk. 7th edn., Lippincott Williams & Wilkins, Philadelphia, 2005.
3. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES: Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry, 2004, 61, 774–780.
4. Burdan F: Developmental effects of propyphenazone in analgesic and antipyretic combination with caffeine or paracetamol. Hum Exp Toxicol, 2004, 23, 235–244.
5. Burdan F, Chałas A, Szumiło J: Cyclooxygenase and prostanoids – biological implications (Polish). Postepy Hig Med Dosw (online), 2006, 60, 129–141.
6. Burdan F, Pliszczynska-Steuden M, Rozylo-Kalinowska I, Chalas A, Rozylo TK, Staroslawska E, Klepacz R, Szumilo J: Developmental outcome after exposure to cyclooxygenase inhibitors during pregnancy and lactation. Reprod Toxicol, 2011, 32, 407–417.
7. Burdan F, Szumilo J, Dudka J, Korobowicz A, Klepacz R: Congenital ventricular septal defects and prenatal exposure to cyclooxygenase inhibitors. Braz J Med Biol Res, 2006, 39, 925–934.
8. Burdan F, Szumilo J, Klepacz R: Maternal toxicity of nonsteroidal anti-inflammatory drugs as an important factor affecting prenatal development. Reprod Toxicol, 2009, 28, 239–244.
9. Burdan F, Szumilo J, Korobowicz-Markiewicz A, Dyndor K, Szumilo M, Klepacz R: Unusual interleukin-1 and -6 expression in fetal cartilage is associated with placental abnormalities. Folia Histochem Cytobiol, 2010, 48, 30–36.
10. Cabbage LA, Neal JL: Over-the-counter medications and pregnancy: An integrative review. Nurse Pract, 2011, 36, 22–28.
11. Capone ML, Tacconelli S, Rodriguez LG, Patrignani P: NSAIDs and cardiovascular disease: transducing human pharmacology results into clinical read-outs in the general population. Pharmacol Rep, 2010, 62, 530–535.
12. Chun LJ, Tong MJ, Busuttil RW, Hiatt JR: Acetaminophen hepatotoxicity and acute liver failure. J Clin Gastroenterol, 2009, 43, 342-349.
13. Conte D, Romanelli F, Fillo S, Guidetti L, Isidori A, Franceschi F, Latini M, di Luigi L: Aspirin inhibits androgen response to chorionic gonadotropin in humans. Am J Physiol, 1999, 277, E1032–1037.
14. Cook JC, Jacobson CF, Gao F, Tassinari MS, Hurtt ME, DeSesso JM: Analysis of the nonsteroidal anti-inflammatory drug literature for potential developmental toxicity in rats and rabbits. Birth Defects Res B Dev Reprod Toxicol, 2003, 68, 5–26.
15. Ericson A, Källén BA: Nonsteroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol, 2001, 15, 371–375.
16. Feldkamp ML, Meyer RE, Krikov S, Botto LD: Acetaminophen use in pregnancy and risk of birth defects, findings from the National Birth Defects Prevention Study. Obstet Gynecol, 2010, 115, 109–115.
17. Food and Drug Administration, HHS: Labeling and effectiveness testing: sunscreen drug products for over-the-counter human use. Final rule. Fed Regist, 2011, 76, 35620–35665.
18. Glover DD, Amonkar M, Rybeck BF, Tracy TS: Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. Am J Obstet Gynecol, 2003, 188, 1039–1045.
19. Graham GG, Scott KF: Mechanism of action of paracetamol. Am J Ther, 2005, 12, 46–55.
20. Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, Henriksen TB, Olsen J: Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology, 2010, 21, 779–785.
21. Källén BA, Otterblad-Olausson P: Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol, 2003, 17, 255–261.
22. Kamysheva E, Wertheim EH, Skouteris H, Paxton SJ, Milgrom J: Frequency, severity, and effect on life of physical symptoms experienced during pregnancy. J Midwifery Womens Health, 2009, 54, 43–49.
23. Klein-Schwartz W, Doyon S: Intravenous acetylcysteine for the treatment of acetaminophen overdose. Expert Opin Pharmacother, 2011, 12, 119–130.
24. Kordić-Bojinović J, Oreščanin-Dušić Z, Slavić M, Radojičić R, Spasić M, Milovanović SR, Blagojević D: Effect of indometacin pretreatment on protamine sulfate-mediated relaxation of the isolated rat uterus: the role of the antioxidative defense system. Pharmacol Rep, 2011, 63, 1019–1028.
25. Koren G: Maternal-fetal toxicology. 2nd edn., Marcel Dekker, New York, 1994.
26. Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G: Aspirin consumption during the first trimester of pregnancy and congenital anomalies, a meta-analysis. Am J Obstet Gynecol, 2002, 187, 1623–1630.
27. Li Z, Ren A, Liu J, Pei L, Zhang L, Guo Z, Li Z: Maternal flu or fever, medication use, and neural tube defects, a population-based case-control study in Northern China. Birth Defects Res A Clin Mol Teratol, 2007, 79, 295–300.
28. Martínez-Frías ML, Rodríguez-Pinilla E, Prieto L: Prenatal exposure to salicylates and gastroschisis, a case-control study. Teratology, 1997, 56, 241–243.
29. McElhatton PR, Sullivan FM, Volans GN: Paracetamol overdose in pregnancy analysis of the outcomes of 300 cases referred to the Teratology Information Service. Reprod Toxicol, 1997, 11, 85–94.
30. Nielsen GL, Sørensen HT, 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.
31. Ofori B, Oraichi D, Blais L, Rey E, Bérard A: 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.
32. Oster ME, Riehle-Colarusso T, Alverson CJ, Correa A: Associations between maternal fever and influenza and congenital heart defects. J Pediatr, 2011, 158, 990–995.
33. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, Doria A et al.: Anti-inflammatory

and immunosuppressive drugs and reproduction. Arthritis Res Ther, 2006, 8, 209–208.
34. Østensen ME, Skomsvoll JF: Anti-inflammatory pharmacotherapy during pregnancy. Expert Opin Pharmacother, 2004, 5, 571–580.
35. Polat B, Albayrak Y, Suleyman B, Dursun H, Odabasoglu F, Yigiter M, Halici Z, Suleyman H: Antiulcerative effect of dexmedetomidine on indomethacin-induced gastric ulcer in rats. Pharmacol Rep, 2011, 63, 518–526.
36. Prescott LF: Paracetamol (acetaminophen) – a critical bibliographic review. Taylor & Francis, London, 1996.
37. Rainsford KD: Ibuprofen – a critical bibliographic review. Taylor & Francis, London, 1999.
38. Rebordosa C, Kogevinas M, Bech BH, Sørensen HT, Olsen J: Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. Int J Epidemiol, 2009, 38, 706–714.
39. Rebordosa C, Kogevinas M, Horváth-Puhó E, Nørgård B, Morales M, Czeizel AE, Vilstrup H et al.: Acetaminophen use during pregnancy, effects on risk for congenital abnormalities. Am J Obstet Gynecol, 2008, 198, 178.e1–7.
40. Rebordosa C, Kogevinas M, Sørensen HT, 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.
41. Rebordosa C, Zelop CM, Kogevinas M, Sørensen HT, Olsen J: Use of acetaminophen during pregnancy and risk of preeclampsia, hypertensive and vascular disorders: a birth cohort study. J Matern Fetal Neonatal Med, 2010, 23, 371–378.
42. Scheafer C, Peters P, Miller RK. Drugs during pregnancy and lactation, therapeutic options and risk assessment. 2nd edn., Academic Press, Oxford, 2007.
43. Scialii A: Teratology. In: Pathology of environmental and occupational disease. Ed. Craighead JE, Mosby, St. Louis, 1995, 573–588.
44. Scialli AR, Ang R, Breitmeyer J, Royal MA: A review of the literature on the effects of acetaminophen on pregnancy outcome. Reprod Toxicol, 2010, 30, 495–507.
45. Shaw GM, Todoroff K, Velie EM, Lammer EJ: Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology, 1998, 57, 1–7.
46. Singh AP, Junemann A, Muthuraman A, Jaggi AS, Singh N, Grover K, Dhawan R: Animal models of acute renal failure. Pharmacol Rep, 2012, 64, 31–44.
47. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA: Association between prenatal exposure to analgesics and risk of schizophrenia. Br J Psychiatry, 2004, 185, 366–371.
48. Stosic R, Dunagan F, Palmer H, Fowler T, Adams I: Responsible self-medication, perceived risks and benefits of over-the-counter analgesic use. Int J Pharm Pract, 2011, 19, 236–245.
49. Suleyman H, Demircan B, Karagoz Y: Anti-inflammatory and side effects of cyclooxygenase inhibitors. Pharmacol Rep, 2007, 59, 247–258.
50. Szczeklik A. Aspirin-induced asthma: a tribute to John Vane as a source of inspiration. Pharmacol Rep, 2010, 62, 526–529.
51. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ: Maternal medications and environmental exposure as risk for gastroschisis. Teratology, 1996, 54, 84–92.
52. U.S. Food and Drug Administration. Pregnancy and lactation labeling [Internet]. http: //www.fda.gov/Drugs/developmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm/ (last access October 20, 2011).
53. Vaish V, Sanyal SN: Chemopreventive effects of NSAIDs on cytokines and transcription factors during the early stages of colorectal cancer. Pharmacol Rep, 2011, 63, 1210–1221.
54. Wang PH, Yang MJ, Lee WL, Chao HT, Yang ML, Hung JH: Acetaminophen poisoning in late pregnancy. A case report. J Reprod Med, 1997, 42, 367–371.
55. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA: Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol, 2005, 193, 771–777.
56. Wilkes JM, Clark LE, Herrera JL: Acetaminophen overdose in pregnancy. South Med J, 2005, 98, 1118–1122.

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