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Published in:
Reproductive Toxicology

DOI:
[10.1016/j.reprotox.2020.04.041](https://doi.org/10.1016/j.reprotox.2020.04.041)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van der Mijle, A. E., de Vries, L. C., Vorstenbosch, S., & van Puijenbroek, E. P. (2020). Use of non-steroidal anti-inflammatory drugs and acetylsalicylic acid in the third trimester of pregnancy. *Reproductive Toxicology*, 97, 8-9. <https://doi.org/10.1016/j.reprotox.2020.04.041>

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Outcomes of phenylramidol exposed pregnant women consulted who Dokuz Eylul University Teratology Information Center: An 8 year retrospective evaluation

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Introduction: Roughly half of pregnant women experience lower back pain and 77–96% of women are prescribed at least 1 medication during pregnancy. Phenylramidol, a centrally active non-narcotic muscle relaxant, is indicated in use for musculoskeletal pain and acute lumbago. To the best of our knowledge, there are two studies evaluating the teratogenic risk of phenylramidol and available data for determining fetal risk of the drug are scarce. In a study evaluating the results of 10 pregnant women using phenylramidol, no congenital anomaly was reported. However, administration of high dose phenylramidol demonstrated harmful effects on neural tube development in chicken embryo model. The objective of this study was to assess the demographics and outcomes of phenylramidol exposed pregnant women who consulted to Dokuz Eylul University Teratology Information Center between January 1, 2012 and December 31, 2019.

Methods: It is a descriptive, cross-sectional study. Pregnant women who had consulted to Dokuz Eylul University Teratology Information Center between January 1, 2012 and December 31, 2019 and with history of phenylramidol exposure at any time during pregnancy were included. Data regarding phenylramidol exposure, concomitant medication/substance/x-ray exposures, obstetric histories, demographics and pregnancy outcomes were obtained from records. The data were analyzed using “Statistical Package for the Social Sciences (SPSS) 22.0”.

Results: Seventeen cases had been exposed to phenylramidol between January 1, 2012 and December 31, 2019. Three out of 17 cases were excluded due to missing data regarding pregnancy outcomes. Median age of 14 women was 30.50 (27–41) and median gestational length was 38 (28–40) weeks. Twelve women (85.7%) were exposed to phenylramidol in the first trimester, while 2 women (14.3%) were exposed in the last 2 trimesters. All cases had concomitant medication use. Additional risk factors were smoking, caffeine intake, X-ray exposure and alcohol consumption in 42.9%, 35.7%, 42.9% and 7.1% of the cases respectively. All cases received phenylramidol by oral route and the exposed daily dose was in the range of 400–1200 mg. Observed outcomes were live birth with no congenital malformation in 11 (78.6%), elective termination in 2 (14.3%) and intrauterine death in 1 (7.1%) cases. Seven pregnancies (63.6%) were ended in cesarean section, 4 pregnancies (36.4%) were ended in vaginal delivery. In the intrauterine death case, fetal autopsy had revealed dextrocardia, but no genetic anomaly. Additional risk factors for this case were smoking, caffeine intake, concomitant medication use and x-ray exposure.

Conclusions: Out of 14 cases with phenylramidol exposure, 1 case of intrauterine death and 2 cases of elective termination were reported. Due to the additional risk factors that might have contributed to this outcome, it was not possible to establish a clear association between intrauterine death and phenylramidol exposure. No congenital malformation was reported in 11 live born. Further studies are needed to clearly determine fetal risk of phenylramidol exposure.

<https://doi.org/10.1016/j.reprotox.2020.04.039>

Increasing interest in medications used for Attention Deficit Hyperactivity Disorder during pregnancy and breast-feeding

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Introduction: The use of Attention Deficit Hyperactivity Disorder (ADHD) medications has increased over the years. According to the Finnish Statistics on Medicines, the number of patients receiving reimbursement for ADHD medications increased almost five-fold from around 6,000 in 2007 to nearly 29,000 in 2017. We wanted to investigate if this increase was also reflected in the calls to the Finnish Teratology Information Service (FIN-TIS). While recent studies have not confirmed a teratogenic risk, there are no data on long term neurocognitive development in prenatally exposed children.

Methods: We searched the call database at Finnish TIS between Jan 1st 2007 – Dec 31st 2019 for calls during preconception, pregnancy and during breastfeeding about drugs indicated for use in ADHD and including atomoxetine, dexamphetamine, guanfacine, lisdexamphetamine and methylphenidate.

Results: Of the total 74,628 calls, 244 (0.3%) concerned ADHD medications; of these, 135 calls (56%) concerned use during preconception or the first trimester and 79 calls (32%) concerned breastfeeding. Methylphenidate was the most commonly used ADHD medication (201 calls), followed by lisdexamphetamine (27 calls, starting since 2016), atomoxetine (14 calls) and dexamphetamine (3 calls). There were no inquiries about guanfacine. In the beginning of our study period only methylphenidate was on the market and the calls received concerning ADHD medication were stable, around 10 calls/year (0.2% of calls). An increase in the calls occurred in 2013 (16 calls; 0.3%) when methylphenidate was granted reimbursement status for adults above 25 years. The number of calls concerning ADHD medication increased further to 42 (0.8%) in 2019. The first calls regarding atomoxetine in the database were recorded in 2014, and for dexamphetamine and lisdexamphetamine in 2016, coinciding with the timing of approved reimbursement status.

Conclusions: The interest in using ADHD medications during pregnancy and breastfeeding is increasing, warranting more research on the short- and long-term safety of these drugs.

<https://doi.org/10.1016/j.reprotox.2020.04.040>

Use of non-steroidal anti-inflammatory drugs and acetylsalicylic acid in the third trimester of pregnancy

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Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid are commonly used in early pregnancy, as second choice after paracetamol, for the management of pain and inflammation. Although contraindicated in the third trimester, the Dutch Teratology Information Service received three telephonic questions in the past half year about the risks of an NSAID that has been used or prescribed in the third trimester of pregnancy. This implies that NSAIDs are still used in the third trimester. However, the frequency of use in the Netherlands in the third trimester

is unknown. The aim of this study is to determine the prevalence of exposure to the NSAIDs diclofenac, ibuprofen, and naproxen, and to acetylsalicylic acid (high dose) in the third trimester of pregnancy in the Dutch Pregnancy Drug Register pREGnant. In the Netherlands these drugs are available over the counter.

Methods: Data on maternal health and lifestyle, medication use, delivery and infant health were obtained in pREGnant prospectively by web-based questionnaires. All women of whom drug use is known from 4 weeks before pregnancy until 8 weeks after delivery, were included. Third trimester exposure is defined as exposure from week 27+0 to diclofenac, ibuprofen, naproxen, or acetylsalicylic acid (high dose defined as a dose of 250 mg or higher).

Results: A total of 2733 participants met the inclusion criteria. Two hundred seventy two participants (10.0%) reported the use of high dose acetylsalicylic acid, naproxen, ibuprofen or diclofenac before, during and/or after pregnancy. Hundred sixty six participants (6.1%) used the drug before or after pregnancy, and not during pregnancy. Of 89 participants (3.3%), the use in pregnancy was ascertained. Of 17 participants (0.6%), exact timing of use was uncertain. Some of the women used several NSAIDs or used them intermittently. Of 89 women who reported use during pregnancy, 11 women (0.4%) have (also) used the drug in the third trimester (8 acetylsalicylic acid, 1 ibuprofen and 2 diclofenac). In these third trimester cases, the indication of use was a variety of pain complaints, common cold or pyrexia. Three women stopped at least 10 weeks before delivery (2 diclofenac and 1 acetylsalicylic acid). Five women (4 acetylsalicylic acid and 1 ibuprofen) were still using the drug at the time of delivery. Of these five pregnancies, 2 were complicated by maternal hypertension/pre-eclampsia and 1 by gestational diabetes. Of these 5 neonates, 1 neonate had unilateral hydronephrosis and 3 neonates had respiratory difficulties (premature neonate with Down syndrome, ASD, pulmonary hypertension; premature neonate with respiratory difficulties; and term neonate with Neonatal Wet Lung Syndrome).

Conclusion: Acetylsalicylic acid, naproxen, ibuprofen and diclofenac were used in pregnancy in 3.3% of the participants in the pregnancy register pREGnant. Although contraindicated, 0.4% of the participants used the drug in the third trimester. It was unknown whether the drug was prescribed or bought over-the-counter.

<https://doi.org/10.1016/j.reprotox.2020.04.041>

Assessing risk perception of anti-emetic drug use during pregnancy and the potential impact of risk communication tools: A study protocol

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Introduction: Many international guidelines recommend pharmacological treatment in the management of nausea and vomiting in pregnancy (NVP). It has been estimated that half of all women in the UK with a diagnosis of NVP were prescribed antiemetic therapy. The potential risks of antiemetic exposure during pregnancy should be balanced with the benefits of managing a severe underlying maternal condition that can lead to adverse pregnancy outcomes. Recently the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA-PRAC) has recommended against the use of ondansetron in the first trimester. There are concerns within the European Network of Teratology Information Services (ENTIS) that currently available data do not support the recommendations against ondansetron in the first trimester, and this may lead to

less effective control NVP and increased morbidity, instead, women should be counselled on the benefits and risks of antiemetic therapy to allow individualized decision making. The aim of this study is to explore the perception of risk associated with antiemetic drug use during pregnancy and the potential impact of risk communication tools on individualized decision making.

Methods: Women who are currently pregnant or who have been pregnant within the last 3 years will be recruited through social media channels and patient support groups. After providing informed consent, women will be randomized to receive one of three locally developed risk communication tools addressing the benefits and risks of ondansetron use in pregnancy. These tools are designed to present the same information using narrative and visual risk communication techniques. We will examine the utility of different risk communication methods by measuring knowledge, realistic expectation, choice predisposition and preparation for decision making before and after use of the risk communication tools. We will assess if a prior history of hyperemesis affects risk perception.

Results: A study protocol has been developed to explore the potential impact of novel risk communication tools on individualized decision making in the context of medication use for NVP.

Conclusions: This study intends to demonstrate the potential impact of risk communication tools on the perception of antiemetic use during pregnancy.

<https://doi.org/10.1016/j.reprotox.2020.04.042>

Lacosamide Levels in Blood and Breastmilk During Pregnancy and Lactation: A Case Report

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Introduction: Lacosamide is a new antiepileptic drug, indicated for treatment of seizures in adults and children from 4 years of age. According to the manufacturer, there are no data on lacosamide use during pregnancy and lactation. Lacosamide has low molecular weight and minimal protein binding and therefore, theoretically, could be transferred into milk, as found in animals. There are only few reports on its safety during pregnancy and a single report on lacosamide levels in breastmilk.

Methods: A pregnant woman treated with lacosamide and levetiracetam was recruited during her first trimester. The woman had monthly monitoring blood levels. A baby girl was born by caesarian section at full term. One month after delivery, lacosamide levels were measured in the mother's blood and milk sample. A series of milk samples were collected during one day, by the woman. Lacosamide levels were measured using HPLC. Follow up on baby's development was performed after 6 months.

Results: Lacosamide blood levels during pregnancy were stable. No congenital malformations were observed after delivery. The infant was exclusively breastfed. Milk/plasma ratio was 0.5 and daily dosage was 2.77 and 0.63 mg/kg/day in the mother and the baby, respectively. The infant/mother ratio was 0.22. A telephone follow-up call was performed at 6 month of age, and revealed that