Chapter 2

Prescribing of NSAIDs and ASA during pregnancy; do we need to be more careful?

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Summary

Aim
This study examines the extent of NSAID and/or ASA prescribing around and during pregnancy.

Methods:
Mothers extracted from iadb.nl (population-based prescription database, 1995-2004), of whom we had drug information three months before conception till three months after delivery, were identified.

Results:
In 3.9% of the pregnancies (N=557) a NSAID (ATC-code: M01A) and/or ASA (ATC-code: N02BA) were prescribed during pregnancy, 2.9% (N=421) received a prescription during first trimester.

Conclusion:
NSAIDs and ASA are prescribed during the first trimester of pregnancy. Future studies are needed to see the effects of the recent warning of the EMEA on prescribing of NSAIDs or ASA.
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Introduction

Use of drugs during pregnancy is and always will be a delicate issue for clinicians and mothers-to-be. With respect to non-steroidal anti-inflammatory drugs (NSAIDs) and Acetylsalicylic acid (ASA), it is recommended not to use both drugs during the third trimester of pregnancy. These recommendations were formulated based on effects such as increased risk of premature closure of the ductus arteriosus\(^1\)^\(^2\). In 2005 European registration authorities (EMEA=European Medicines Agency) warned about use of NSAIDs and ASA during first trimesters of pregnancy; NSAIDs and ASA should not be used during first trimesters of pregnancy except when this is strictly indicated\(^3\). This warning was based on recent studies describing associations between NSAIDS and/or ASA use and congenital heart defects\(^4\)^\(^-\)^\(^7\), gastroschisis\(^8\)^\(^-\)^\(^1\)^\(^1\), neural tube defects\(^1\)^\(^0\) and orofacial clefts\(^5\)^\(^;\)^\(^1\)^\(^0\). Although the studies were not conclusive for most congenital malformations, with respect to gastroschisis most studies found an increased risk\(^8\)^\(^-\)^\(^1\)^\(^1\).

Little is known about prescribing of NSAIDs and ASA in daily practice, therefore this study will described to which extend NSAIDs and ASA are prescribed during pregnancy.

Method

Setting

This study was performed using pharmacy dispensing data from IADB.nl (population-based database) in Northern and Eastern Netherlands\(^1\)^\(^2\). In 2003, IADB.nl contained prescriptions from an estimated population of 500,000 individuals. Each prescription record contains among others name of the drug, date of dispensing, amount dispensed, dose regimen and all drugs are coded according to the Anatomical Therapeutic Chemical (ATC)-classification\(^1\)^\(^3\). Date of birth and gender of each patient are available and all patients have an unique anonymous identifier. Due to high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, medication records for each patient are virtually complete\(^1\)^\(^2\). This database comprises all prescription drugs, excluding drugs dispensed during hospitalizations and OTC drugs.
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Study population and design
The pregnancy-IADB.nl (1995-2004) was extracted from the main IADB.nl database. Children were selected by date of birth and by using an address-code the mother of this child was identified. This method is validated and described by Schirm et al.\textsuperscript{14}. The gestational age is calculated for every mother by subtracting 273 days (3 trimesters of 91 days, approx. 9 months) from birth date of the child; this date will be referred to as conception. The period between conception and birth date of the child will be considered as gestation and is per definition 273 days. We included all mothers of whom we had drug information about the defined time-window of three months before conception till three months after delivery. All women to whom NSAIDs (ATC-code: M01A) and/or ASA (ATC-code: N02BA) were prescribed at some point during this time-window were selected (N=2020), small dose ASA-preparations (ATC: B01AC06/08) were excluded. We calculated prevalence before, during and after pregnancy based on exposure rate. Exposure rate is defined as the number of pregnancies in which in theory a women has availability to a drug or class of drugs, i.e. those who received a prescription in one trimester which was extended into the next trimester, are counted for both trimesters in which they had access to the drug\textsuperscript{15}.

Results
From the IADB.nl (1995-2004), 14,666 pregnancies were identified, in 13.8% (N=2020) NSAIDs or ASA were prescribed in the time-window three months before pregnancy till three months after delivery. Among those users 96% received a NSAID and less than 5.5 % were prescribed ASA, approximately 1.5% received both drugs. Diclofenac, Ibuprofen and Naproxen are the most prescribed NSAIDs. Average age at time of delivery of women to whom a NSAID or ASA was prescribed (29.74 years, range 16-49) did not differ of those without having prescribed these drugs (29.91 years, p=0.077).

Figure 1 shows the number of pregnancies in which NSAIDs and/or ASA were prescribed in the investigated time-window. In 7.6% (1113/14,666) of the pregnancies these drugs were prescribed before conception, in 3.8% (557/14,666) during gestation and in 5.3% (781/14,666) after pregnancy.
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Women to whom a NSAID and/or ASA was prescribed during that period,
- Women who did not receive a NSAID and/or ASA during that period

Figure 1. Number of pregnancies in which a NSAID and/or ASA was prescribed before, during and after pregnancy.

Women to whom NSAIDs and/or ASA were prescribed during gestation, 61% (337/557) started these drugs for the first time during gestation (in the investigated time-window). The drugs were restarted by 13% (103/781) after discontinuation during pregnancy and 73% (570/781) started it for the first time after delivery during the investigated time window.

In 557 pregnancies NSAIDs and/or ASA were prescribed during gestation, 2.9% (421/14,666) received it during first trimester, in the second and third trimester this was 0.74% (N=108) and 0.64% (N=94) respectively.

Discussion
This study reports on NSAID and ASA prescribing before, during and after pregnancy in a population-based database. In 3.9% of the pregnancies NSAIDs and/or ASA are prescribed during pregnancy, in 2.9% NSAIDs and/or ASA are
being prescribed during first trimester. Our data does not contain information about OTC-use or sales and therefore the results found in this study underestimate actual use. Unpublished data of the EUROCAT-registration Northern-Netherlands showed that 60% received a prescription for NSAIDs approx. 35% retrieved their NSAID OTC.

Prescribing of NSAIDs and/or ASA during third trimester is low (0.6%) which was to be expected due to existing guidelines not to prescribe these drugs during the third trimester. In 2005 a warning from the EMEA stated that NSAIDs and/or ASA should not be used during the first trimesters of pregnancy unless this was strictly indicated. This warning was based on studies showing increased associations with among others gastroschisis\textsuperscript{8-11}. Our data showed low prescribing of NSAIDs during the second and third trimester being 0.7 and 0.6% respectively, but prescribing during the first trimester was much higher (2.9%).

In the Netherlands approx. 200,000 children per year are born\textsuperscript{16}, approx. 1 per 5000 children\textsuperscript{17} is born with gastroschisis. If 3% of the pregnant women are prescribed NSAIDs (or ASA) during first trimester, approx. 6000 pregnant women are eligible for exposure to these drugs in that period. If we assume an OR of 4.0 on the risk of gastroschisis, found by Torfs et al.\textsuperscript{11} to be true, 4.8 children (6000*4/5000) with gastroschisis will be born among the women using NSAIDs and/or ASA. Based on the data from EUROCAT we can assume that the 3% found in the IADB.nl will be an underestimation of actual use.

We do realize this data represent prescribing of NSAIDs and/or ASA before the warning from the EMEA. However, we strongly recommend that prescribing physicians have to be careful in prescribing these drugs to women in the fertile age, especially when use of these drugs during pregnancy increases the risk of certain birth defects such as gastroschisis. If the warning of the EMEA will result in less prescribing of NSAIDs and/or ASA, especially during first trimester of pregnancy, has to be examined in future research.

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References