

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

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Abstract

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

Design and setting Population based cohort study and a case-control study, both based on data from a prescription registry, the Danish birth registry, and one county's hospital discharge registry.

Participants Cohort study: 1462 pregnant women who had taken up prescriptions for non-steroidal anti-inflammatory drugs in the period from 30 days before conception to birth and 17 259 pregnant women who were not prescribed any drugs during pregnancy. Case-control study: 4268 women who had miscarriages, of whom 63 had taken non-steroidal anti-inflammatory drugs, and 29 750 primiparous controls who had live births.

Main outcome measures Incidences of congenital abnormality, low birth weight, preterm birth, and miscarriage.

Results Odds ratios for congenital abnormality, low birth weight, and preterm birth among women who took up prescriptions for non-steroidal anti-inflammatory drugs were 1.27 (95% confidence interval 0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39) respectively. Odds ratios for the taking up of prescriptions in the weeks before miscarriage ranged from 6.99 (2.75 to 17.74) when prescriptions were taken up during the last week before the miscarriage to 2.69 (1.81 to 4.00) when taken up between 7 and 9 weeks before. The risk estimates were no different when the analysis was restricted to missed abortions.

Conclusions Use of non-steroidal anti-inflammatory drugs during pregnancy does not seem to increase the risk of adverse birth outcome but is associated with increased risk of miscarriage.

Introduction

Anti-inflammatory drugs are among the commonest drugs prescribed to pregnant women.^{1,2} All non-steroidal anti-inflammatory drugs are inhibitors of cyclo-oxygenase and can have adverse effects in both mother and fetus.³ Some investigators have linked fetal exposure to aspirin or indomethacin with a higher risk of congenital abnormality and low birth weight,^{4,5} though other investigators have failed to confirm this.⁶⁻⁹ The risk of adverse birth outcome in users of non-steroidal anti-inflammatory drugs other than aspirin and indomethacin has been examined only in studies with low numbers of participants, and few have been population based.¹⁰

As non-steroidal anti-inflammatory drugs are widely used, even a small increase in the risk of adverse effects may have major implications for public

health. We examined the risk of adverse birth outcome among Danish women who had taken up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy.

Subjects and methods

Study population

The study was conducted in the Danish county of North Jutland (population approximately 490 000). It included data on all women who between 1991 and 1998 had a live birth or a stillbirth after the 28th week of gestation or who had a miscarriage (including missed abortions). The data were obtained from the Danish birth registry and the county's hospital discharge registry. Risk of adverse birth outcome (congenital abnormality, low birth weight, and preterm birth) was examined in a cohort study and risk of miscarriage in a case-control study.

Use of non-steroidal anti-inflammatory drugs

As part of its tax funded health care for all inhabitants the Danish national health service reimburses 50% of all expenditure on a wide range of prescribed medicines, including non-steroidal anti-inflammatory drugs (international anatomical therapeutical classification code M01A) prescribed at doses equivalent to 400 mg or 600 mg ibuprofen (doses equivalent to 200 mg ibuprofen may be purchased without a prescription). North Jutland is served by 33 pharmacies equipped with electronic accounting systems that are used primarily to secure reimbursement from the national health service. These systems include information on the anatomical therapeutical classification code, the amount of the drug prescribed, the personal identification number of the patient, and the date of dispensing the drug.¹¹ All data are transferred to the pharmaco-epidemiological prescription database of North Jutland, which holds key data on all reimbursed prescribed drugs sold at pharmacies in the county since 1 January 1991.¹² During the period studied indomethacin was regarded as the drug of choice to delay premature delivery. As this may introduce a confounding factor, our analyses both included and excluded data on women who took indomethacin during pregnancy. We validated data on the use of non-steroidal anti-inflammatory drugs by verifying prescriptions in general practitioners' and hospital records of a randomly selected subset of 46 pregnant women.

Outcome data

Registries

The Danish birth registry, which comprises data collected by midwives and doctors attending deliveries, contains information on all births in Denmark since 1



Further data on
congenital
abnormalities
appear on the
BMJ's website

January 1973.¹³ The main data are maternal age, self reported smoking status, order of birth, gestational age, length and weight of neonate at birth, and personal identifiers for both mother and child.

We identified all cases of congenital abnormality and miscarriage from the regional hospital discharge registry (established in 1977), from which data are transferred to the national Danish hospital discharge registry. The national registry comprises data on 99.4% of all discharges from Danish hospitals and includes 10 digit personal identifiers, dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses,¹⁴ classified according to the Danish versions of ICD-8 (international classification of diseases, 8th revision) until the end of 1993 and ICD-10 after this date. The codes for miscarriage were 634.61, 643.8-9, and 645.1 in ICD-8 and O02 and O03 in ICD-10, and those for congenital abnormalities were 740.00-752.09, 752.29-755.59, and 755.79-759.99 in ICD-8 and Q00.0-Q52.9, Q54.0-Q64.9, and Q66.0-Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their low validity.

The personal identifiers were used to link prescription records with both registries. Follow up, using the regional hospital discharge registry, ended on 31 December 1998.

Cohort analysis

The association between use of non-steroidal anti-inflammatory drugs and adverse birth outcome was studied in a cohort of women who had a live birth or a stillbirth after the 28th week of gestation. The women were divided into two groups according to the stage of gestation (based on information from the birth registry) at which they took up prescriptions for non-steroidal anti-inflammatory drugs: the "early pregnancy" group comprised women who took up prescriptions from 30 days before conception to the end of the first trimester and the "later pregnancy" group comprised women who took up prescriptions in the second or third trimesters. The reference group was all pregnant women who were not prescribed any kind of reimbursed medicine in the study period. To

determine whether there was a dose-response relation, we compared the outcomes of pregnancies of women during which only one prescription of a non-steroidal anti-inflammatory drug was recorded with those of women in which more than one prescription was recorded.

Case-control analysis

We used a case-control study to determine any association between non-steroidal anti-inflammatory drugs and first recorded miscarriage. Cases were defined as first recorded miscarriages in women who had taken up a prescription for non-steroidal anti-inflammatory drugs in the 12 weeks before the date of discharge from hospital after the miscarriage. The control group was primiparous women who had live births. The first trimester was used as the exposure period in the control group. The risk estimates were calculated for time intervals of 1, 2-3, 4-6, 7-9, and 10-12 weeks before the day of discharge after miscarriage. All non-steroidal anti-inflammatory drug prescriptions were categorised according to these periods.

Statistical analysis

Cohort study

We performed logistic regression analyses to estimate the risk of congenital abnormality, low birth weight (<2500 g), and preterm birth (<37 weeks) associated with non-steroidal anti-inflammatory drugs, adjusted for maternal age, birth order, and smoking status. We used data from the early pregnancy group to estimate the risk of congenital abnormality and data from the later pregnancy group to estimate the risk of preterm birth and low birth weight (analysis of risk of low birth weight was restricted to full term births).

Case-control study

We performed logistic regression analyses to estimate the risk of miscarriage associated with non-steroidal anti-inflammatory drugs. We included as a variable the period of time from when the prescription was taken up to the day of discharge after the miscarriage, adjusting for maternal age.

Table 1 Comparison of pregnancies during which prescriptions for non-steroidal anti-inflammatory drugs were taken up and those during which no drugs were prescribed.

Variable	Prescriptions taken up			
	Between 30 days before conception and end of first trimester	In second and third trimester	Any time from 30 days before conception to term	No drug prescribed during pregnancy
No of pregnancies	1106	997	1462	17 259
First pregnancies	449	381	576	9 263
Subsequent pregnancies	657	616	886	7 996
No of prescriptions	1257	1176	1742	—
Mean age (range) of mothers	28.1 (16-43)	28.3 (16-43)	28.3 (16-43)	28.5 (13-47)
No (%) of smokers	398 (36)	409 (41)	600 (41)	4 833 (28)
Gestational age:				
≥37 weeks	1041	936	1374	16 268
34-6 weeks	41	40	59	682
<34 weeks	24	21	29	309
Mean weight (range) of babies at birth (grams)	3464 (639-5530)	3453 (639-5710)	3466 (639-5710)	3 483 (605-5 630)
No (%) of babies with congenital abnormalities	46 (4.2)	37 (3.7)	56 (3.8)	564 (3.3)
No (%) of preterm deliveries	65 (5.9)	61 (6.1)	88 (6.0)	991 (5.7)
No (%) of babies of low birth weight at term*	19 (1.8)	13 (1.4)	22 (1.6)	268 (1.6)

*Excluding preterm deliveries.

Table 2 Logistic regression analyses of birth outcome in women who took up prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and in women who were not prescribed any drug during pregnancy. Figures are crude and adjusted odds ratios (95% confidence intervals)

Variable	Congenital abnormalities		Low birth weight		Preterm delivery	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Drugs:						
No drugs prescribed	1	1	1	1	1	1
Prescriptions taken up	1.29 (0.95 to 1.75)	1.27 (0.93 to 1.75)	0.84 (0.48 to 1.47)	0.79 (0.45 to 1.38)	1.07 (0.82 to 1.40)	1.05 (0.80 to 1.39)
Pregnancy:						
First	1	1	1	1	1	1
Subsequent	0.86 (0.73 to 1.01)	0.84 (0.70 to 1.01)	0.63 (0.50 to 0.81)	0.59 (0.45 to 0.77)	0.79 (0.69 to 0.89)	0.74 (0.64 to 0.85)
Smoking status:						
Non-smoker	1	1	1	1	1	1
Smoker	1.16 (0.97 to 1.39)	1.15 (0.96 to 1.38)	3.66 (2.86 to 4.67)	3.72 (2.90 to 4.77)	1.41 (1.23 to 1.61)	1.4 (1.23 to 1.61)
Maternal age:						
<25	1	1	1	1	1	1
25-30	0.89 (0.71 to 1.10)	0.93 (0.75 to 1.16)	0.68 (0.51 to 0.92)	0.93 (0.68 to 1.27)	0.85 (0.72 to 0.99)	0.88 (0.75 to 1.04)
>30	0.93 (0.76 to 1.15)	0.97 (0.76 to 1.23)	0.84 (0.63 to 1.14)	1.28 (0.92 to 1.79)	0.9 (0.77 to 1.07)	1.06 (0.88 to 1.27)

Results

Cohort study

A total of 1462 women who had a live birth or stillbirth after the 28th week took up 1742 prescriptions for non-steroidal anti-inflammatory drugs; 1106 women took up prescriptions in early pregnancy and 997 in later pregnancy (table 1). Apart from a lower proportion of smokers among the women who were not prescribed any drugs, no other significant differences in the study variables were found.

We identified 46 congenital abnormalities in 1106 pregnancies of women who took up prescriptions of non-steroidal anti-inflammatory drugs during early pregnancy (4.2% (95% confidence interval 3.0% to 5.3%)), compared with 564 in 17 259 pregnancies in the reference cohort (3.3% (3.0% to 3.5%)). Details of these congenital abnormalities are shown on the *BMJ's* website. The adjusted odds ratios of congenital abnormalities, low birth weight, and preterm birth among women who took up prescriptions of non-steroidal anti-inflammatory drugs were 1.27 (0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39), respectively (table 2). There were no stillbirths among the women who took up prescriptions.

Comparison of pregnancies during which more than one non-steroidal anti-inflammatory drug prescription was taken up with those in which only one was taken up gave adjusted odds ratios for taking up more than one prescription of 0.66 (0.20 to 2.17) for congenital abnormalities, 3.09 (0.91 to 10.52) for low birth weight, and 0.65 (0.26 to 1.68) for preterm birth.

Fifty women had taken up prescriptions for indomethacin. Review of hospital records confirmed that the risk of miscarriage was an indication for the prescribing of indomethacin in 38 cases; in 10 use of indomethacin could not be confirmed, and one record could not be traced. Exclusion of these data did not change the risk estimates shown in table 2 (data not shown).

Case-control study

Table 3 shows the odds ratios for miscarriage, compared with pregnancies ending in a birth, in women who took up prescriptions for non-steroidal anti-inflammatory drugs. The ratio decreases as the time from taking up the prescriptions to discharge from hospital increases. Neither restricting the calculations to missed abortions only (ICD-8, 634.61 and 645.1; ICD-10, O02.1) nor inclusion or exclusion of pregnancies during which indomethacin was taken changed the risk estimates given in table 3 (data not shown).

Validation of non-steroidal anti-inflammatory drug use

To validate use of the drugs, we studied a randomly selected subgroup of general practitioners' records and hospital records for 46 pregnancies in the cohort study. In 71% of these pregnancies, the records indicated that non-steroidal anti-inflammatory drugs were prescribed, mostly for benign conditions of the muscles and skeleton.

Discussion

We found no significant association between take up of prescriptions for non-steroidal anti-inflammatory drugs during pregnancy and risk of congenital abnormality, low birth weight, or preterm birth. There was, however, a significant association with miscarriage.

Table 3 Prescription of NSAIDs among women recorded as having a miscarriage in their first pregnancy compared with women who had a live birth (reference group). Figures are Nos of pregnancies*

Variable	Miscarriage (n=4268)	Live birth (n=29 750)	Adjusted odds ratio (95% CI)
Time from taking up prescriptions for NSAIDs to date of discharge after miscarriage:			
1-12 weeks	63	318	1
1 week	3	9	6.99 (2.75 to 17.74)
2-3 weeks	5	15	3.00 (1.21 to 7.44)
4-6 weeks	14	41	4.38 (2.66 to 7.20)
7-9 weeks	19	92	2.69 (1.81 to 4.00)
10-12 weeks	22	161	1.26 (0.85 to 1.87)
Maternal age:			
<25 years (reference)	1022	8 284	1
25-29 years	1509	12 424	0.99 (0.91 to 1.07)
30-34 years	1128	6 728	1.36 (1.24 to 1.49)
>35 years	609	2 314	2.13 (1.91 to 2.38)
NSAIDs not prescribed during pregnancy	4205	29 432	

NSAIDs=non-steroidal anti-inflammatory drugs.

*Only primigravidas are included in the analysis.

The comparison period used for the reference group was the first trimester.

The full and independent registration of prescriptions and birth outcome prevented selection bias and some types of information bias. In the cohort study potential misclassification in the registration of congenital abnormalities would be unlikely to be related to the prescribing of non-steroidal anti-inflammatory drugs. The case-control study was based on routinely recorded data and was independent of diagnosis, thus there was no risk of recall bias, which can invalidate case-control studies that rely on interviews.¹⁵ Previous studies have shown high validity of data in both the prescription database and the birth registry.^{16, 17} In a recent, as yet unpublished study that was based on a review of hospital records in the period 1 January 1991 to 31 December 1995, we found that more than 80% of patients coded as having a congenital abnormality in the regional hospital discharge registry were correctly coded. Data on the major confounding factors of maternal age, smoking status, and birth order were available in the cohort study; the case-control study, however, lacked data on smoking status.

We had no specific information on compliance. That the prescriptions for non-steroidal anti-inflammatory drugs were taken up at the pharmacy and paid for in part by the patient may improve compliance. Furthermore, a relevant indication for the use of non-steroidal anti-inflammatory drugs was documented in general practitioners' records in a high proportion of pregnancies. These drugs, however, are often used as short term analgesics and may be purchased over the counter, which may increase the likelihood of misclassification of women with respect to drug use and bias the risk estimates towards one.

Teratogens do not uniformly increase the risk of all congenital abnormalities, but rather of specific abnormalities.¹⁵ We did not find any specific trend in the distribution of congenital abnormalities, and we did not find evidence for a dose-response relation between mothers' use of non-steroidal anti-inflammatory drugs and adverse birth outcome. Like other researchers we did not find an increased risk of reduced fetal growth.^{8, 9}

Use of non-steroidal anti-inflammatory drugs in pregnancy is clearly associated with increased risk of miscarriage. We had no information about the gestational age at time of miscarriage. A critical factor in the case-control study, therefore, is the time period that was selected for the controls, as general practitioners may change their prescribing practice when they know that a woman is pregnant. Such a bias would probably be independent of any particular drug among drugs that have the same estimated risk profile; we therefore repeated the analyses for penicillin V instead of non-steroidal anti-inflammatory drugs and found an odds ratio of 1. This result, as well as the decreasing odds ratio with increasing time interval between time of prescribing of non-steroidal anti-inflammatory drugs and miscarriage, indicates that such bias was minimal but does not exclude the possibility of confounding by indication (for example, the prescribing of a drug to treat pain that may be a precursor of miscarriage). However, we cannot determine from our non-experimental data whether this association is causal or due to undetected confounding. Thus, in the case-control study we were not able to adjust for smoking status, as we did in the cohort study.

What is already known on this topic

Current knowledge on the safety of taking non-steroidal anti-inflammatory drugs during pregnancy is based on studies with small sample sizes

What this study adds

Risk of adverse outcome at birth (congenital abnormality, low birth weight, or preterm birth) was not associated with the taking up of prescriptions for non-steroidal anti-inflammatory drugs during pregnancy

The taking up of such prescriptions was, however, associated with miscarriage

Apart from an unpublished study of use of ibuprofen in a cohort of 3178 pregnant women from the Michigan Medicaid surveillance study,¹⁸ we have not been able to identify any systematic studies of non-steroidal anti-inflammatory drug use in pregnant women. We have not found any studies of the association between non-steroidal anti-inflammatory drugs and miscarriage in humans. Because of the necessarily limited nature of studies of drug safety during pregnancy, it is important that all available data are combined to obtain the highest possible precision in the calculation of risk estimates. Our observation of an increased risk of miscarriage in women exposed to non-steroidal anti-inflammatory drug is new and needs to be confirmed.

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Contributors: GLN helped formulate the primary study hypothesis, discussed core ideas, finalised the study protocol, participated in data collection, analysis, and interpretation of findings, and undertook the main writing of the paper. HTS initiated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, and participated in data collection, analysis, interpretation of findings, and writing the paper. HL participated in the design of the study, data analysis, and interpretation of findings and edited the paper. LP participated in data collection, conducted the analyses, and took part in interpretation of findings. HTS is the guarantor of the study.

Competing interests: None declared.

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Impact on malaria morbidity of a programme supplying insecticide treated nets in children aged under 2 years in Tanzania: community cross sectional study

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A table showing the impact of net use on anaemia reported by other trials is available on the BMJ's website. This article is part of the BMJ's trial of open peer review, and documentation relating to this also appears on the website

Abstract

Objective To assess the impact of a social marketing programme for distributing nets treated with insecticide on malarial parasitaemia and anaemia in very young children in an area of high malaria transmission.

Design Community cross sectional study. Annual, cross sectional data were collected at the beginning of the social marketing campaign (1997) and the subsequent two years. Net ownership and other risk and confounding factors were assessed with a questionnaire. Blood samples were taken from the children to assess prevalence of parasitaemia and haemoglobin levels.

Setting 18 villages in the Kilombero and Ulanga districts of southwestern Tanzania.

Participants A random sample of children aged under 2 years.

Main outcome measures The presence of any parasitaemia in the peripheral blood sample and the presence of anaemia (classified as a haemoglobin level of < 80 g/l).

Results Ownership of nets increased rapidly (treated or not treated nets: from 58% to 83%; treated nets: from 10% to 61%). The mean haemoglobin level rose from 80 g/l to 89 g/l in the study children in the successive surveys. Overall, the prevalence of anaemia in the study population decreased from 49% to 26% in the two years studied. Treated nets had a protective efficacy of 62% (95% confidence interval 38% to 77%) on the prevalence of parasitaemia and of 63% (27% to 82%) on anaemia.

Conclusions These results show that nets treated with insecticide have a substantial impact on morbidity when distributed in a public health setting.

Introduction

Several studies have shown that malarial parasitaemia is positively correlated with anaemia and that parasitaemia is the primary cause of anaemia in very

young children in Africa.¹ As a result, because malarial infection is the norm in high transmission areas, anaemia is common in young children. Assessment of the impact of chemoprophylaxis in Tanzanian infants showed that over 60% of the anaemia could be due to malaria.² The emergence and spread of parasite resistance to commonly used antimalarial agents has exacerbated the problem of anaemia in sub-Saharan Africa.³

Hopes for controlling malaria and malarial anaemia have recently been revitalised by the demonstration that nets treated with insecticide can reduce morbidity and mortality. A summary of randomised controlled trials showed an average protective effect of about 50% on mild malaria episodes in areas where the rate of transmission of malaria was stable.⁴ Moreover, protective effects were shown on the prevalence of parasitaemia with a high level (> 5000/μl) of trophozoites (31%) and on overall mortality (19%). A modest improvement in packed cell volume (a rise of 0.02 (2%)) and weight gain was also observed in children sleeping under treated nets.⁴ Large scale implementation of programmes to supply treated nets is under way in several African countries.⁵

It is not known whether the impact of treated nets in the context of well controlled randomised controlled trials can be replicated under programme conditions.⁶ We report the first assessment of the impact of treated bed nets when supplied in the context of a large scale social marketing programme (an approach using marketing techniques to promote and distribute socially beneficial interventions rather than commercial products) on morbidity indicators in children aged under 2 years in an area of Tanzania with a high prevalence of malaria.

Methods

Study area and population

Social marketing of treated bed nets started in the Kilombero net project (KINET) in 1997,⁷ covering the