

Maternal drug use during pregnancy and asthma risk among children

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Abstract

Background: Maternal use of some drugs, notably paracetamol and drugs for gastroesophageal reflux, has been associated with an increased risk of childhood asthma in the child. We wanted to analyze these associations with consideration to the confounding of maternal asthma.

Methods: Childhood asthma was identified from the Swedish National Prescription Register and maternal drug use during the latter part of pregnancy from antenatal records, computerized in the Swedish Medical Birth Register. Risks were estimated as odds ratios (OR) with 95% confidence intervals, using Mantel–Haenszel technique with adjustment for year of birth, maternal age, parity, smoking habits, and BMI.

Results: A statistical association between maternal use of many different drugs, including paracetamol, and childhood asthma existed but was mainly due to concomitant drug use, related to maternal asthma. The only associations that appeared to be true were with drugs for gastroesophageal reflux (adjusted (OR) = 1.32, 95% CI, 1.18–1.54) and with opiates (adjusted OR = 1.56 (96% CI, 1.05–2.34).

Conclusions: Maternal use of paracetamol did not seem to increase the risk of childhood asthma, but the previously described association with drugs for gastroesophageal reflux was supported. The analysis is complicated by the confounding from maternal asthma.

Maternal use of drugs during pregnancy may affect the newborn infant in various ways. An increased risk of preterm birth, low birth weight, and various signs of neonatal morbidity has been described as associated with maternal use of many different drugs (1). Preterm birth has been associated with increased childhood morbidity, among other things like childhood asthma (2, 3). Some studies have found an association between maternal use of paracetamol (acetaminophen) with an increased risk of asthma (4–7), and one study (8) described a link between maternal use of gastric acid-suppressive drugs and childhood asthma.

A major problem in the interpretation of such associations is the fact that maternal asthma may act as a confounder. Maternal asthma may be associated with an excess use of other drugs than antiasthmatics, and this could result in a false association between such drugs and childhood asthma. Some of these are directly related to asthma-like antibiotics, systemic corticosteroids, drugs for rhinitis, and antihistamines, not

related to nausea and vomiting in pregnancy (NVP). Women using antiasthmatic drugs in early pregnancy also used drugs for gastroesophageal reflux diagnosis (GERD) and drugs for hypertension, drugs for thyroid disease, and drugs for migraine in excess, and this was true also for opiates, CNS-active drugs, and antihistamines used for NVP (9). This will complicate the analysis of associations between maternal use of drugs during pregnancy and childhood asthma.

The purpose of this study was to investigate the statistical association between maternal use of various drug categories (including paracetamol and drugs for GERD) and the risk of childhood asthma with special attention to the confounding effect of maternal asthma and concomitant drug use.

Material and methods

From the Swedish Medical Birth Register (MBR) (10), we identified singleton children born in 1999–2007, who survived

the perinatal period and whose mothers were born in Sweden ($n = 685,015$). Among them, children who received prescriptions for drugs for asthma during the period July 1, 2005–2009 were identified ($n = 113,095$). This was made with the aid of the Swedish Prescribed Drug Register that contains the personal identification numbers of all persons who have a filled prescription in Sweden (11). To qualify as having asthma, at least five prescription events for antiasthmatic drugs were required in a child, at least 2 yr of age. This was valid for 43,127 children. By requesting at least five separate prescription events, the likelihood for the identification of true asthma was thought to be increased (3).

Since July 1, 1994, MBR contains information on drug use during pregnancy. Such information is based on midwife interviews in early pregnancy (toward the end of the first trimester, not used in this study) and from prescriptions and recommendations made by the antenatal care staff later during pregnancy (mainly 2nd and 3rd trimesters). This means that the information, for instance, regarding an over the counter (OTC) drug, like paracetamol, will be restricted to situations when a more extended drug use is likely and temporary use will not be recorded. The drugs are recorded in clear text and later transferred to anatomical therapeutic chemical (ATC) codes.

In an effort to more completely identify women with asthma, all women who gave birth during 1999–2007 were searched in the Prescribed Drug Register for the period July 1, 2005 up till the end of 2011. Any prescription of an antiasthmatic drug during these six and a half years was taken as an indicator of a possible asthma. In the analysis of possible effects of other drugs on asthma in the child, such women were removed from the analysis as were women who had received antiasthmatic drugs (and also women who had received other drugs that were associated with asthma risk).

The risk of asthma among children, defined as above, was studied according to maternal use of various drug categories using Mantel–Haenszel methodology that gave odds ratios (OR) adjusted for year of birth, maternal age, parity, smoking, and body mass index (BMI), all factors that could affect both asthma risk and the use of specific drugs. This information was obtained from the MBR where the information on smoking and BMI was based on a midwife interview at the first antenatal care visit. Miettinen's technique was used to estimate approximate 95% confidence intervals (95% CI).

Linkage between registers was made with the use of the unique personal identification number, which everyone living in Sweden has.

Results

Table 1 shows the effect of removal of women from the analysis if they had obtained a prescription of antiasthmatic drugs during the period 2005–2011 as an indicator of maternal asthma. The total number of children was reduced by 16.6%, but the number of children with asthma by 30.4%. The adjusted OR for childhood asthma when the mother was identified as asthmatic by this way was 2.24 (95% CI, 2.19–2.29). Prescription of antiasthmatics during 2005–2011 did not identify all women with asthma during pregnancy. Among

Table 1 Presence of childhood asthma among all children and after exclusion of mothers who had prescriptions for asthma drugs during 2005–2012

Study group	Number of children with asthma	Total number of children	Percentage with asthma
All women	43,127	685,015	6.3
Women with prescriptions for antiasthmatic drugs 2005–2011	13,132	113,738	11.5
Women without prescriptions for antiasthmatic drugs 2005–2011	29,995	571,277	5.3

11,300 women who had used antiasthmatics during pregnancy, 2527 (23%) were not identified as asthmatic based on prescriptions during 2005–2011. When the OR for childhood asthma was determined after maternal use of antiasthmatics during pregnancy, it was 2.59 (95% CI 2.47–2.73), and when women who received prescriptions for antiasthmatics during 2005–2011 were excluded, the OR was significantly lower, 2.04 (95% CI 1.80–2.32).

Table 2 shows the risk of childhood asthma after maternal use of any ATC drugs during the 2nd or 3rd trimesters. Multivitamins, folic acid, iron, or minerals were not included. This table shows data for children with exclusion of those children whose mothers had prescriptions for antiasthmatics during 2005–2011. There is a clear-cut increased asthma risk after maternal use of drugs during late pregnancy. This effect is similar in children born term or preterm and after vaginal delivery or cesarean sections. The effect is markedly stronger after the use of antiasthmatic drugs than after other drug categories.

Table 3 shows the effect of specific drug categories when used during trimester 2 or 3 on asthma risk. In this table, the OR for asthma is first given for all women and then after exclusion of women who had used any other of the drugs specified in this table or had prescriptions for asthma medicines during the years 2005–2011. In this way, we hoped to eliminate or at least reduce the effect of concomitant drug use or concomitant untreated asthma. The strongest effect is seen for antiasthmatics, followed by opiates including codeine drugs containing paracetamol. The OR is high also for drugs for migraine, but as numbers are low, this association can be random. Drugs for treatment of GERD showed an intermediate and significantly increased OR. For most other drugs, the OR varied between 1.10 and 1.25, statistically significant for antibiotics and thyroid drugs. Paracetamol without codeine belonged to this category, but statistical significance was not reached. Only non-steroid antiinflammatory drugs (NSAID) drugs showed a low OR, but it was based on only few exposures. When all the specified drugs were excluded from the analysis, exposure for any other ATC drug gave only a weak increase in OR, but statistical significance was reached. In this

Table 2 Maternal use of any ATC drug (except for multivitamins, folic acid, iron, minerals) or antiasthmatic drug during the 2nd–3rd trimesters and the risk of childhood asthma. Women who had prescriptions for antiasthmatics during 2005–2011 were excluded

Drugs used by mother	Drug-exposed children with asthma	Total children with asthma	Total drug-exposed children	All children	OR	95% CI
Any ATC drug	5353	29,995	85,895	571,277	1.26	1.22–1.30
Any ATC drug, preterm births	504	2591	4588	27,763	1.23	1.10–1.37
Any ATC drug, term births	4849	27,391	81,206	542,892	1.25	1.21–1.29
Any ATC drug, vaginal delivery	4148	24,106	70,891	484,429	1.24	1.20–1.29
Any ATC drug, cesarean section	1205	5889	15,004	86,848	1.26	1.20–1.29
Antiasthmatics	259	29,995	2577	571,277	2.04	1.80–2.32
No antiasthmatics but other ATC drugs	5094	29,995	104,795	571,277	1.21	1.18–1.24

ATC, anatomical therapeutic chemical.

Number of children with asthma = 29,995, total number of children = 571,277. Odds ratio (OR) after adjustment for year of birth, maternal age, parity, smoking, and BMI and 95% confidence intervals (95% CI).

Table 3 Maternal use during the 2nd–3rd trimesters of specific drugs and none other among the drugs shown in this table

Drug group	All women				Women after exclusion*			
	Exposed children with asthma	All exposed children	OR	95% CI	Exposed children with asthma	All exposed children	OR	95% CI
<i>Drugs used at asthma and allergy</i>								
Antiasthmatics	1704	11,300	2.59	2.47–2.73	145	1501	1.96	1.66–2.32
Cough medicines	211	2349	1.44	1.21–1.67	33	514	1.16	0.81–1.68
Antibiotics	1592	21,064	1.27	1.20–1.33	686	12,395	1.10	1.02–1.19
Drugs for rhinitis	773	7132	1.81	1.61–1.95	140	2085	1.27	1.07–1.50
Antihistamines	1704	17,867	2.59	2.47–2.73	614	9287	1.26	1.16–1.37
<i>Analgesics</i>								
Opiates excl. drugs with paracetamol	96	1657	1.90	1.64–2.21	26	325	1.56	1.05–2.34
Paracetamol alone	569	5974	1.50	1.37–1.63	138	2203	1.13	0.95–1.31
Paracetamol and codeine	105	746	1.96	1.60–2.40	25	219	1.89	1.24–2.89
NSAID	67	704	1.50	1.16–1.93	5	207	0.46	0.20–1.10
<i>Other drug categories</i>								
Drugs for GERD	475	4768	1.60	1.40–1.76	161	2275	1.32	1.12–1.55
Drugs for cardiovascular disease	378	4576	1.24	1.11–1.37	178	2781	1.14	0.98–1.35
Thyroid drugs	634	7719	1.26	1.16–1.36	352	5137	1.25	1.15–1.40
Drugs for migraine	41	411	1.57	1.19–2.17	13	141	1.75	0.99–3.12
Sedatives/hypnotics	137	1512	1.45	1.23–1.73	23	351	1.19	0.78–1.82
Antidepressants	403	4570	1.30	1.17–1.44	137	2152	1.12	0.93–1.33
Any ATC drug except those listed above	2618	40,693	1.07	1.03–1.12	1904	34,838	1.09	1.04–1.15

NSAID, non-steroid antiinflammatory drugs; ATC, anatomical therapeutic chemical; GERD, gastroesophageal reflux diagnosis.

Odds ratio (OR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI.

*Women using other specified drug categories in this table or who received antiasthmatic drugs during 2005–2011 were excluded. Total number of children with asthma = 29,995, total number of children = 571,277 after these exclusions.

group, some drugs associated with atopy were still included, for example, various administration forms of glucocorticosteroids and other antiallergy drugs.

Discussion

This study is large and based on health registers. Some non-asthmatic children may have been included although antiasthmatic drugs had been prescribed; if so, this will slightly bias the risk estimates toward 1.0.

The information on drug use during pregnancy was prospective in relation to outcome as it was generated from medical documents made during pregnancy. All drug use may not have been recorded. Thus, the total rate of women who were identified to have used paracetamol was lower than what was noted in interview studies (5, 12). For the drugs under study, this is of less importance as it will only slightly bias the OR toward 1.0, but it will more severely affect the exclusion of concomitant drug use. If, for instance, all antiasthmatic use was not recorded, the effect of simultaneously used antiasthmatics will not be completely removed.

There is a clear association between maternal drug use during pregnancy and childhood asthma. The OR is about the same for preterm and term births and for vaginal and cesarean deliveries in spite of the fact that both preterm birth (2, 3) and cesarean section (13, 14) are risk factors for childhood asthma.

These analyses are complicated by the fact that maternal asthma is associated with the use of drugs other than antiasthmatics and that maternal asthma is a risk factor for childhood asthma for genetic reasons. So is also paternal asthma, but this will not act as a confounder as it hardly affects maternal drug use. In an effort to identify further the women who could have a genetic disposition for asthma, we checked the prescriptions for antiasthmatic drugs obtained during the period July 1, 2005 to 2011. The risk of asthma among children born of these women was significantly increased. After exclusion of these women, 2577 (23%) remained among the 11,300 women who had used antiasthmatics during late pregnancy. Some of these women may have used the drugs for other reasons than asthma, which is indicated by the observation that the OR for childhood asthma when the mother had used antiasthmatics during pregnancy decreased significantly from 2.59 to 2.04. The women who remain were asthmatic who had not been identified by the prescription analysis. It is likely that some women with asthma were still not identified, and they will confound the further analysis. Ideally, also other types of atopy should have been handled in a similar way but that was not practically possible as they cannot easily be identified from drug usage.

The effect of maternal drug use was strongest for antiasthmatics, but even after exclusion of such drugs, a significant association remained with use of any ATC drug. When individual drug categories were analyzed including only individuals without recorded use of any of the other drug category, ORs declined further, but some remained statistically significant. Especially when the OR was low, this may be an effect of residual confounding by unidentified maternal asthma or related atopic disease or by unidentified concomitant drug use.

Drugs for asthma or rhinitis and antihistamines

The association between maternal use of antiasthmatics and childhood asthma is strong and is reasonably explained by a genetic link between maternal and child asthma. Allergic rhinitis and asthma are strongly associated, even though drugs for rhinitis are also used for other reasons. The association between drugs for rhinitis and childhood asthma is strong but declines markedly when signs of maternal asthma are taken into consideration (Table 3). A similar pattern is seen for antihistamines that are used at allergy but also at other conditions, for instance, NVP. Also, use of antibiotics and cough medicines gave increased risk estimates, which declined when indicators of maternal asthma were considered.

Analgesics

According to some studies in the literature, there is an association between maternal use of paracetamol and childhood asthma. A review on this subject (4) identified eight studies and concluded that at that time the evidence for an association was inconclusive. Three studies of this association have been published since then. In one study from Sweden (5), an association was found between maternal paracetamol use and inhaled corticosteroid treatment for pre-school wheeze (OR = 2.1; 95% CI, 1.1–4.0). Data were obtained by questionnaires with a rather high non-response rate (31% at 6 months age and 40% at 12 months age). The second study came from Denmark (6), and exposure to paracetamol was evaluated from redeemed prescriptions, thus excluding OTC use of the drug. An increased risk of childhood asthma was seen both after the prescription of paracetamol and for NSAID drugs with an OR of 1.52 (95% CI, 1.24–1.88) and 1.26 (1.20–1.33), respectively. In the third study from Norway, based on prospectively recorded use of paracetamol and follow-up at the age of 10, no association between the use of paracetamol during pregnancy and asthma was found (OR = 1.04; 95% CI, 0.39–2.75) (12). A meta-analysis performed on six studies gave a pooled random effect of 1.21 (95% CI, 1.02–1.44), but the confounding effect of maternal asthma was not taken into consideration (7).

We found an OR = 1.50 for paracetamol use and childhood asthma, but it was reduced to 1.13 (not any longer statistically significant) when consideration was taken to indicators of maternal asthma. A similar situation existed for NSAIDs, also with an OR of 1.50, which disappeared when indicators of maternal asthma were taken into consideration. The rate of NSAID use was low, however. There is a general pregnancy warning against use of these drugs in late pregnancy.

Another group of analgesics showed a high OR, namely opioids. Also this OR decreased when consideration was taken to concomitant drug use and maternal asthma, but remained elevated with an OR of 1.56 (95% CI, 1.05–2.34).

Drugs for GERD

One previous paper in the literature (8) found an association between maternal use of drugs for GERD and childhood

asthma with an OR of 1.51 (1.35–1.69). This study was performed on a Swedish material, which partly covers the present material. Also in our study we found an increased OR for childhood asthma (OR = 1.60; 95% CI, 1.40–1.76), which was attenuated when concomitant drug use, and women with asthma were excluded but remained statistically significantly increased (OR = 1.32; 95% CI, 1.12–1.55).

Other drug categories

The OR for childhood asthma is only slightly increased after maternal use of thyroid drugs (mainly thyroxine), and the OR is hardly influenced by removal of concomitant drugs and of women with asthma. Comorbidity between thyroid disease and asthma has been described (15) and may be linked to a common immunological pathway.

The ORs without considering concomitant drugs or maternal asthma for other studied drugs varied from 1.24 (drugs for cardiovascular diseases) to 1.57 (drugs for migraine). Exclusion of women who used other drugs or had asthma left no statistically significant OR, but most ORs were increased and for drugs for migraine close to statistical significance.

These remaining associations may be the result of incomplete identification of concomitant drug use or maternal asthma.

Our data do not support the idea that use of paracetamol during pregnancy is a risk factor for childhood asthma but give some support to such an effect of drugs for GERD and for opiates. A background in experimental work exists for drugs

for GERD (8), while the possible association with opiates seems not to have been described previously, and the observation needs confirmation. An increased risk of neonatal respiratory conditions after maternal use of opioids is known, however (16).

To conclude, our study illustrates the problems that arise when one tries to link maternal drug use during pregnancy with childhood asthma. The two most likely associations are with drugs for treatment of GERD and opioids, but further studies are needed to verify or reject the associations. We found little evidence for an effect of paracetamol on childhood asthma risk, which agrees with the most recent publication on the subject (12), also based on prospectively collected data.

Ethics

The study was performed within the responsibilities of the National Board of Health and Welfare, and therefore, no ethical approval from outside ethical committees was needed.

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Competing interests

None of the authors declare any competing interests.

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