Maternal Asthma and Use of Antiasthmatic Drugs in Early Pregnancy and Congenital Malformations in the Offspring

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Abstract

**Objectives:** To investigate the risk of congenital malformations in infants born of women who had used antiasthmatic drugs in early pregnancy.

**Methods:** Data were obtained from the Swedish Medical Birth Register for 1996-2011. Information on drug use was based on midwife interviews towards the end of the first trimester. Presence of congenital malformations was ascertained from three national health registers. Risk estimates were made with Mantel-Haenszel odds ratios after adjustment for delivery year, maternal age, parity, smoking, and body mass index. Consideration was taken to concomitantly used drugs.

**Results:** Among more than 1.5 million women who gave birth, 2.9% reported the use of antiasthmatics. These women had characteristics which distinguished them from other women who gave birth and they more often than these used other drugs than antiasthmatics. These differences seemed to affect malformation risk only little. The risk for a major malformation was slightly but significantly increased (odds ratio=1.09, 95% confidence interval 1.03-1.12), specifically this was seen for cardiovascular defects, median cleft palate, and pyloric stenosis. There was no specific association with specific drugs or drug groups, the highest risk estimate was seen for women who used only one drug and notably a short-acting adrenergic or used three or more antiasthmatic drugs groups.

**4 Conclusion:** The absolute risk for a congenital malformation in infants born of women using antiasthmatics is low and some evidence indicates that it is due to underlying asthma. A good control of asthma seems important and scare of teratogenicity of the common antiasthmatic drugs should not prevent adequate use.

Keywords: Adrenergic; Antiasthmatic; Asthma; Cardiovascular defect; Cleft palate; Congenital malformation; Glucocorticosteroid; Leukotriene receptor antagonist; Pyloric stenosis; Xanthine

Introduction

Numerous studies have been published on the effect of maternal asthma on pregnancy and pregnancy outcome, including the presence of congenital malformations. A summary of the early literature was published in 2007 [1]. Since then further studies have appeared and recent reviews are available [2,3]. A meta-analysis in the latter article found a weighted total odds ratio for a major malformation from four relatively large cohort studies of 1.18 (95% CI 1.00-1.36). Other studies used case-control approaches [4-6] and found statistically significant associations between use of antiasthmatics and specific congenital malformations. As pointed out by many authors [2], a major problem in the interpretation of these results is the question of confounding by indication, that the underlying asthma and not the use of drugs caused the malformations.

The present study updates previous information from the Swedish Medical Birth Register on the association between maternal use of antiasthmatics and infant congenital malformations [7].

Material and Methods

The study was based on the Swedish Medical Birth Register which contains medical information on nearly all births in Sweden [8]. Since July 1, 1994, information on maternal drug use in early pregnancy was recorded from midwife interviews at the first prenatal care visit, usually in pregnancy weeks 10-12. Drug names were recorded in clear text and were later centrally transferred to ATC (Anatomical, Therapeutic, Chemical) codes. Women who had reported any antiasthmatic drug (ATC code R03) were identified and compared with women who did not report such drugs. The Medical Birth Register also gave information on putative confounders consisting of maternal characteristics and of concomitant use of other drugs than antiasthmatics. The maternal characteristics were maternal age (5 year classes, <20, 20-24 etc.), parity (1, 2, 3, 4, where parity 1 is the first baby born), maternal smoking (unknown, none, <10 cigarettes per day, ≥10 cigarettes per day), and BMI (unknown, <18.5, 18.5-24.9, 25-29, 30-34, ≥35) calculated from prepregnancy weight and height recorded at the midwife interview.

Outcomes were congenital malformations in the infants born. These were ascertained from three sources [9]: diagnoses in the Medical Birth Register given by the pediatrician who examined the newborn, the Birth Defect Register (previously called the Register of Congenital Malformations), and the inpatient discharge diagnoses in the Patient Register (previously Hospital Discharge Register). Information from the three registers was linked using the identification number which every person living in Sweden has.

In order to reduce variability in the ascertainment of congenital malformations, a subgroup called relatively severe malformations was formed where infants who only had one or more of the following malformations were excluded: preauricular tags, tongue tie, patent ductus in preterm infants, single umbilical artery, undescended testicle, hip (sub)luxation, and nevus. As cardiovascular defects were counted all cases with the exception of those with only a patent ductus at preterm birth or with single umbilical artery. In studies of specific malformations infants with chromosome anomalies were excluded.

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Risk estimates were made with the Mantel-Haenszel methodology as Odds Ratios (OR) with approximate 95% confidence intervals (95% CI) estimated with Miettinen's method. Adjustment was made for year of delivery, maternal age, parity, smoking in early pregnancy, and BMI. When the expected number of infants with the outcome under study was <10, a risk ratio was instead calculated as the observed/expected numbers were calculated with the adjustments mentioned above.

**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.

**Results**

Among 1,552,342 women who gave birth and were registered in the Medical Birth Register in 1996-2011, 44 772 reported the use of antiasthmatics in early pregnancy (2.9%). Table 1 shows the number of exposed children.

| Drug name               | ATC code          | Number of women | Number of infants |
|-------------------------|-------------------|-----------------|-------------------|
| Adrenergics,            |                   |                 |                   |
| epinephrine             | R03AA01/R03CA01   | 104 104         |                   |
| ephedrine               | R03CA02           | 31 31           |                   |
| salbutamol              | R03AC02/R03CC02   | 8485 8597       |                   |
| terbutaline             | R03AC03/R03CC03   | 27056 27362     |                   |
| fenoterol               | R03AC04           | 36 37           |                   |
| Long-acting             |                   |                 |                   |
| salmeterol              | R03AC12           | 1806 1837       |                   |
| formoterol              | R03AC13           | 1821 1850       |                   |
| bumbuterol              | R03CC12           | 15 15           |                   |
| Adrenergics+anticholinergics | R03AK04 | 41 41          |                   |
| salmeterol+ipratropium  | R03AK04           | 41 41           |                   |
| Adrenergics+gluco-corticoids | 5291 5380 |                   |
| salmeterol+fluticasone  | R03AK06           | 1730 1754       |                   |
| formoterol+budesonide   | R03AK00/R03AK07   | 3571 3635       |                   |
| Inhaled gluco-corticoids|                   | 19258 19549     |                   |
| beclometazone           | R03BA01           | 700 706         |                   |
| budesonide              | R03BA02           | 17672 17901     |                   |
| fluticasone             | R03BA00/R03BA05   | 949 962         |                   |
| mometazone              | R03BA07           | 70 71           |                   |
| Anticholinergics        |                   | 221 228         |                   |
| ipratropium             | R03BB01           | 209 214         |                   |
| thirotropium            | R03BB04           | 13 14           |                   |
| Antiallergics except corticosteroids | 1681 1709 |                   |
| cromoglic acid          | R03BC01           | 1692 1709       |                   |
| Xanthines               |                   | 209 214         |                   |
| choline theophyllinate   | R03DA02           | 43 43           |                   |
| theophylline            | R03DA04           | 163 168         |                   |
| amnophylline            | R03DA05           | 5 5             |                   |
| Leukotriene receptor antagonists | 506 512 |                   |
| montelukast             | R03DC03           | 506 512         |                   |
| Antibodies              |                   | 2 2             |                   |
| omalizumab              | R03DX05           | 2 2             |                   |
| Unspecified             |                   | 96 96           |                   |

| Malformation             | With drug | Total | OR/RR | 95% CI |
|--------------------------|-----------|-------|-------|--------|
| Any malformation         | 2206      | 70317 | 1.07  | 1.03-1.12 |
| Rel. severe malformation | 1544      | 45652 | 1.09  | 1.03-1.15 |
| Chromosome anomalies     | 84        | 2932  | 1.01  | 0.81-1.26 |
| Neural tube defect       | 24        | 734   | 1.13  | 0.75-1.70 |
| Other CNS malformation   | 31        | 1131  | 0.92  | 0.64-1.32 |
| Severe eye malformation  | 12        | 579   | 0.72  | 0.41-1.28 |
| Severe ear malformation  | 4         | 280   | 0.45  | 0.12-1.58 |
| Cleft lip/palate         | 44        | 1704  | 0.87  | 0.64-1.57 |
| Median cleft palate      | 42        | 1002  | 1.45  | 1.06-1.98 |
| Cardiovascular defects   | 533       | 16145 | 1.13  | 1.04-1.23 |
| Septum defects           | 144       | 4380  | 1.11  | 0.94-1.31 |
| Esophageal atresia       | 14        | 445   | 1.12  | 0.66-1.90 |
| Small gut atresia        | 13        | 392   | 1.22  | 0.70-2.13 |
| Anal atresia             | 21        | 590   | 1.21  | 0.78-1.87 |
| Pyloric stenosis         | 46        | 1101  | 1.42  | 1.06-1.91 |
| Abdominal wall defect    | 10        | 413   | 0.84  | 0.44-1.60 |
| Diaphragmatic hernia     | 9         | 368   | 0.79  | 0.41-1.52 |
| Hypoospladias            | 120       | 4552  | 0.87  | 0.73-1.05 |
| Severe renal malformation| 26        | 882   | 1.00  | 0.68-1.48 |
| Pes equinovus            | 74        | 2127  | 1.14  | 0.90-1.43 |
| Poly/syndactyly          | 106       | 3084  | 1.21  | 0.99-1.47 |
| Limb reduction defects   | 29        | 838   | 1.16  | 0.80-1.68 |
| Diaphragmatic hernia     | 84        | 812   | 1.02  | 0.69-1.51 |
| Rel. severe malformation except a cardiovascular defect | 1090 | 34940 | 1.07 | 1.01-1.14 |

Table 1: Number of women reporting different specified antiasthmatics and number of exposed children.
the OR for malformations and women who had reported the use of antiasthmatics and no other drugs had roughly the same risks as all women using antiasthmatics.

According to Table 4, significant effects on relatively severe malformations are seen after the use of one group of antiasthmatics alone and when three or more groups had been used while the OR estimates for use of two drug groups appeared to be lower. Table 4 also shows effects of different groups of antiasthmatics on the presence of relatively severe malformations. Even though only some reach statistical significance, there seems to be no clear-cut difference in effect between the groups – statistical significance is associated with large number of exposures. Also when individual antiasthmatics with at least 500 exposures were analyzed, ORs varied between 0.84 (95% CI 0.56-1.19) and 1.79 (95% CI 0.34-5.09, based on only 10 exposed cases) for long-acting adrenergics, and 1.65 (95% 1.11-2.44) for inhaled glucocorticosteroids. The use of combined long-acting adrenergic and inhaled glucocorticosteroids had an OR=1.83 (95% CI 0.84-3.47), based on only nine cases. None of the specific drug groups showed an increased OR for cleft lip/palate.

Among 512 infants exposed to montelukast, 17 had relatively severe malformations which are specified in Table 5.

## Discussion

This study is based on a large material where drug exposure was identified by interviews in early pregnancy and congenital malformations from three national health registers. It has some weaknesses. Drug exposure occurred in early pregnancy and mainly during the first trimester but exact timing was not known. Some women may have used the drugs outside the period of organogenesis – this will result in a reduction of risk estimates. Another problem is that the study does not include cases where a congenital malformation was identified by interviews in early pregnancy and congenital malformations were not identified by interviews in early pregnancy and congenital malformations.

### Table 3: Effect on relatively severe malformations or cardiovascular defects analyzed with respect to concomitant drug use. Odds ratio (OR) with 95% confidence interval (95% CI). Bold text marks statistical significance.

| Group | Total number | Number malformed | OR/RR | 95% CI | Number malformed | OR/RR | 95% CI |
|-------|--------------|------------------|-------|--------|------------------|-------|--------|
| All included | 45612 | 1544 | 1.09 | 1.03-1.15 | 533 | 1.13 | 1.04-1.23 |
| Excluding "teratogens" | 42437 | 1441 | 1.10 | 1.04-1.16 | 491 | 1.12 | 1.03-1.23 |
| Excluding all concomitant drugs | 23556 | 794 | 1.08 | 1.00-1.16 | 270 | 1.11 | 0.98-1.25 |

Excluded "teratogens" are drugs used for functional gastrointestinal disease, drugs used for immunological bowel disease, antihypertensives, systemic glucocorticosteroids, thyroid hormones, and NSAIDs.

### Table 4: Presence of relatively severe malformations or cardiovascular defects according to antiasthmatic used. Odds ratio (OR) or risk ratio (RR) with 95% confidence interval (95% CI). Bold text shows statistical significance.

| Antiasthmatic | Total number | Number malformed | OR/RR | 95% CI | Number malformed | OR/RR | 95% CI |
|---------------|--------------|------------------|-------|--------|------------------|-------|--------|
| Any antiasthmatic | 45612 | 1544 | 1.09 | 1.03-1.15 | 533 | 1.13 | 1.04-1.23 |
| Number of drug groups | | | | | | | |
| One | 24144 | 842 | 1.11 | 1.04-1.19 | 284 | 1.13 | 1.01-1.28 |
| Two | 16749 | 534 | 1.03 | 0.94-1.12 | 187 | 1.08 | 0.93-1.25 |
| Three or more | 4145 | 166 | 1.18 | 1.01-1.38 | 61 | 1.27 | 0.98-1.63 |
| Groups of drugs | | | | | | | |
| Short-acting adrenergics | 35453 | 1219 | 1.10 | 1.04-1.10 | 433 | 1.17 | 1.07-1.29 |
| Long-acting adrenergics | 8947 | 287 | 1.08 | 0.96-1.22 | 102 | 1.12 | 0.92-1.36 |
| Inhaled glucocorticosteroids | 24594 | 817 | 1.08 | 1.01-1.16 | 281 | 1.11 | 0.99-1.25 |
| Anticholinergics | 267 | 11 | 1.24 | 0.62-2.11# | 3 | - | - |
| Antiallergics | 1709 | 57 | 1.01 | 0.77-1.32 | 18 | 1.01 | 0.63-1.61 |
| Xanthines | 214 | 8 | 1.04 | 0.45-7.06# | 3 | - | - |
| Leukotriene receptor antagonists | 512 | 17 | 1.13 | 0.61-1.83 | 5 | 0.97 | 0.32-2.27# |
| Drug combinations | | | | | | | |
| Only short-acting adrenergics | 20394 | 716 | 1.13 | 1.04-1.21 | 257 | 1.22 | 1.07-1.38 |
| Long-acting adrenergic or glucocorticoids only | 8467 | 270 | 1.07 | 0.95-1.21 | 86 | 1.01 | 0.81-1.25 |
| Short-acting adrenergics+long-acting adrenergics or glucocorticoids | 535 | 16078 | 1.07 | 0.98-1.67 | 192 | 1.15 | 0.99-1.32 |
| Ditto+other antiasthmatics | 24 | 598 | 1.24 | 0.82-1.86 | 10 | 1.52 | 0.73-2.71# |

#RR as observed/expected numbers with exact 95% CI.
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Risk was actually found for short-acting adrenergics. The association between use of asthma medication and infant gastroschisis seen in one retrospective case-control study [14] was not verified in the present study – among 251 cases of gastroschisis only five had been exposed while seven were expected under a no-effect hypothesis.

The statistical association between maternal asthma and use of antiasthmatic drugs and the occurrence of congenital malformations can have many explanations. Maternal characteristics differ between these and other women. The effect of this is, however, small. The crude OR for a relatively severe malformation, adjusted only for year of delivery, is 1.13 (95% CI 1.11-1.15) and when adjusted also for age, parity, smoking and BMI it declines to 1.09 (95% CI 1.03-1.15). The corresponding figures for a cardiovascular defect is 1.15 (95% CI 1.05-1.25) and 1.13 (95% CI 1.04-1.23).

Another explanation is that women using antiasthmatic drugs use many other drugs more often than other women and if such concomitantly used drugs have an effect of their own on the malformation risk, this would confound the analysis. There was very little indication that this was true – the OR for a relatively severe malformation or for a cardiovascular defect was about the same when no other drugs had been used concomitantly or when women using drugs with a putative teratogenic risk were removed from the analysis.

A third explanation to the association is that asthma has an effect of its own, a confounding by indication. Such an effect can act in different ways, one possibility is that asthma exacerbations during early pregnancy could result in embryonic asphyxia and in this way cause malformations. Another possibility is a genetic link between the disease and some malformations. In the first situation, severity of the disease may decide the level of the malformation risk - a well-controlled asthma should have less or no effect. This may explain why the group with two antiasthmatics belonging to different groups seemed to have the lowest malformation risk. The one-drug group may be undertreated and the three or more drugs group may have asthma which is difficult to control needing a combination of many drugs.

Theoretically it would be ideal to be able to quantify the severity of the asthma in some way and add it as an explanatory variable [2]. There are clinical possibilities to do this, e.g., with spirometry or FEV, measurements [15]. A problem is that in order to demonstrate effects which are as weak as those we are discussing, large materials are needed. A power analysis (alfa=0.05, beta=0.80) shows that in order to demonstrate a 15% increased risk for any major malformation (supposing a 3% prevalence in the population) one would need to study about 11 900 women with asthma which in practice means the use of health registers where it is unlikely that data on clinical variables can be collected. The question whether the effect is due to drugs or to underlying disease most likely has to be answered in indirect ways. One way is to compare the effects of different drugs with the same indication. As seen in Table 4, no major differences are seen between different drug groups but the analysis is complicated by the fact that the drugs to some extent are used together and there are also differences between the drugs with respect to their clinical use.

Table 4 also shows that when different treatment situations are compared, no very strong difference appears but there is a suggestion that the OR is lower for women who are on prophylactic therapy with long-acting adrenergics and/or inhaled glucocorticosteroids. When other antiasthmatics had to be added (e.g., xanthines or leukotriene antagonists) the OR estimate increased but so did the confidence interval width. These observations suggest that the disease status in early pregnancy plays the major role for the slight malformation risk.

| Malformation | Number |
|--------------|--------|
| ASD+VSD+PS+ CNS malformation | 1 |
| VSD | 3 |
| Unspecified cardiac defect | 1 |
| Larynx malformation | 1 |
| Tracheomalacia | 1 |
| Pyloric stenosis | 1 |
| Sponge kidney | 1 |
| Hydronephrosis | 1 |
| Pes equinovarus | 1 |
| Polydactyly hand | 2 |
| Syndactyly hand and foot | 1 |
| Upper limb malformation | 1 |
| Arthrogryposis | 1 |
| Wolf-Hirschorn syndrome | 1 |

ASD=atrium septum defect, CNS=central nervous system, PS=pulmonary valve stenosis, VSD=ventricular septum defect.

Table 5: Specification of relatively severe congenital malformations in infants exposed to montelukast.
increase and the consequence of this should be that as good control of the asthma as possible should be beneficial for the embryo and there is no reason to reduce or avoid therapy with adrenergics or glucocorticosteroids in early pregnancy for fear of teratogenicity.

In the arsenal of antiasthmatic drugs, some relatively recent additions are of special interest. One such drug group is leukotriene receptor antagonists, e.g., montelukast. Previous studies [16,17] were based on few exposures (96 and 180, with five and one infant with major malformations, respectively). The present material contained 512 exposed infants among which 17 had a relatively severe malformation. The risk estimate, 1.13 (95% CI 0.69-1.83) was of the same order of magnitude as for other antiasthmatics. So far, this drug seems not to carry a specific teratogenic risk but to exclude a weak such risk, a much larger material is needed. Another recent addition is the antibody omalizumab. Only two women reported the use of this drug, both with normal infants.

In conclusion, the present data show only a small risk increase for a congenital malformation in infants born of women using antiasthmatics and it seems likely that this risk is associated with poorly controlled asthma and not with drug use. Other obstetric and perinatal effects than congenital malformations may occur with maternal asthma. These have not been studied in the present investigation.

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