

## Research Article

# Maternal use of montelukast in early pregnancy and infant congenital malformations

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## Abstract

**Background:** Only few studies are published about maternal use of montelukast in early pregnancy and infant congenital malformations.

**Material:** The study was performed on data from the Swedish Medical Birth Register. Between 1999 and 2013, 633 women prospectively reported the use of montelukast in early pregnancy. The rate of congenital malformations and certain types of malformations were compared with corresponding rates in the general population after adjustment for year of birth, maternal age, parity, smoking in early pregnancy and pre-pregnancy body mass index. Another comparison group consisted of infants whose mothers had used long-acting adrenergic drugs or inhaled corticosteroids but not montelukast.

**Results:** A total of 30 malformed infants were identified, OR=1.07 (95% confidence interval 0.74–1.55) after montelukast exposure. Among them 23 were relatively severe, OR=1.17, 95% CI 0.77–1.78. Eight had cardiovascular defects (RR=1.16, 95% CI 0.50–2.29). Similar risk estimates were seen in the comparison group, then statistically significant.

**Conclusion:** More information is needed about use of montelukast in early pregnancy but at present no major teratogenic effect is found and the weak effects seen are similar to those seen after other anti-asthmatic drugs and may be a result of the underlying asthma disease.

## Introduction

Montelukast is a leukotriene receptor inhibitor, in Sweden mainly used as an asthma medication or at allergic rhinitis. Its use during pregnancy has been studied in a limited number of investigations. In a pregnancy register of montelukast, kept by Merck, a clustering of six transverse limb reductions was noted [1]. The first epidemiological study identified 190 infants, exposed in early pregnancy to montelukast, seven of them with malformations among which three had cardiac defects [2]. A small study was published on leukotriene receptor antagonists (72 montelukast, 22 zafirlukast and 2 with both drugs) among which 85% had used the drug during the first trimester. One concluded that the malformation risk was increased compared with unexposed infants but similar to that in infants treated with other asthma drugs [3]. Another small study identified 160 livebirths exposed to montelukast (90% of them during the first trimester) with only one twin infant with a cardiac defect -one fetus with Down syndrome had been aborted after prenatal diagnosis [4].

The largest study comes from Merck as a letter to the Editor [5]. This study identified maternal exposure to montelukast during the first trimester from a prescription register and presence of congenital malformations in the infants from insurance claims. A total of 1,187 first trimester exposures were identified and compared with 5,018 exposures for inhaled corticosteroids and 38,828 unexposed controls. A number of different malformations were identified and the percentage of certain heart malformations (14 cases) was higher after montelukast than in the two comparison cohorts (1.2% vs. 0.7%). This was also the case for malformations in the digestive tract (based on 6 cases) and “other congenital limb anomalies” (ICD-9 code 755, 16 cases). A detailed analysis of the latter revealed no case of a limb reduction of the type observed in the pregnancy register (but one case

had an unspecified lower limb malformation) and most of the limb anomalies were poly- or syndactyly or hip subluxation. No adjustment for putative confounders was presented.

The present report is an update from the Swedish Medical Birth Register. The total number of exposed infants is a little more than half of the number in the study mentioned [5] above but larger than in other previous studies.

## Material and methods

Data were obtained from the Swedish Medical Birth Register, where information on maternal drug use is obtained from midwife interviews in early pregnancy (usually in week 10–12) [6]. The register also contains information on maternal characteristics which may confound the analysis [7]. Congenital malformations in the infants were identified from three sources: diagnoses given in the Medical Birth Register at the pediatric examination of the newborn, diagnoses from the Birth Defect Register (previous Register of Congenital Malformations) and from discharge diagnoses in the Hospital Discharge Register [8]. Linkage between registers was made with the unique personal identification number each person living in Sweden has.

Statistical analysis was made with the Mantel-Haenszel method, comparing malformation rate among exposed infants with the malformation rate among all other infants, adjusted for year of

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birth, maternal age, parity, maternal smoking in early pregnancy, and pre-pregnancy body mass index (BMI). Risks were expressed as odd ratios (OR) with 95% confidence intervals (95% CI). When the observed number of exposed cases was <10, risk ratios (RR) were instead calculated as observed/expected numbers (expected numbers calculated with adjustments as above) and the 95% CI was based on exact Poisson distributions. The first woman who reported the use of montelukast in early pregnancy was delivered in 1999. As data were only available up to and including 2013, the analysis was made for the period 1999-2013.

The definition of a group of “other congenital limb anomalies” followed that used by Nelsen *et al.* [5].

For comparison a material was prepared of infants whose mothers had reported the use of long-acting adrenergic drugs and/or inhaled corticosteroids but not montelukast.

## Results

During 1999-2013, 1,528,044 infants were registered in the Medical Birth Register. Among them, 633 were born in 624 deliveries of women who had reported the use of montelukast in early pregnancy. In the comparison group there were 24,547 infants exposed to other long-acting adrenergic drugs and/or inhaled corticosteroids.

Table 1 shows some maternal characteristics. Use of montelukast increased with a maternal age over 35, decreased with parity and increased at obesity. There was no certain effect of maternal smoking. There were nine twin deliveries.

The characteristics of women who had reported the use of long-acting adrenergic drugs or corticosteroids were similar but the effect of

parity was less marked than for montelukast and the effect of smoking was clear-cut.

In 99 women, montelukast was the only anti-asthmatic drug reported. Eighty-two women reported one, 268 two, 161 three, 13 four and one five further anti-asthmatics. Table 2 shows the nature of the simultaneously used anti-asthmatics.

Among the 663 montelukast-exposed infants, 30 had a congenital malformation. Table 3 lists the identified malformations and Table 4 gives ORs for some groups. None reaches statistical significance but the OR for the heterogeneous group “other congenital limb defects” is relatively high. This group contains poly- or syndactyly, unstable hip, arthrogryposis and one unspecified limb malformation. In the group of infants whose mothers had used other long-acting anti-asthmatics than montelukast, there was a significant increase of any malformation, of relatively severe malformations and of cardiovascular defects. The estimates for the two groups were rather similar except for the “other congenital limb defects”, but the higher RR for the montelukast group was not statistically significant.

## Discussion

The present study has the advantage that it is based on exposure information obtained in early pregnancy without recall bias and on independent outcome registers. The disadvantage is that information of the time of usage is crude: only that it was used during pregnancy before the first prenatal visit which usually takes place in weeks 10-12. Furthermore there is no information on dosage, but the standard dose of montelukast in adults is 10 mg/day.

The number of montelukast-exposed infants is not very large but there is only one previous large material published [5], nearly twice the

**Table 1.** Some characteristics of women reporting the use of montelukast or other anti-asthmatics\* in early pregnancy. Odds ratios (OR) with 95% confidence intervals (95% CI). For each variable, adjustment was made for the other variables. Bold text marks statistical significance.

Variable	Population	With monte-lukast	OR	95% CI	With other anti-asthmatics*	OR	95% CI
Maternal age							
<20	25568	12	0.97	0.53-1.77	446	1.02	0.93-1.13
20-24	195988	86	0.92	0.71-1.19	3225	0.96	0.92-1.01
25-29	455097	193	1.00	Reference	7133	1.00	Reference
30-34	521625	174	0.89	0.72-1.09	8139	1.02	0.99-1.06
35-39	255672	130	<b>1.34</b>	<b>1.05-1.71</b>	4314	<b>1.14</b>	<b>1.09-1.18</b>
≥40	51823	29	<b>1.62</b>	<b>1.06-2.50</b>	933	<b>1.22</b>	<b>1.13-1.32</b>
Parity							
1	674350	371	1.00	Reference	11782	1.00	Reference
2	545126	167	<b>0.52</b>	<b>0.44-0.63</b>	7910	<b>0.78</b>	<b>0.76-0.80</b>
3	199886	63	<b>0.49</b>	<b>0.36-0.65</b>	3102	<b>0.80</b>	<b>0.76-0.83</b>
≥4	86415	23	<b>0.35</b>	<b>0.22-0.56</b>	1396	<b>0.73</b>	<b>0.89-0.78</b>
Smoking							
Unknown	87228	4	-	-	393	-	-
None	1301806	574	1.00	Reference	21387	1.00	Reference
<10 cigs/day	86370	32	0.82	0.57-1.18	1706	<b>1.07</b>	<b>1.02-1.13</b>
≥10 cigs/day	30373	14	1.36	0.80-2.32	704	<b>1.36</b>	<b>1.26-1.47</b>
BMI							
Unknown	162259	32	-	-	1620	-	-
<18.5	32625	12	0.90	0.51-1.59	479	0.98	0.89-1.07
18.5-24.9	817784	320	1.00	Reference	11728	1.00	Reference
25-29.9	336874	163	<b>0.73</b>	<b>0.60-0.88</b>	6303	<b>0.77</b>	<b>0.75-0.80</b>
30-34.9	110549	65	1.30	0.99-1.71	2652	<b>1.45</b>	<b>1.39-1.51</b>
≥35	45686	41	<b>2.15</b>	<b>1.55-3.00</b>	1408	<b>2.05</b>	<b>1.94-2.17</b>

\*Long-acting adrenergic drugs or inhaled corticosteroids

size of the present material. In that report, no adjusted risk estimates were presented but the numbers of malformation cases in different groups of malformations were given. Among 20 such groups, four showed marked rate differences when compared with the reference cohort of non-asthmatic cases or the cohort treated with inhaled corticosteroids. These are shown in Table 5 with crude odds or risk ratio estimates, calculated from the numbers given in that paper. There were three groups of cardiovascular defects. One group (bulbous or septal defects) showed similar rates in the three groups, one (other cardiac defects) showed a statistically non-significant increase when

compared with the population but not when compared with infants exposed to inhaled corticoids (ICS), and the third group (non-cardiac circulatory defects) showed a significant increase compared with the reference group and a higher but not statistically significant increase compared with the ICS group. It can be noted that this malformation group includes patent ductus arteriosus – an increased risk for this condition could be the result of the well-known increased risk of preterm births at maternal asthma. Also in the present study there was an increased risk for cardiovascular defects (excluding preterm patent ductus arteriosus), similar in size in the montelukast and the asthma comparison group but not statistically significant in the former.

**Table 2.** Simultaneous use of other anti-asthmatic drugs together with montelukast.

Type of anti-asthmatic	Number of women
Short-acting adrenergic drugs	291
Long-acting adrenergic drugs	375
Inhaled corticosteroids	456
Anticholinergic drugs	13
Cromoglicic acid	11
Xanthines	16
Systemic corticosteroids	0

**Table 3.** List of congenital malformations after exposure to montelukast in early pregnancy.

Malformation	Number
Relatively major malformations	
Encephalocele	1
Unspecified CNS malformation + VSD + ASD + pulmonary valve stenosis	1
Truncus arteriosus	1
VSD	4
Pulmonary valve stenosis	1
Tricuspidal stenosis	1
Unspecified cardiac defect	1
Laryngeal stridor, tracheomalacia	2
Pylorostenosis	1
Medullary cystic kidney with hydronephrosis	1
Hydronephrosis	1
Pes equinovarus	2
Polydactyly	2
Syndactyly	1
Unspecified malformation upper limb (no reduction)	1
Arthrogryposis	1
Deletion chromosome 4	1
Less severe and variably recorded malformations	
Tongue tie	1
Undescended testicle1	2
Hip subluxation/unstable hip	4
ASD = atrium septum defect, CNS = central nervous system, VSD = ventricular septum defect	

**Table 4.** Odds ratio (OR) or Risk Ratio (RR) for congenital malformations after maternal use of montelukast or other long-acting anti-asthmatic drugs, adjusted for year of birth, maternal age, parity, smoking and BMI. Bold text marks statistical significance

Malformation	Population	With monte-lukast	OR/RR	95% CI	With other long-acting anti-asthmatics	OR	95% CI
Any	65247	30	1.07	0.74-1.55	1151	<b>1.07</b>	<b>1.01-1.14</b>
Rel. severe	46818	23	1.17	0.77-1.78	848	<b>1.11</b>	<b>1.04-1.19</b>
Any cardiac defect	10513	8	1.16	0.50-2.29#	364	<b>1.13</b>	<b>1.02-1.20</b>
“Other congenital limb anomaly”*	3971	9	1.59	0.73-3.02#	66	1.06	0.83-1.36

# RR as observed/expected ratio with exact Poisson 95% CI. Other anti-asthmatics” are cases with long-acting adrenergic drugs and/or inhaled corticosteroids.

\*Corresponding to the group pin-pointed by Nelsen et al. [5], ICD-10 codes Q65, Q69-Q74

The increase in “lower digestive malformations” was based on few cases and not statistically significant – in the present material there was no such case after montelukast exposure. In the asthma comparison group there were 80 infants with anal atresia, OR=1.12 (95% CI 0.90-1.40). The population rate was 3 per 1000 infants.

The last group showing an excess in the Nelsen *et al.* [5] paper consisted of limb defects of a non-deformity type (thus for instance pes equino-varus was not included but arthrogryposis and hip dislocation was). The increase compared with the reference cohort was statistically significant while the excess compared with the ICS cohort could be random. Also in the present material such an increase was indicated after montelukast even though statistical significance was not reached. No such increase was seen for the asthma comparison cohort. In the two large montelukast studies when added, 25 infants were recorded with such malformations. Among them 13 had unstable hip and nine had polydactyly or syndactyly. Among the remaining three infants, there was one with arthrogryposis and two with unspecified lower limb malformations. In none of the two small studies [3,4] were malformations of this type reported.

Hip dysplasia is a relatively mild anomaly, the rate of which varies considerably between hospitals and with year of birth depending on the diagnostic criteria applied and also varies with gestational duration [9]. There is also a variation of the rate of polydactyly (notably of postaxial polydactyly) and of syndactyly (notably of webbing of toes). Crude comparisons of the rates of these relatively common anomalies are therefore not very useful.

## Conclusion

There are now two relatively large studies on the use of montelukast in early pregnancy. It seems likely that the indicated weak teratogenic effect of this drug is similar to that of other drugs used for long-term treatment of asthma, probably explained by an effect of underlying disease.

**Ethics:** The data for this study were collected as part of the routine analysis of drug use during pregnancy by the National Board of Health

**Table 5.** Summary of groups of malformations which showed increased rates in the paper by Nelsen *et al.* [5]. Crude odds ratios (OR) calculated by the present author with chi-square or Fisher exact test, respectively. Reference group: no anti-asthmatic drugs or women treated with inhaled corticosteroids (ICS). Bold text shows statistical significance

Malformation group	ICD-9 code	Reference	Monte-lukast	ICS	OR vs. reference (95% CI)	OR vs. ICS (95% CI)
Total number of exposed infants	-	38 828	1187	2 285	-	-
Cardiac defects, excl. bulbus cordis and septal defects	746	269	14	16	1.72 (0.90-3.00)	1.69 (0.76-3.71)
Non-cardiac circulatory system	747	570	31	44	<b>1.80</b> <b>(1.23-2.63)</b>	1.37 (0.83-2.23)
Lower digestive system	751	79	6	8	2.48 (0.79-8.33)	0.91 (0.34-2.22)
Non-deformity limb malformations	755	251	16	17	<b>2.10</b> <b>(1.22-3.56)</b>	1.82 (0.81-3.85)

ICD = International Classification of Disease, ICS = inhaled corticosteroids

and Welfare. No external ethical committee evaluation was needed for this process.

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### Conflict of interest

The author reports no conflict of interest.

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