

Congenital Malformations in the Offspring when Drugs for Functional Gastrointestinal Disease were used during Early Pregnancy

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Abstract

Background: Little is known about the risk for congenital malformations among infants born of women who are treated for functional gastrointestinal diseases during early pregnancy.

Material and methods: Data from the Swedish national health registers were used to investigate possible associations between different drugs used at functional gastrointestinal diseases and occurrence of congenital malformations in the offspring. Drug use was ascertained by midwife interviews in early pregnancy recorded in the Medical Birth Register and the presence of congenital malformations by the use of three national health registers. Risk estimates were made with Mantel-Haenszel methodology and confidence interval estimates with Miettinen's method. The effect of maternal characteristics and concomitant drug use was controlled. Women using drugs for inflammatory bowel disease were excluded from the analysis.

Results: Among 1.5 million women 1282 (1301 infants) reported the use of drugs for functional gastrointestinal diseases in early pregnancy, 1048 (1062 infants) reported the use of antipropulsives, 3579 (3635 infants) the use of laxatives, and 13103 (13332 infants) the use of drugs for GERD. An increased risk for congenital malformations was found after the use of drugs for functional gastrointestinal diseases or of antipropulsives which could not be explained by concomitant drug use or maternal characteristics. It is unclear if it is a direct drug effect or is due to underlying disease. A specific effect was seen of dimethicone and of loperamide. No certain teratogenic effect was seen from laxatives or from most drugs used for GERD. An association between the use of sucralfate and congenital malformations was seen, however. Further independent data on these specific drugs are needed.

Conclusion: A small risk for congenital malformations is associated with maternal use of drugs for functional gastrointestinal diseases, if due to drug effects or to underlying pathology is unclear.

Keywords: Dimethicone; Drugs for GERD; Functional gastrointestinal disease; Laxatives; Loperamide; Sucralfate

Introduction

In a review of gastrointestinal medications in pregnancy [1] it was pointed out that no large epidemiological study had been published on pregnant women with irritable bowel syndrome and that other forms of functional gastrointestinal disorders during pregnancy are also rather little studied. Some drugs used at such conditions have been investigated for a possible effect on the unborn child like drugs used for gastric ulcers or gastro-esophageal reflux diagnosis (GERD) [2-5] and loperamide [6].

The present study presents information from the Swedish Medical Birth Register and other national Swedish Registers on the outcome of pregnancies in women who in early pregnancy had reported the use of drugs for functional gastrointestinal disorders according to the ATC (Anatomic, Therapeutic, Chemical) drug classification but also some related drug groups. As outcome were studied congenital malformations in the infants born.

Material and Methods

The Swedish Medical Birth Register contains medical information on nearly all deliveries in Sweden since 1973 (1-2% are missing) [7]. It is based on copies of medical documents from the prenatal care, delivery, and pediatric neonatal examination of the newborn. The form for such documents is the same in all hospitals in Sweden since 1982. From the register are obtained date of delivery, maternal age, and parity. Information on smoking habits in early pregnancy and on pre-pregnancy weight and height (from which BMI can be calculated) are obtained from midwife interviews at the first prenatal visit (usually in weeks 10-12). With a beginning during 1994, information was

added on maternal drug use, also based on midwife interviews at the first prenatal visit. The question stated was: "What drugs have you used since you became pregnant?" The drug names are written down in clear text and are later centrally transferred into ATC codes. Both prescription drugs and over the counter drugs are included.

The following drug categories were selected for analysis:

- 1) Drugs for functional gastrointestinal disorders, ATC-code A03 with the exception of metoclopramide. The reason for this was that metoclopramide is mainly used at nausea and vomiting of pregnancy.
- 2) Antipropulsives.
- 3) Laxatives.
- 4) Drugs used for GERD.

Sometimes these drugs had been used together with drugs for inflammatory bowel disease. These cases were removed from the analysis.

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The presence of congenital malformations was ascertained from multiple sources: the Medical Birth Register, the special Register of Birth Defects (previously called Register of Congenital Malformations), and from discharge diagnoses at inpatient treatments from Patient Register (previously called Hospital Discharge Register). With the use of the personal identification number everyone living in Sweden has, these sources of information were linked [8]. In order to reduce variability in recording, a number of less clinically important and variably diagnosed conditions were excluded: preauricular appendix, tongue tie, patent ductus in preterm infants, single umbilical artery, hip (sub)luxation, undescended testicle, and nevus. The remaining conditions were called "relatively severe malformations" but may contain some minor conditions.

The statistical analysis consisted of different steps. In the first step, the concomitant use of other drugs was studied. For each drug category, the odds ratio (OR) with 95% confidence interval (95% CI) for use of that drug category together with the specific drug group under study was estimated with the usage among women who did not use the specific drug group as reference. This was partly made in order to characterize drug usage pattern, partly to identify drugs with a certain or probable teratogenic effect of its own. If such a drug had been used in excess together with the special drug under study, it could cause a false increase in the malformation risk. Therefore analyses were repeated after exclusion of women who had used in excess other drugs with a possible teratogenic effect.

Second, maternal characteristics (age, parity, smoking, BMI) were studied and each variable was adjusted for the other variables and year of delivery. As reference groups were used: maternal age 25-29 years, parity 1 (first baby born), non-smoking, and BMI 18.5-24.9.

Third, the presence of congenital malformations was studied in infants whose mothers had used specific drugs or drug groups. When numbers were large enough, some specific malformations were analyzed.

All ORs were determined using Mantel-Haenszel procedures and approximate 95% CI were calculated with Miettinen's method. Adjustments were made for year of birth, maternal age, parity, smoking, and BMI. When the expected number of outcomes was <10, risk ratios (RR) as observed/expected numbers were instead calculated (expected numbers adjusted as above). Confidence intervals were then based on Poisson distributions.

Results

Concomitant use of drugs

Table 1 identifies simultaneous use of drugs from the four drug categories analyzed. As can be seen from this Table, the four groups of drugs are used together in a much higher frequency than they are used among other women.

Table 2 identifies the concomitant use of some other drug groups which may have teratogenic properties according to studies on the Swedish registers: insulin [9], drugs for hypertension [10], systemic corticosteroids [11], thyroid drugs [12], immunosuppressants [13], NSAIDs [14], opioids [15], anticonvulsants [16], neuroleptics [17], and antiasthmatics [18]. Other drugs like antidepressants have no major teratogenic effect [15].

Maternal characteristics

For all drug categories there was an increased use with increased

Drug 1	Drug 2	Number drug 1+ drug 2	OR	95% CI
A03	A02B	140	12.5	10.8-14.4
	A06	86	24.7	19.8-30.5
	A07D	33	20.9	14.4-29.3
A06	A02B	209	6.88	6.09-7.79
	A07D	26	9.39	6.77-13.0
A07D	A02B	41	4.05	3.01-5.45

Table 1: Simultaneous pairwise use of drugs under study. A02B = drugs for GERD (n=13103), A03 = drugs for functional gastrointestinal disorder (except metoclopramide) (n=1307), A06 = laxatives (n=3601), A07D = antipropulsives (n=1081). OR = odds ratio, adjusted for year of birth, maternal age, parity, smoking and BMI, with 95% confidence intervals (95% CI).

Drug 2	Drug 1	Number with drug	OR/RR	95% CI
Insulin (n=5277)	A02B	50	0.99	0.74-1.31
	A03	11	2.10	1.05-3.76#
	A06	7	0.56	0.27-1.17#
	A07D	2	-	-
Drugs for hypertension (n=5467)	A02B	127	2.20	1.84-2.63
	A03	16	2.70	1.59-4.52#
	A06	16	1.14	0.89-1.89
	A07D	8	1.97	0.85-3.88#
Systemic corticosteroids (n=5022)	A02B	138	3.18	2.70-3.74
	A03	11	2.47	1.23-4.42#
	A06	23	1.81	1.21-2.71
	A07D	6	1.52	0.56-3.31#
Thyroid drugs (n=24017)	A02B	264	1.11	0.98-1.26
	A03	29	1.24	0.86-1.81
	A06	83	1.29	1.04-1.61
	A07D	14	0.84	0.49-1.44
Immunosuppressants (n=800)	A02B	41	6.09	4.61-8.04
	A03	4	5.00	1.36-12.8#
	A06	5	2.38	0.77-5.56#
	A07D	12	21.1	10.9-36.8#
NSAID (n=23517)	A02B	492	2.34	2.13-2.55
	A03	62	3.20	2.49-4.10
	A06	82	1.42	1.14-1.76
	A07D	53	3.15	2.41-4.10
Opioids (n=7530)	A02B	305	4.18	3.74-4.67
	A03	52	7.42	5.52-9.44#
	A06	61	3.41	2.68-4.35
	A07D	16	3.05	1.74-4.95#
Anticonvulsants (n=4370)	A02B	59	1.47	1.14-1.91
	A03	3	0.72	0.15-2.10#
	A06	15	1.46	0.88-2.43
	A07D	2	-	-
Neuroleptics (n=3817)	A02B	162	4.87	4.32-5.63
	A03	12	3.95	2.04-6.90#
	A06	16	1.82	1.04-2.96#
	A07D	4	1.53	0.42-3.91#
Antiasthmatics (n=44679)	A02B	665	1.69	1.56-1.82
	A03	79	2.06	1.64-2.58
	A06	178	1.70	1.47-1.98
	A07D	35	1.09	0.78-1.54

Table 2: Concomitant use of drugs which may have teratogenic properties. Bold text marks statistical significance. #Relative risks (RR) as observed over expected number with exact 95% confidence intervals (95%CI). A02B = drugs for GERD, A03 = drugs for functional gastrointestinal diseases (except metoclopramide), A06 = laxatives, A07D = antipropulsives.

maternal age (Figure 1A). Second parity had a decreased use compared with first parity for all drug categories but for higher parities results varied with no effect for drugs against GERD but a tendency of a diminishing use with higher parity for the other drugs, notably for laxatives (Figure 1B). With increasing BMI, use of drugs for functional gastrointestinal disease and use of drugs for GERD increased while for antipropulsives an increased use was seen only at obesity and for laxatives the trend was of a decreasing use with increasing BMI. For all four groups, there was a tendency to an increased use at low BMI (Figure 1C). Maternal smoking was associated with an increased use of this entire drug with the exception of laxatives (Figure 1D).

Drugs used for functional gastrointestinal disease (ATC code A03)

Table 3 shows the drugs included in this analysis. Use of metoclopramide was not included as it is mainly used for nausea and vomiting in pregnancy. There were 1282 remaining women with 1301 infants.

The presence of congenital malformations among infants born of women who reported the use of these drugs is shown in Table 4. All tabulated risk estimates were increased but that for septal heart defects or for hypospadias did not reach statistical significance. The risk for a relatively severe malformation varied according to group of drugs

used from 0.89 (anticholinergics with tertiary amino group) to 3.19 (spasmolytics with psycholeptics) but none of the individual groups showed statistically significant ORs and the rate of malformed infants did not differ significantly between the groups (Fisher test, $p=0.38$). Among these drugs, dimethicone was of some interest. Among 349 infants born after maternal use of this drug (but not metoclopramide or drugs for IBD), 24 had a malformation diagnosis (OR=1.72, 95% CI 1.14-2.59), 16 of them were relatively severe (OR=1.69, 95% CI 1.03-2.78). Eight had a cardiovascular defect (RR=2.31, 95% CI 1.00-4.56), two had esophageal atresia, two pyloric stenosis, and one small gut atresia.

In order to see if the increased risk could be explained by concomitantly used drugs with a possible teratogenic activity, the analysis of the risk for a relatively severe malformation was repeated after the exclusion of women who had reported the use of antipropulsives, insulin, drugs for hypertension, NSAID, opioids, and antiasthmatics. The OR estimates declined marginally and remained statistically just significant: OR 1.36 (95% CI 1.00-1.83).

Antipropulsives (ATC codes A07D)

Among 1048 women with 1062 infants who reported the use of antipropulsives, 1010 had used loperamide, 21 loperamide oxide and 25 loperamide with dimethicone. Three had used both loperamide and

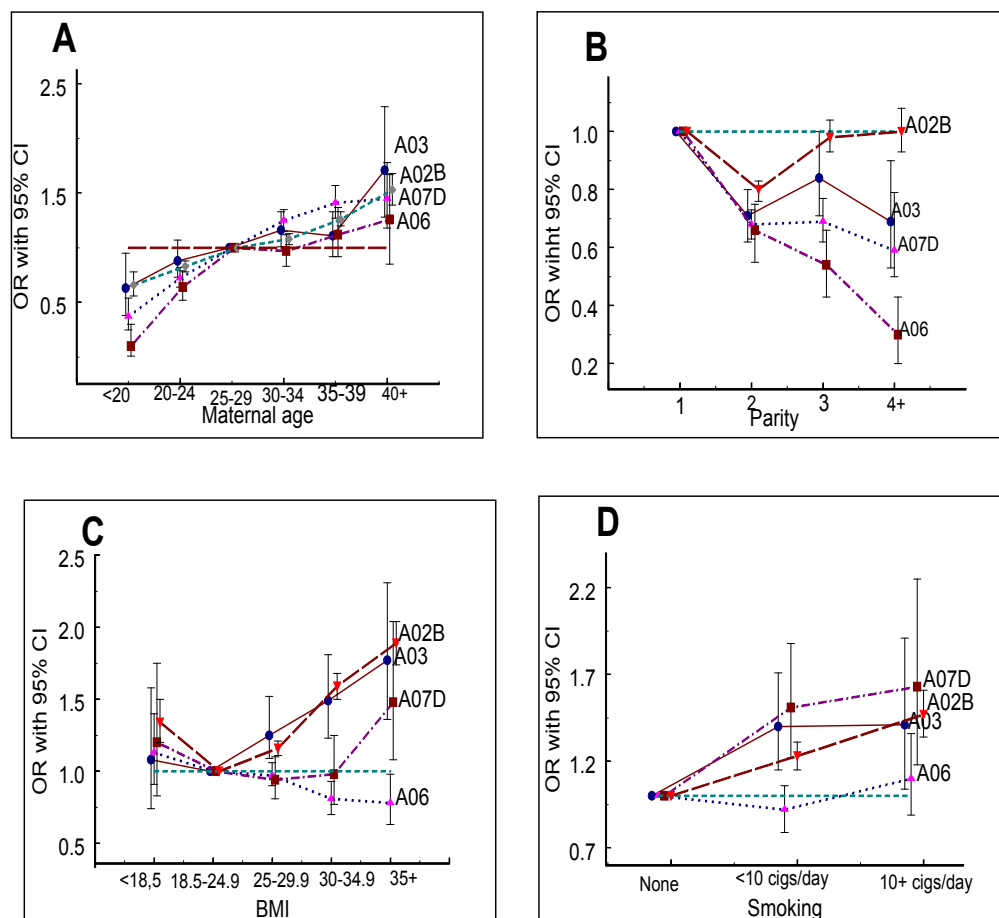


Figure 1: Maternal characteristics: age (A), parity (B), BMI (c) and smoking (D). Odds ratios (OR) are adjusted for year of birth and the other maternal characteristics. Vertical lines mark 95% confidence intervals (95% CI). A03 = drugs for functional gastrointestinal diseases, A07D = antipropulsives, A06 = laxatives, A02B = drugs for GERD.

Drug	ATC code	Women	Infants
<i>Anticholinergics with tertiary amino group</i>	A03AB		
Propantheline	A03AB05	4	5
Mepenzolate	A03AB12	126	128
Prifinium	A03AB18	1	1
<i>Spasmolytics of papaverine type</i>	A03AD		
Papaverine	A03AD01	570	579
Drotaverine	A03AD02	1	1
<i>Silicones</i>	A03AX		
Dimethicone	A03AX13	354	358
<i>Atropine-like spasmolytics</i>	A03BA		
Atropine	A03BA01	3	3
Hyoscyamine	A03BA03	101	101
<i>Butylscopolamine</i>	A03BB		
Butylscopolamine	A03BB01	47	48
<i>Spasmolytic + psycholeptic</i>	A03CA		
Clinidium + chlordiazepoxide	A03CA02	20	21
Oxyphencylimine +hydroxesine	A03CA03	2	2
<i>Motility stimulating drugs</i>	A03FA		
Cisapride	A03FA02	104	105
Domperidone	A03FA03	6	6

Table 3: List of drugs for functional gastrointestinal symptoms and reported in early pregnancy. Metoclopramide is not included as its major use is for nausea and vomiting in pregnancy.

Malformation	No. with drug	Total number	OR/RR	95% CI
<i>Drugs for functional gastrointestinal disease</i>				
Any	79	70317	1.36	1.08-1.70
Relatively severe	57	48478	1.42	1.09-1.85
Cardiovascular	23	16145	1.67	1.11-2.52
Septum defect	12	11157	1.22	0.63-2.13#
Orofacial cleft	2	2755	-	-
Hypospadias	6	4552	1.55	0.57-3.38#
<i>Antipropulsives</i>				
Any	65	70317	1.31	1.02-1.68
Relatively severe	52	48478	1.54	1.17-2.03
Cardiovascular	17	16145	1.46	0.91-2.34
Septum defect	12	11157	1.53	0.81-2.34
Orofacial cleft	3	2755	1.53	0.32-4.47#
Hypospadias	7	4552	2.24	0.90-4.62#

Table 4: Congenital malformations in infants whose mothers reported the use of drugs for functional gastrointestinal symptoms or antipropulsives in early pregnancy. Odds ratios (OR) with 95% confidence intervals (95% CI). Bold text marks statistical significance. #RR calculated as observed over expected number with exact 95% CI.

loperamide with dimethicone and five had used both loperamide and loperamide oxide.

Table 4 summarizes the presence of congenital malformations exposed in early pregnancy to antipropulsives. It can be seen that there is an increased risk for relatively severe malformations and the risk estimates (although not statistically significant) are elevated and similar for the tabulated malformation types. A sub analysis was made after exclusion of women who also used one or more of the following drugs: drugs for functional gastrointestinal disease, immunosuppressants, NSAIDs and opioids. The OR for a relatively severe malformation declined only little and remained statistically significant: OR=1.48 (95% CI 1.10-2.01).

Laxatives (ATC code A06)

Use of laxatives in early pregnancy was reported by 3579 women

with 3635 infants. Among them 326 (329 infants) reported the use of bowel irritating drugs, 1740 (1784 infants) of bulk laxatives, 1547 (1572 infants) of osmotically active drugs, 74 (76 infants) of clysmata, and 10 (10 infants) of carbon dioxide releasing drugs.

Table 5 shows the presence of some malformation groups. Only one of the ten estimates showed a statistically significant effect, pyloric stenosis based on seven exposed cases. After removal of women who had used drugs for functional gastrointestinal disease, antipropulsives, systemic corticosteroids, thyroid drugs, neuroleptics, or antiasthmatics six exposed cases remained but statistical significance was lost: OR=2.62 (95% CI 0.96-5.70).

Drugs for GERD (ATC code A02B)

There were 13103 women with 13332 infants exposed to drugs for GERD. Table 7 shows the specific drugs used.

The presence of congenital malformations in infants whose mothers used drugs for GERD in early pregnancy is shown in Tables 7 and 8. Only one of the 17 OR estimates in Table 7 reached statistical significance: cardiovascular defects. A sub-analysis was made where women who had used any of the following drugs were excluded: antipropulsives, antihypertensives, systemic corticosteroids, thyroid drugs, immunosuppressive drugs, NSAIDs, anticonvulsants,

Malformation	Number with laxatives	Total number	OR/RR	95%CI
Any	179	70317	1.12	0.96-1.30
Relatively severe	122	48478	1.13	0.94-1.35
Neural tube defects	3	734	2.05	0.42-6.01#
Cardiovascular	38	16145	1.03	0.75-1.43
Septum defect	28	11157	1.09	0.75-1.58
Orofacial cleft	11	2755	1.79	0.89-3.20#
Pyloric stenosis	7	1101	2.62	1.05-5.40#
Hypospadias	13	4552	1.24	0.72-2.14#
Pes equinovarus	9	2127	1.86	0.85-3.52#
Poly/syndactyly	5	3084	0.70	0.23-1.64#

Table 5: Congenital malformations in infants whose mothers reported the use of laxatives in early pregnancy. Odds ratios (OR) with 95% confidence intervals (95% CI). Bold text marks statistical significance. # RR calculated as observed over expected number with exact 95% CI.

Drug	No. of women	No. of infants
<i>H2-receptor antagonists</i>		
Cimetidine	101	101
Ranitidine	1905	1923
Famotidine	497	507
Nizatidine	7	7
Famotidine+antacids	33	34
<i>Prostaglandins</i>		
Misoprostol	35	37
<i>Proton pump inhibitors</i>		
Omeprazole	7440	7529
Pantoprazole	218	223
Lansoprazole	947	960
Rabeprazole	15	15
Esomeprasole	574	577
Esomeprazole + antibiotics	3	3
<i>Other drugs for GERD</i>		
Sucralfate	1400	1425
Alginic acid	744	757
Bismuth subcitrate	1	1

Table 6: Specified drugs for GERD, used in early pregnancy.

Malformation	No. with drug	Total No.	OR/RR	95% CI
Any	610	70317	1.02	0.94-1.21
Relatively severe	424	48478	1.03	0.93-1.13
Neural tube defects	6	734	1.04	0.38-2.26#
Severe eye malformations	7	1131	0.76	0.31-1.57#
Severe ear malformations	1		-	-
Orofacial clefts	14	2755	0.59	0.36-0.99
Cardiovascular defects	166	16145	1.21	1.03-1.41
Septum defects	109	11157	1.15	0.95-1.34
Esophageal atresia	7	445	1.85	0.74-3.82#
Small gut atresia	7	392	2.10	0.85-4.33#
Anal atresia	6	590	1.16	0.42-2.52#
Pyloric stenosis	8	1101	0.82	0.35-1.61#
Abdominal wall defects	1	413	-	-
Diaphragmatic hernia	2	368	-	-
Hypospadias	38	4552	0.94	0.68-1.30
Severe renal malformation	4	882	0.81	0.49-1.34#
Pes equinovarus	15	2127	0.81	0.49-1.34
Poly/syndactyly	22	3084	0.84	0.55-1.28
Limb reduction defect	9	838	1.32	0.60-2.51#
Craniosynostosis	9	862	1.21	0.56-2.31#

Table 7: congenital malformations among infants whose mothers reported the use of drugs for GERD in early pregnancy. Odds ratios (OR) with 95% confidence intervals (95% CI). Bold text marks statistical significance. # RR calculated as observed over expected number with exact 95% CI.

neuroleptics, and antiasthmatics. The OR for relatively severe malformations remained low: OR=1.04, 95% CI 0.93-1.16). The OR for cardiovascular defects declined slightly and only a marginal statistical significance remained: OR=1.19 (95% CI 1.00-1.41).

Among the different drugs for GERD (Table 8) only one showed a statistically significant risk increase, sucralfate. Roughly equally high ORs were seen for cardiovascular defects (23 cases, 1.57, 95% CI 1.04-2.36), orofacial clefts (4 cases, RR=1.63, 95% CI 0.44-4.16) and hypospadias (6 cases, RR=1.56, 95% CI 0.57-3.39) but statistical significance was lacking for the latter two conditions.

If concomitant drug use was excluded (see above) the OR for relatively severe malformations after sucralfate remained significant: OR=1.51 (95% CI 1.16-1.96).

Discussion

The previous literature found little effect on malformation risk of the use of laxatives or drugs for GERD [1]. Only little information is available on drugs for functional gastrointestinal diseases. The Perinatal Project [19] found a teratogenic effect of belladonna, based on 554 exposures. A previous study from Sweden, partly based on the same material as the present one, found a weak teratogenic effect of loperamide [6].

There are advantages and disadvantages with the study presented here. Among advantages are the large study material (more than 1.5 million births) and the prospective exposure ascertainment in early pregnancy, before any knowledge of the presence of congenital malformations exists. The study also made it possible to take some putative confounders into consideration, including the concomitant use of other drugs. Among the disadvantages can be mentioned that no information existed on the clinical diagnosis which motivated the use of the drugs. Another problem is the presence of induced abortions undertaken because of prenatally diagnosed congenital malformations. Such cases are reported to the Register of Birth Defects but Swedish law prevents the registration with identification why exposure

information cannot be identified. If a drug causes a malformation which is nearly always detected and aborted (like anencephaly) it would not be possible to detect the association. If the malformation is only sometimes detected (like spina bifida) it is still possible to detect an association but the power of the study declines. It is likely that drug use is underreported - this will influence estimates on exposure rates but will hardly affect risk estimates. It will mean that some exposed cases are regarded as unexposed but they will represent a very small proportion of all unexposed individuals and will hardly affect the odds for a malformation among unexposed individuals.

The central drug group under study was drugs used for functional gastrointestinal diagnoses and to some extent also the antipropulsives. Both these drug groups can have been used for other conditions. One important such was inflammatory bowel disease (IBD) but it was tried to remove such cases which were defined by the use of drugs for inflammatory intestinal diseases (A07E). This may not be completely successful and a few remaining IBD cases may have been included. The teratogenic effect of IBD or drugs used for IBD is debated [20,21].

Except for these two drug groups, data on laxatives and on drugs used for GERD were included. Both drug groups have extensive use for other conditions than what are included in the concept of functional gastrointestinal disease and it is also apparent that the characteristics of women using these two drug groups deviated from those of the other two groups, for laxatives with respect to the relation with maternal smoking and BMI, for drugs for GERD to the effect of parity.

The study found some statistical associations between maternal use of some of these drugs and the presence of congenital malformations in the offspring. Such associations can be due to various forms of confounding or to an actual drug effect. Some observed associations may be the result of multiple testing.

Women who have used these drugs have characteristics which deviate from those of the comparison group, maternal age, parity, smoking, BMI. All these factors may more or less strongly affect malformation rate and can therefore confound the analysis. Adjustment for these factors and for year of delivery was therefore made.

Drug	No. malformed	Total number	OR/RR	95% CI
<i>H2-receptor antagonists</i>	86	2537	1.01	0.82-1.26
Cimetidine	5	101	1.48	0.48-3.45#
Ranitidine	63	1923	0.98	0.76-1.26
Famotidine	19	507	1.10	0.69-1.73
Nizatidine	1	7	-	-
Famotidine+antacids	1	34	-	-
<i>Prostaglandins</i>	0	37	-	-
Misoprostol	0	37	-	-
<i>Proton pump inhibitors</i>	270	9088	0.98	0.86-1.10
Omeprazole	225	7529	0.99	0.86-1.13
Pantoprazole	4	223	0.59	0.16-1.51#
Lansoprazole	35	960	1.17	0.83-1.64
Rabeprazole	0	15	-	-
Esomeprazole	11	577	0.63	0.35-1.14
Esomeprazole + antibiotics	0	3	-	-
<i>Other drugs for GERD</i>	79	2161	1.20	0.96-1.50
Sucralfate	65	1425	1.42	1.11-1.81
Alginate acid	15	757	0.73	0.44-1.22

Table 8: Relatively severe malformations divided after the specific drug for GERD. Bold text marks statistical significance. # RR calculated as observed over expected number with exact 95% CI.

A second source of confounding is the concomitant use of other drug categories. In order to act as a confounder, such a drug must be used in excess and also have an effect of its own on malformation risk. Some such drugs were identified (slightly differing between the four drug categories) and subanalyses were made after exclusion of women who had reported the use of such drugs. In most cases this resulted in a marginal reduction of the odds ratio which remained statistically significant.

The most difficult source of confounding is a confounding by indication, when the underlying medical condition explains the association between drug use and outcome. Functional gastrointestinal diseases are seldom registered as a delivery diagnosis - for the period 1998-2011, among 1.4 million infants born, only 364 had a maternal diagnosis of a functional gastrointestinal disease (ICD-10 code K 58 or K59), 2.6 per 10 000. This diagnosis was given to only 16 women reporting the use of drugs for functional gastrointestinal disease and five women reporting the use of antipropulsives. It is therefore not realistic to try to directly study the impact of underlying disease. For a confounding by indication speaks the fact that the effect estimates on relatively severe malformations for both groups of drugs were relatively similar and that no clear-cut drug specificity existed. It is, however, unclear how a teratogenic effect can be obtained from a functional gastrointestinal disease. A possible explanation could be a nutritional deficiency.

In the exploration of the effect of laxatives or drugs for GERD, no clear-cut teratogenicity was evident. After laxatives, a seemingly increased risk for pyloric stenosis was seen but it declined (but was still marginally significant) after exclusion of concomitantly used drugs with a possible teratogenicity of their own. It should be remembered that many statistical tests have been made and some "significances" may arise by chance due to the multiple testing situation.

Another observed association was between maternal use of sucralfate and infant congenital malformations. This association remained after exclusion of possibly teratogenic concomitantly used drugs. This was the only one among drugs for GERD which showed a teratogenic effect. The drug acts locally and absorption is limited. It is an aluminum salt and a fetal toxicity could be related to aluminum resorption [22]. Only little information exists in the literature on the use of this drug during pregnancy and no relevant data on this specific drug [5].

A similar situation exists with dimethicone, a drug used for flatulence and acts by reducing surface tension in the gut. A significantly increased risk for any malformations was seen and a marginally increased risk for cardiovascular defects. There was also a suggested aggregation of cases with atresia or stenosis of the gastrointestinal tract.

Both these findings may also be a result of multiple testing but independent data are needed to verify or reject the association.

Conclusion

In conclusion, there are some indications that functional gastrointestinal disease or drugs used for these conditions may slightly increase the risk for a congenital malformation in the offspring. The finding offers a dilemma. If the effect is from underlying disease, adequate therapy may decrease the risk, if it is a drug effect, the opposite is true. This risk increase is of little significance for the individual but may, on a population level, be important as it is a common condition.

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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