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ORIGINAL ARTICLE

Placental transporter-mediated drug interactions and offspring congenital anomalies

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Aims: P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are efflux transporters expressed in the placenta, limiting their substrates from reaching the foetus. Our aim was to investigate if concomitant prenatal exposure to several substrates or inhibitors of these transporters increases the risk of congenital anomalies.

Methods: The national *Drugs and Pregnancy* database, years 1996–2014, was utilized in this population-based birth cohort study. In the database, the Medical Birth Register, the Register on Induced Abortions, the Malformation register and the Register on Reimbursed Drug Purchases have been linked. The University of Washington Metabolism and Transport Drug Interaction Database was used to identify substrates and inhibitors of P-gp and BCRP. We included singleton pregnancies ending in birth or elective termination of pregnancy due to foetal anomaly. Known teratogens were excluded. We identified women exposed 1 month before pregnancy or during the first trimester to P-gp/BCRP polytherapy (n = 21 186); P-gp/breast cancer resistance protein monotherapy (n = 97 906); non-P-gp/BCRP polytherapy (n = 78 636); and unexposed (n = 728 870). We investigated the association between the exposure groups and major congenital anomalies using logistic regression adjusting for several confounders.

Results: The prevalence of congenital anomalies was higher in the P-gp/BCRP polytherapy group (5.5%) compared to the P-gp/BCRP monotherapy (4.7%, OR 1.13; 95% CI 1.05–1.21), the non-P-gp/BCRP polytherapy (4.9%, OR 1.14; 95% CI 1.06–1.22), and to the unexposed groups (4.2%, OR 1.23; 95% CI 1.15–1.31).

Conclusion: The results suggest a role of placental transporter-mediated drug interactions in teratogenesis.

KEYWORDS

birth defects, drug transporters, P-glycoprotein, placenta, pregnancy

1 | INTRODUCTION

Drug use during pregnancy is common. In Finland, more than half of pregnant women use prescription drugs during the entire course of pregnancy, and 1 out of 4 use 2 or more prescription drugs.[1] A web-based survey in several European countries reported use of prescription or over-the-counter drugs in nearly 80% of pregnancies.[2] A recent study from the USA reported that nearly 8%

of pregnant women used more than 4 drugs during the first trimester.[3]

Drug transporters play an important role in the absorption, disposition and toxicity of drugs. P-glycoprotein (P-gp, encoded by *ABCB1* gene) and breast cancer resistance protein (BCRP, encoded by *ABCG2* gene) belong to the ATP-binding cassette transporters.[4] They are expressed in several human tissues and considered the 2 most important drug transporters in the human placenta.[5] The level of P-gp expression in the placenta is similar to that in the liver and small intestine,[6] and the expression of BCRP in the human placenta is higher than in any other human tissue.[7] These efflux transporters are already expressed on the maternal blood-facing surface of the syncytiotrophoblast of the placenta in the first trimester. Both P-gp and BCRP transport their substrates out of the syncytiotrophoblast back into the maternal circulation and prevent the substrate from reaching the foetus. Both transporters are also involved in the regulation of several endogenous compounds entering the foetal circulation.[7] Their presence in the placenta suggests an important barrier in preventing drugs from entering the foetal circulation and protecting the foetus from exogenous chemicals. P-gp substrates include several commonly used pharmaceuticals such as cetirizine, calcium channel inhibitors, macrolides, opioids, selective serotonin reuptake inhibitors and second-generation antipsychotic drugs.[5] BCRP has many overlapping substrates with P-gp, but the individual substrates have different affinities to these transporters. Both P-gp and BCRP are inhibited by numerous drugs, and in addition, their substrates may competitively inhibit transport function. This could affect the function of the placental barrier and alter the degree of foetal exposure to the specific substrate.[8] Indeed, placental perfusion studies have shown that pharmacological blockade of P-gp function can increase the transfer of P-gp substrates to the foetal side by several-fold.[9,10] Particularly in the case where a transporter substrate is a teratogen, its teratogenic potential may increase if it is used together with another substrate or an inhibitor of the same transporter.[9] As teratogenesis is a dose-dependent phenomenon, higher exposure to a harmful agent would be expected to result in an increased risk of foetal adverse effects including congenital anomalies. The potential role of drug interactions involving transporters in teratogenesis is not known and research in this field is only starting to emerge.[10]

2 | OBJECTIVES

The objective of the study was to investigate if concomitant use of 2 or more P-gp or BCRP drug transporter substrates or inhibitors during 1 month before pregnancy or first trimester is associated with an increased risk of major congenital anomalies in offspring, compared to use of only 1 drug classified as P-gp or BCRP drug transporter substrate or inhibitor, to use of 2 or more drugs not classified as P-gp or BCRP drug transporter substrates or inhibitors, and to no use of drugs.

What is already known about this subject

- P-glycoprotein and breast cancer resistance protein are efflux transporters expressed in the placenta.
- Polypharmacy may lead to inhibition of the transporters and increased foetal exposure to their substrates.
- The potential role of drug interactions involving transporters in teratogenesis is not known.

What this study adds

- The results suggest a role of placental drug transporter interactions in teratogenesis.
- This study should direct future research to assess the role of drug transporter -mediated drug interactions in teratogenesis.

3 | MATERIAL AND METHODS

This is a population-based cohort study using national register data extracted from the existing database of the *Drugs and Pregnancy* project in Finland, established by the National Institute for Health and Welfare (presently the Finnish Institute for Health and Welfare, THL), the Social Insurance Institution in Finland (Kela) and the Finnish Medicines Agency (Fimea).[1] The objective of the *Drugs and Pregnancy* project is continuous surveillance of drug safety during pregnancy. In the project, the Medical Birth Register, the Abortion Register, the Register of Congenital Malformations, and the Drug Prescription Register, including also the Special Reimbursement Register, have been linked by the personal identification number (PIN) assigned to all citizens and permanent residents upon immigration in Finland. The *Drugs and Pregnancy* database contains data from births, terminations of pregnancy, and prescription drug purchases since 1 January 1996. In the project, the beginning of pregnancy is calculated from the best clinical estimation of gestational age at birth. This estimation is primarily based on ultrasound but if this is not available, the estimation is based on the day of last menstrual period, both registered in the Medical Birth Register. If this information is not available, the beginning of pregnancy is calculated by subtracting 280 days from the date of birth. Pregnancy trimesters have been divided into first (until 84 days' gestation), second (days 85–182) and third (day 183 until birth).

The study material presented here is based on 1 080 655 singleton pregnancies identified from the *Drugs and Pregnancy* database between 1 January 1996 and 31 December 2014. Of these pregnancies, 1 075 349 ended in birth and 5306 ended in elective termination of pregnancy due to foetal anomaly. For the pregnancies in our cohort, we identified all reimbursed drug purchases from 1 month prior to pregnancy until the end of the first trimester of pregnancy. The International Anatomic Therapeutic Chemical classification codes of these purchases were compared to those identified in the University of Washington (UW) Metabolism and Transport Drug Interaction

Database (DIDB) to define exposure groups (see below). Pregnancies exposed to known teratogens were excluded from study material (Table S1; Figure 1). The utilization of sensitive health register data for scientific research and the data linkages in the *Drugs and Pregnancy* project have been approved by the register administrators and the national data protection authority. The study protocol was approved by the Institutional Review Board at THL. Since the study subjects are not contacted, according to the Finnish legislation informed consent is not required for large register studies. The study was registered in The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register before data collection started (Study reference number ENCePP/SDPP/13051). The study was granted the ENCePP seal on 27 April 2016, following the ENCePP principles of standards, transparency and independence of good pharmacoepidemiology practice throughout the research process (www.encepp.eu).

4 | DESCRIPTION OF THE REGISTERS INCLUDED IN THE STUDY

The *Medical Birth Register (MBR)*, maintained by the THL since 1987, is a nationwide register collecting data on maternal demographic characteristics, medical history including reproductive history, smoking, diagnoses during pregnancy and delivery, and neonatal outcome data up to 6 days' age. Data in the MBR include all live and stillbirths with gestational age of 22 weeks or more or birth weight of 500 g or more. The register data are confirmed and complemented from the maternity hospital records in cases of conflicting or missing information. The definitions and variables included in this registry are based on established international concepts and use the 10th version of the WHO International Classification of Diseases (ICD) since 1996. The PIN is required for a patient to access subsidized health care, which means that there are virtually no births in Finland that take place without being registered in the MBR.[1,11,12]

The *Register on Congenital Malformations* (maintained by the THL since 1963) includes information on live and stillbirths and foetuses from pregnancy terminations due to severe foetal anomaly. Minor anomalies are excluded principally according to the exclusion list of the European Surveillance of Congenital Anomalies, EUROCAT (www.eurocat-network.eu). In case of a severe foetal congenital anomaly or disease, permission for termination of pregnancy may be granted upon mother's request by a national board at the National Supervisory Authority for Welfare and Health until 24 completed gestational weeks. The validity of the register is considered good (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/quality-descriptions/congenital-anomalies).

The *Drug Prescription Register* (maintained by Kela since 1995) contains data on 99% of reimbursed prescription drug purchases (Finnish Statistics on Medicines, 2010). Prescription-only medicines

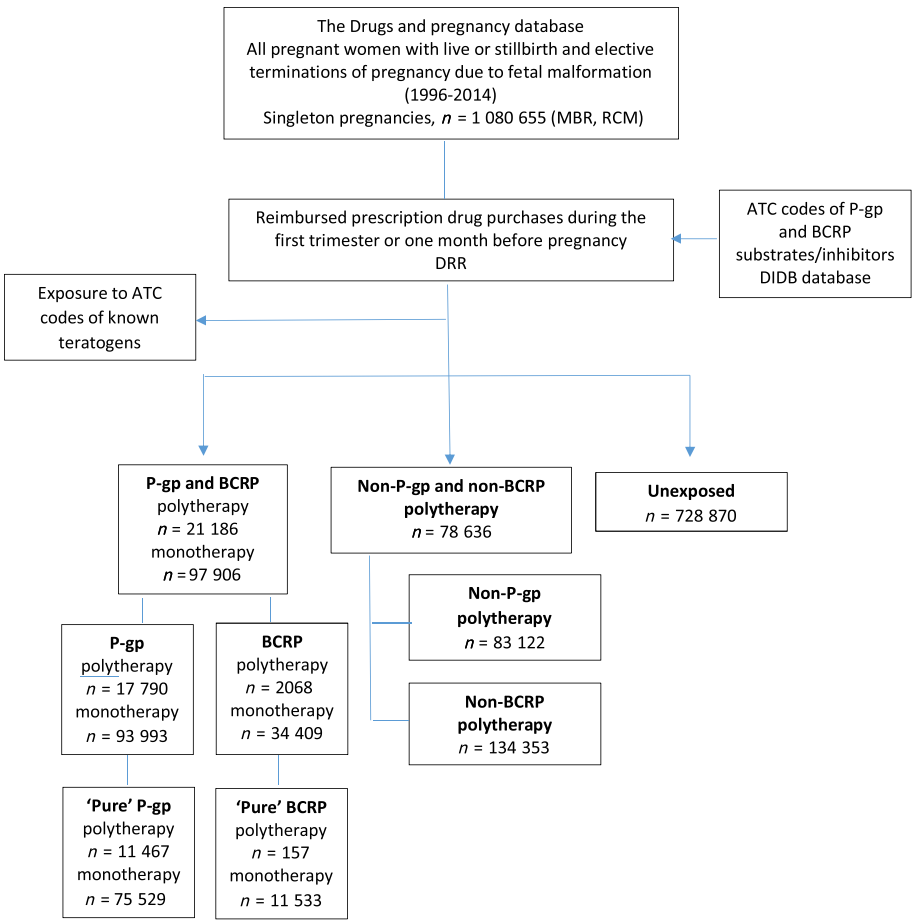

FIGURE 1 Flow chart of the register-based sources of information used in the study. P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; MBR, Medical Birth Register; RCM, Register of Congenital Malformations; DRR, Drug Reimbursement Register; DIDB, Drug Interaction Database, Washington University; ATC, Anatomic Therapeutic Chemical code

deemed necessary for the treatment of an illness are reimbursed under the Social Insurance System, which covers all permanent residents in Finland. Drug purchases are reimbursed concomitantly upon purchase at pharmacies and drugs are supplied to the patient for a maximum of 3 months at a time. Data in the register include the date of the purchase and the Anatomic Therapeutic Chemical code indicating the generic name of the drug. Over-the-counter drugs or medications given to institutionalized persons are not included in the register. Kela also maintains the Special Reimbursement Register since 1964 with data on patients who are entitled for higher reimbursement for chronic illnesses requiring continuous drug treatment. We excluded pregnancies exposed to proven and suspected teratogens from the study material (Figure 1, Table S1).

The *UW Metabolism and Transport DIDB* (Copyright University of Washington 1999–2019. UW Metabolism and Transport DIDB, accessed: 10 December 2015) is a manually curated knowledge base containing both *in vitro* and *in vivo* drug–drug interaction data developed by UW's Department of Pharmaceutics, School of Pharmacy. The substrates and inhibitors of P-gp and BCRP were identified based on *in vitro* data with queries: "transporter queries/in vitro/transporter with objects/P-gp", "transporter queries/in vitro/transporter with precipitants /P-gp", "transporter queries/in vitro/transporter with objects/BCRP", "transporter queries/in vitro/transporter with precipitants/BCRP". All drugs demonstrating transporter affinity in vitro were classified as substrates, and all drugs showing inhibitory activity in vitro were classified as inhibitors.

5 | DEFINITION OF EXPOSED AND UNEXPOSED GROUPS

- *P-gp/BCRP polytherapy group.* Women with purchases of 2 or more drugs that are substrates or inhibitors of either P-gp or BCRP (*n* = 21 186; Figure 1).
- *P-gp/BCRP monotherapy group.* Women with purchase(s) of 1 drug that is either a substrate or an inhibitor of either P-gp or BCRP (*n* = 97 906).
- *Non-P-gp/BCRP polytherapy group.* Women with purchases of 2 or more drugs that are not substrates or inhibitors of P-gp or BCRP (*n* = 78 636).
- *Unexposed.* Pregnant women with no purchases of drugs (*n* = 728 870).

Exposure classified by drug transporter, but allowing overlap between transporter-specific substrates and inhibitors

- *P-gp polytherapy group.* Women with purchases of 2 or more drugs that are substrates or inhibitors of P-gp (*n* = 17 790).
- *P-gp monotherapy group.* Women with purchase(s) of 1 drug that is either a substrate or an inhibitor of either P-gp (*n* = 93 993).
- *Non-P-gp polytherapy group.* Women with purchases of 2 or more drugs that are not substrates or inhibitors of P-gp (*n* = 83 122).
- *BCRP polytherapy group.* Women with purchases of 2 or more drugs that are substrates or inhibitors of BCRP (*n* = 2068).
- *BCRP monotherapy group.* Women with purchase(s) of 1 drug that is either a substrate or an inhibitor of BCRP (*n* = 34 409).
- *Non-BCRP polytherapy group.* Women with purchases of 2 or more drugs that are not substrates or inhibitors of BCRP (*n* = 134 353).

Exposure classified by drug transporter, but allowing no overlap between transporter-specific substrates and inhibitors

- *Pure P-gp polytherapy group.* Women with purchases of 2 or more drugs that are substrates or inhibitors of P-gp (*n* = 11 467).
- *Pure P-gp monotherapy group.* Women with purchase(s) of 1 drug that is either a substrate or an inhibitor of P-gp (*n* = 75 529).
- *Pure BCRP polytherapy group.* Women with purchases of 2 or more drugs that are substrates or inhibitors of BCRP (*n* = 157).
- *Pure BCRP monotherapy group.* Women with purchase(s) of 1 drug that is either a substrate or an inhibitor of BCRP (*n* = 11 533).

6 | MATERNAL CHARACTERISTICS AND COVARIATES

Data on covariates were derived from the registers described above. Covariates included maternal demographic, social and medical characteristics and use of other drugs as categorized in Table 1. Data on body mass index (BMI) were available only beginning from 2006. Alcohol use is not routinely collected in the MBR and could therefore not be included in analyses.

7 | OUTCOME

A major congenital anomaly registered in the Congenital Malformation Register, using the International Classification of Diseases (ICD-9 Atlanta modification) coding system.

8 | STATISTICAL ANALYSES

All data in the *Drugs and Pregnancy* database have been pseudonymized. The prevalence of congenital anomalies was calculated in the different exposure groups. We assessed the association between the level of exposure (*P-gp/BCRP polytherapy*, *P-gp/BCRP monotherapy*, *non-P-gp/BCRP polytherapy*) and major congenital anomalies using logistic regression. First, association between level of exposure and maternal characteristics and other clinically relevant or plausible covariates was tested with χ^2 (Table 1). Multivariate models were then built based on all significant univariate covariates and subsequent removal of non-significant covariates from the model ($P < 0.05$) using stepwise regression (backward elimination). Model

TABLE 1 Maternal characteristics by exposure status to P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates or inhibitors

	P-gp/BCRP polytherapy[a]		P-gp/BCRP monotherapy[b]		Non-P-gp/BCRP polytherapy [c]		Unexposed		Association with level of exposure χ^2
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***P*-value**
Total	21 186	100.0	97 906	100.0	78 636	100.0	728 870	100.0	
Birth year									
1996–1999 (ref)	3315	15.7	18 007	18.4	14 975	19.0	162 171	22.3	<.0001
2000–2002	3049	14.4	14 429	14.7	9463	12.0	115 427	15.8	
2003–2005	3508	16.6	15 057	15.4	8498	10.8	119 455	16.4	
2006–2008	2813	13.3	14 757	15.1	12 558	16.0	116 696	16.0	
2009–2011	3956	18.7	17 545	17.9	16 362	20.8	110 714	15.2	
2012–2014	4545	21.5	18 111	18.5	16 780	21.3	104 407	14.3	
Maternal age (y)									
<25	2590	12.2	14 216	14.5	12 786	16.3	143 672	19.7	<.0001
25–29 (ref)	5654	26.7	28 528	29.1	23 575	30.0	236 727	32.5	
>30	12 942	61.1	55 162	56.3	42 275	53.8	348 471	47.8	
University hospital district									
Helsinki	8203	38.7	36 289	37.1	28 158	35.8	254 020	34.9	<.0001
Turku	3446	16.3	15 852	16.2	12 024	15.3	115 237	15.8	
Tampere	4051	19.1	18 418	18.8	15 200	19.3	138 296	19.0	
Kuopio	2922	13.8	13 877	14.2	11 578	14.7	105 234	14.4	
Oulu (ref)	2561	12.1	13 444	13.7	11 658	14.8	114 752	15.7	
No data	3	<0.1	26	<0.1	18	<0.1	1331	0.2	
Previous deliveries									
0	10 383	49.0	44 840	45.8	35 079	44.6	292 378	40.1	<.0001
≥1 (ref)	10 762	50.8	52 921	54.1	43 443	55.3	435 230	59.7	
No data	41	0.2	145	0.2	114	0.1	1262	0.2	
Body mass index									
<18.5	373	1.8	1717	1.8	1635	2.1	15 511	2.1	<.0001
18.5–24.9 (ref)	6754	31.9	32 921	33.6	29 004	36.9	249 362	34.2	
≥25.0	5700	26.9	22 349	22.8	18 405	23.4	122 751	16.8	
No data	8359	39.5	40 919	41.8	29 592	37.6	341 246	46.8	
Cohabitation									
Married or cohabiting (ref)	18 041	86.9	86 051	87.9	69 065	87.8	64 4112	88.4	<.0001
Not cohabiting	1400	6.6	5771	5.9	4 384	5.6	37 973	5.2	
No data	1385	6.5	6084	6.2	5 187	6.6	46 785	6.4	
Smoking									
No (ref)	17 049	80.5	79 899	81.6	63 194	80.4	601 425	82.5	<.0001
Yes	3513	16.6	15 322	15.7	13 210	16.8	104 665	14.4	
No data	624	3.0	2685	2.7	2232	2.8	22 780	3.1	
Socioeconomic status									
Upper white collar (ref)	3877	18.3	17 285	17.7	13 126	16.7	120 375	16.5	<.0001
Lower white collar	7635	36.0	35 405	36.2	27 654	35.2	248 992	34.2	
Blue collar	2536	12.0	12 766	13.0	10 578	13.5	101 165	13.9	
Student	1671	7.9	7703	7.9	6443	8.2	68 977	9.5	
Entrepreneur	377	1.8	1842	1.9	1504	1.9	12 611	1.7	
Other or no data	5090	24.0	22 905	23.4	19 331	24.6	176 750	24.3	

(Continues)

TABLE 1 (Continued)

Characteristic	P-gp/BCRP polytherapy[a]		P-gp/BCRP monotherapy[b]		Non-P-gp/BCRP polytherapy [c]		Unexposed		Association with level of exposure χ^2
	n	%	*n*	%	*n*	%	*n*	%	*P*-value
Entitlement to special reimbursement									
Diabetes	302	1.4	934	1.0	3420	4.4	404	<0.1	<.0001
Severe mental disorders	615	2.9	1042	1.1	353	0.5	1158	0.2	<.0001
Connective tissue diseases	941	4.4	2028	2.1	687	0.9	2494	0.3	<.0001
Asthma	3596	17.0	8467	8.7	4311	5.5	8932	1.2	<.0001
Hypertension	434	2.1	1101	1.1	348	0.4	760	0.1	<.0001
Inflammatory bowel disease	393	1.9	1165	1.2	1366	1.7	1403	0.2	<.0001
Other									
Gestational diabetes	1995	9.4	6885	7.0	5665	7.2	33 409	4.6	<.0001
Gestational hypertension	570	2.7	2145	2.2	1749	2.2	10 656	1.5	<.0001

[a]Two or more P-gp and/or BCRP substrates or inhibitors.
[b]One P-gp or BCRP substrate or inhibitor.
[c]Two or more drugs other than P-gp and/or BCRP substrates or inhibitors.
Connective tissue diseases; including rheumatoid arthritis and comparable conditions

selection was based on maximum likelihood. A total of 40% of data on BMI data were missing (see above) and missing values were treated as a separate category by itself in the adjusted models.

We performed sensitivity analyses by drug transporter but allowing overlap between transporter-specific substrates and inhibitors (*P-gp polytherapy group*, *P-gp monotherapy group*, *BCRP polytherapy group*, *BCRP monotherapy group*) and, further, allowing no overlap (*pure P-gp polytherapy group*, *pure P-gp monotherapy group*, *pure BCRP polytherapy group*, *pure BCRP monotherapy group*). The monotherapy group was chosen as a *neutral* control group with no expectation of drug transporter interactions in all models.

All analyses were performed in SAS/STAT (SAS 12.1, NC, USA).

9 | RESULTS

The characteristics of the women in the 4 exposure groups are presented in Table 1 and pregnancy outcome (live birth, still birth, elective termination of pregnancy due to foetal anomaly) in each group is presented in Table S2. Women in the P-gp/BCRP polytherapy group were more than twice as likely as women in the P-gp/BCRP monotherapy group, 4 times as likely as women in the non-P-gp/BCRP polytherapy group, and >10 times as likely as women in the unexposed group to have a diagnosis of connective tissue disease. Similarly, severe mental disorders and asthma were several-fold more common in the P-gp/BCRP polytherapy group than in the other exposure groups (Table 1). The 30 most commonly used drugs in the P-gp/BCRP polytherapy group are presented in Table 2, and in more detail in the P-gp/BCRP polytherapy and monotherapy groups in Tables S3 and S4, respectively. The prevalence of major congenital anomalies was 5.5% in the P-gp/BCRP polytherapy group, 4.7% in the P-gp/BCRP monotherapy group, 4.9% in the non-P-gp/BCRP polytherapy group, and 4.2% in the unexposed group (Table 3). In crude and adjusted models, the risk was statistically significantly increased in the P-gp/BCRP polytherapy group compared to all other groups (Table 3).

Exposed to P-gp substrates or inhibitors. The prevalence of major congenital anomalies was 5.4% in the P-gp polytherapy group, 4.6% in the P-gp monotherapy group, and 5.0% in the non-P-gp polytherapy group (Table 4). The risk estimates of major congenital anomalies associated with P-gp exposure were very similar to those of P-gp/BCRP exposure (Table 4).

Exposed to BCRP substrates or inhibitors. The prevalence of major congenital anomalies was 6.2% in the BCRP polytherapy group, 5.1% in the BCRP monotherapy group, and 4.9% in the non-BCRP polytherapy group (Table 5). In crude models, the risk of major anomalies was increased in the BCRP polytherapy group compared to all other exposure groups, but the risk estimates were attenuated after adjustment (Table 5). The risk remained marginally increased when compared to the non-BCRP polytherapy group and remained statistically significant when comparing BCRP polytherapy to unexposed (Table 5).

The characteristics of women grouped according to P-gp substrate/inhibitor and BCRP substrate/inhibitor exposure status allowing no overlap between transporter-specific substrates and inhibitors (*pure* P-gp and *pure* BCRP groups) are presented in Tables S5 and S6, respectively. In the sensitivity analyses defining exposure by transporter-specificity without overlap, the risk of major congenital anomalies was statistically significantly increased in the P-gp polytherapy group when compared to unexposed, while the results did not remain statistically significant in the BCRP polytherapy group when compared to the other exposure groups (Tables S7 and S8).

TABLE 2 Number (*n*) of users of the most commonly used drugs classified as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates (S) or inhibitors (I) in the P-pg/BCRP polytherapy group

Drug	*n*	P-gp transporter substrate/inhibitor	BCRP transporter substrate/inhibitor
Cetirizine	3242	S, I	
Progesterone	2985	I	
Oestradiol (17-β)	2813		I
Fluticasone (nasal)	2765	S	
Azithromycin	2369	S, I	
Fluticasone (inhalation)	1976	S	
Budesonide (inhalation)	1955	S	
Prednisolone	1893	S	
Citalopram	1835	S, I	
Diclofenac	1426		S, I
Omeprazole	1202	S, I	I
Pantoprazole	1137	S, I	S, I
Loratadine	1028	S	
Roxithromycin	1020	S, I	
Desloratadine (descarboethoxyloratadine)	973	S	
Clarithromycin	805	S, I	
Levocetirizine ((R)-cetirizine)	787	S	
Sertraline	757	I	
Propranol	749	I	
Sulfasalazine	741	S	S, I
Montelukast	725	I	
Quetiapine	717	I	
Ranitidine	717	S	
Lansoprazole	715	S, I	I
Metformin	710	S	S
Erythromycin	586	S, I	S
Prednisone	537	S	
Ciprofloxacin	469	S	S
Methylprednisolone	458	S	I
Etoricoxib	449	I	

10 | DISCUSSION

In this large, register-based study we found that concomitant use of multiple substrates or inhibitors of the drug transporters P-gp and BCRP during 1 month before pregnancy or first trimester was associated with an increased risk of major congenital anomalies in the offspring compared to their use in monotherapy, to use of 2 or more drugs other than P-gp or BCRP substrates or inhibitors, and to no drug use.

There are only 2 studies published to date that have tried to assess whether simultaneous use of transporter substrates increases malformation rate in humans. Both are register-based studies (malformation and pharmacy register) from the northern provinces of the Netherlands. In the first study, an increase in certain malformation types was seen when several substances affecting the P-gp system were used simultaneously during the first trimester of pregnancy.[13] In the second study, no effect on malformation rate was observed with concomitant use of substrates of other transporters.[14] However, there are a couple of important limitations. First, registration of malformations into the EUROCAT northern Netherlands register can only be done after obtaining parental consent, and approximately 1/5 of the malformation cases in the provinces are therefore not registered.[15] Second, the grouping of drugs to transporter substrates and inhibitors was made by the authors based on individual research papers. The list of substrates and inhibitors may therefore have been incomplete and interpretation challenging due to the numerous methods used in assessment of drug transporters and conflicting data in the literature.[16-18]

In our study, antihistamines and drugs for asthma, together with macrolide antibiotics, proton pump inhibitors, oral glucocorticoids and selective serotonin reuptake inhibitors (citalopram, sertraline) were among the most commonly used drugs in the P-gp/BCRP polytherapy

TABLE 3 Major congenital anomalies by exposure status to P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates or inhibitors

P-gp/BCRP polytherapy[1]		P-gp/BCRP monotherapy[2]		Non-P-gp/BCRP polytherapy[3]		Unexposed		P-gp/BCRP polytherapy *vs.* P-gp/BCRP monotherapy				P-gp/BCRP polytherapy *vs.* non-P-gp/BCRP polytherapy				P-gp/BCRP polytherapy *vs.* unexposed			
								Crude		Adjusted[4]		Crude		Adjusted[4]		Crude		Adjusted[4]	
n	%	*n*	%	*n*	%	*n*	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
1156	5.5	4574	4.7	3880	4.9	30 371	4.2	1.18	1.10–1.26	1.13	1.05–1.21	1.14	1.06–1.22	1.14	1.06–1.22	1.33	1.25–1.41	1.23	1.15–1.31

[1]Two or more P-gp and/or BCRP substrates or inhibitors.
[2]One P-gp or BCRP substrate or inhibitor.
[3]Two or more drugs other than P-gp and/or BCRP substrates or inhibitors.
[4]Adjusted by: birth year (child), maternal age, parity, cohabitation, smoking during pregnancy, socioeconomic status, body mass index, university hospital district, prepregnancy diabetes, connective tissue diseases, severe mental disorders, gestational diabetes.

TABLE 4 Major congenital anomalies by exposure status to P-glycoprotein (P-gp) substrates or inhibitors

P-gp polytherapy[1]		P-gp monotherapy[2]		Non-P-gp polytherapy[3]		Unexposed		P-gp polytherapy *vs.* P-gp monotherapy				P-gp polytherapy *vs.* non-P-gp polytherapy				P-gp polytherapy *vs.* unexposed			
								Crude		Adjusted[4]		Crude		Adjusted[4]		Crude		Adjusted[4]	
n	%	*n*	%	*n*	%	*n*	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
964	5.4	4342	4.6	4133	5.0	30 371	4.2	1.18	1.10–1.27	1.11	1.03–1.20	1.10	1.02–1.18	1.11	1.03–1.19	1.32	1.23–1.41	1.20	1.12–1.29

[1]Two or more P-gp substrates or inhibitors.
[2]One P-gp substrate or inhibitor.
[3]Two or more drugs other than P-gp substrates or inhibitors.
[4]Adjusted by: birth year (child), maternal age, parity, cohabitation, smoking during pregnancy, socioeconomic status, body mass index, university hospital district, prepregnancy diabetes, connective tissue diseases, severe mental disorders, gestational diabetes.CI, confidence interval.

TABLE 5 Major congenital anomalies by exposure status to breast cancer resistance protein (BCRP) substrates or inhibitors

BCRP polytherapy[1]		BCRP monotherapy[2]		non-BCRP polytherapy[3]		Unexposed		BCRP polytherapy *vs.* BCRP monotherapy				BCRP polytherapy *vs.* non-BCRP polytherapy				BCRP polytherapy *vs.* unexposed			
								Crude			Adjusted[4]	Crude			Adjusted[4]	Crude			Adjusted[4]
n	%	*n*	%	*n*	%	*n*	%	OR	95% CI		OR	95% CI		OR	95% CI	OR	95% CI		OR	95% CI
129	6.2	1763	5.1	6527	4.9	30 371	4.2	1.23	1.02–1.48		1.16	0.96–1.40		1.30	1.09–1.56	1.19	0.99–1.43	1.53	1.28–1.83		1.28	1.06–1.54

[1]Two or more BCRP substrates or inhibitors.
[2]One BCRP substrate or inhibitor.
[3]Two or more drugs other than BCRP substrates or inhibitors.
[4]Adjusted by: birth year (child), maternal age, parity, cohabitation, smoking during pregnancy, socioeconomic status, body mass index, university hospital district, prepregnancy diabetes, connective tissue diseases, severe mental disorders, gestational diabetes.
CI, confidence interval.

group (Table 2). While use of these drugs during pregnancy is generally considered safe,[19-22] we are not aware of studies investigating their teratogenicity when used concomitantly with other drugs not considered as teratogens.

The observed increased risk of congenital anomalies is not necessarily causally associated with drug transporter interactions but may have other possible explanations. First, pregnancy safety data for coxibes, meloxicam and itraconazole—all included in the commonly used drugs in Table 2—are limited or lacking and do not allow reliable risk assessment on their potential for teratogenicity. Further, conflicting results about teratogenicity have been reported for drugs commonly used in the P-gp/BCRP polytherapy group including erythromycin,[23] citalopram and paroxetine.[24,25] A study based on the Swedish Medical Birth Register reported an increased risk of cardiovascular anomalies associated with erythromycin use in early pregnancy.[23] Erythromycin has the potential to inhibit a cardiac potassium current channel and may induce cardiac arrythmias in the embryo predisposing to teratogenicity.[26] Further, serotonin (5-HT) has a role in regulating neural crest cell migration, and regulation of 5-HT by serotonin transporter has been demonstrated in cell culture to play a role in heart development.[27] However, most studies, including large numbers of exposed to erythromycin or citalopram and paroxetine, have been reassuring.[20,28] Further, the specific cardiac anomalies reported with paroxetine use are extremely rare[24] and consequently unlikely to offer an explanation to our results.

Second, some P-gp and BCRP inhibitors can also affect CYP enzymes. Most notably, several P-gp inhibitors also inhibit CYP3A4, whereas P-gp substrates are typically CYP3A4 substrates.[29] Third, polytherapy might be related more strongly to illness or illness severity than monotherapy or not using any drugs. Different pathological states, including diabetes,[30] inflammation,[31] hypoxia[32] and obesity[33] may alter the expression of P-gp and BCRP. If the drug transporters do not function optimally, there is an increased exposure not only to drugs but also to endogenous substances that are in normal conditions transported from the placenta by the transporters.[7] Placental accumulation of these substances may affect placental function and may have detrimental effects on foetal development. To overcome these possible biases, we included a control group of women using 2 or more drugs that were not drug transporter substrates or inhibitors (non-P-gp/BCRP polytherapy group). In this comparison, the risk of major congenital anomalies was higher in the P-gp/BCRP polytherapy group, suggesting an association not solely explained by maternal illness. We also adjusted for BMI and gestational diabetes, together with several chronic diseases, including connective tissue diseases, prepregnancy diabetes and severe mental disorders but the results remained significant. The most commonly used transporter substrates/inhibitors in our material were drugs used for asthma, allergies and depression, none of which have been associated with an increased risk of malformations. Further, the antimicrobials included in the study were prescribed to out-patients (hospital use is not included in the Drug Reimbursement Register) indicating that the treated condition itself was mild and therefore unlikely to affect foetal development.

When analysing P-gp and BCRP substrate/inhibitor use separately but allowing overlap between the groups, we found an increased risk of major congenital anomalies with P-gp polytherapy when compared to all the comparison groups. BCRP polytherapy was also associated with an increased risk in all comparisons but the risk turned insignificant after adjustment to confounders when compared to BCRP monotherapy group and remained marginally significant when compared to the non-BCRP polytherapy group. The expression of P-gp is known to vary with gestational age being highest during the first trimester, corresponding to the organogenetic period, and diminishing towards term.[34,35] The effect of gestation on BCRP expression in human placenta is less clear. Comparing BCRP expression in first trimester placentas to term placentas, the expression levels have been stable,[34] increased towards term[36] or decreased towards term.[37] A possible explanation for our findings could be that of these 2 transporters, P-gp is more highly expressed during the first trimester and may therefore be a major component in the placental barrier limiting the passage of harmful substrates to the foetus. However, when restricting the analyses to *pure* P-gp and *pure* BCRP substrates/inhibitors by excluding drugs with overlapping substrate/inhibitor status to both transporters, the risk remained statistically significantly increased in the *pure* P-gp polytherapy group only when compared to unexposed. In the *pure* BCRP polytherapy group the odds ratios were increased (33–53% increased risk) but the results were not statistically significant. The wide confidence intervals in the *pure* BCRP polytherapy analyses might be related to the fact that the numbers included in the analyses were much lower (n = 157 in the *pure* BCRP polytherapy group) than in the primary analyses (n = 2,068). A possible explanation is that there is a different teratogenic potential between the P-gp and BCRP substrates/inhibitors and the *pure* P-gp and *pure* BCRP substrates/inhibitors.

It is also possible that within the group of individual drugs that are substrates or inhibitors to both P-gp and BCRP there may be drug transporter-mediated interactions that may predispose to teratogenicity. For example, several statins and bupropion are both P-gp and BCRP substrates/inhibitors and were not included in the *pure* P-gp and *pure* BCRP groups. While statin use has previously been contraindicated during pregnancy, research has been reassuring and statin use may in individual cases be continued until pregnancy is confirmed.[38] However, a recent study observed a 5-fold increased risk of congenital cardiac anomalies related to statin use.[39] Further, bupropion use in early pregnancy has been associated with an increased risk of cardiac anomalies in some but not all, studies.[40-42] While these conflicting results may be to some extent related to different study methodologies, the role of drug transporter interactions might also play a role in explaining the conflicting results.

Our study has several strengths. First, the data are derived from the Finnish national health registers covering 18 years and virtually all births and elective terminations of pregnancy due to foetal anomaly. The registers have extensive coverage, high quality and include data on several important potential confounders.[11,12] The PIN allows all women, their children and reimbursed drug purchases to be linked and followed in the registers in a reliable manner. We included all pregnancy terminations due to major foetal anomaly. This is important, as approximately 12% of all pregnancies with a major anomaly in Finland are terminated.[43] We excluded women who had purchased previously known teratogenic drugs during 1 month before the pregnancy or during the first trimester. Unlike previous research, we systematically utilized the UW DIDB to identify P-gp and BCRP substrates and inhibitors. This database is maintained by a team of research scientists with extensive knowledge in the field who assess published information continuously and it provides an unbiased tool to assess drug–drug interactions. It should be noted, however, that our definition of transporter substrate and inhibitor status was solely based on in vitro data. This does not necessarily translate to effect in vivo, but since placental transporter inhibition is still poorly characterized and our primary aim was to see if there is a signal indicating need for further studies, we chose this approach.

Our study also has some limitations. First, the registers do not have information on certain important confounders such as use of alcohol or illicit substances. Second, a registered drug purchase does not necessarily mean actual use and the results may be biased by compliance. In addition, we cannot confirm that the exposure in the polytherapy groups occurred simultaneously. However, several P-gp/BCRP substrates or inhibitors are drugs for chronic diseases such as psychiatric disorders and hypertension and simultaneous use is likely. Lastly, we had no information on over-the-counter drug use. The drug transporter substrate with the most significant over-the-counter use during the study period was cetirizine, a P-gp substrate. Based on the Finnish statistics on medicines, around 1.5–2% of the population used cetirizine between years 2002–2011.[44-47] However, regular use of cetirizine is likely to be covered by prescription.[44]

In conclusion, polytherapy with P-gp and BCRP drug transporter substrates or inhibitors is associated with an increased risk of congenital anomalies. This study may direct future research to consider the role of drug transporter-mediated drug interactions in teratogenesis. Specifically, studying certain substrate-inhibitor pairs would be an interesting direction for future studies.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. Heli Malm

takes the responsibility for the integrity of the work as a whole, from inception to the published article. All authors have given substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data. All authors have contributed to drafting of the work and revising it critically for important intellectual content, given final approval of the version to be submitted, and have given agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. *Study concept and design:* All authors. *Acquisition of data:* M.K.L., A.-M.L.-K., H.M., M.E. *Analysis or interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* M.K.L., A.-M.L.-K. *Obtained funding:* H.M. *Administrative, technical or material support:* All authors. *Study supervision:* H.M.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available. According to the national data protection legislation, permission to obtain the research data must be applied from the Finnish Institution for Health and Welfare.

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REFERENCES

1. Lahesmaa-Korpinen A-M, Artama M, Gissler M, Heino A, Malm H, Ritvanen A. Raskaudenaikainen lääkkeidenkäyttö, syntyneiden lasten perinataaliterveys sekä epämuodostumat 1996–2010. [Maternal medicine use during pregnancy, risks for perinatal health and major congenital anomalies 1996–2010]. In: National Institute of Health and Welfare (THL), 2014: 92.
2. Tronnes JN, Lupattelli A, Nordeng H. Safety profile of medication used during pregnancy: results of a multinational European study. *Pharmacoepidemiol Drug Saf*. 2017;26(7):802-811.
3. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *Am J Obstet Gynecol*. 2011;205:51.e1-51.e8.
4. The International Transporter C, Giacomini KM, Huang S-M, et al. Membrane transporters in drug development. *Nat Rev Drug Discov*. 2010;9:215-236.
5. Iqbal M, Audette MC, Petropoulos S, Gibb W, Matthews SG. Placental drug transporters and their role in fetal protection. *Placenta*. 2012;33(3):137-142.
6. Hutson JR, Koren G, Matthews SG. Placental P-glycoprotein and breast cancer resistance protein: influence of polymorphisms on fetal drug exposure and physiology. *Placenta*. 2010;31:351-357.
7. Aye ILMH, Keelan JA. Placental ABC transporters, cellular toxicity and stress in pregnancy. *Chem Biol Interact*. 2013;203(2):456-466.
8. Staud F, Ceckova M. Regulation of drug transporter expression and function in the placenta. *Expert Opin Drug Metab Toxicol*. 2015;11:533-555.
9. Mölsä M, Heikkinen T, Hakkola J, et al. Functional role of P-glycoprotein in the human blood-placental barrier. *Clin Pharmacol Ther*. 2005;78(2):123-131.
10. Nanovskaya T, Nekhayeva I, Karunaratne N, Audus K, Hankins GDV, Ahmed MS. Role of P-glycoprotein in transplacental transfer of methadone. *Biochem Pharmacol*. 2005;69:1869-1878.
11. Gissler M, Shelley J. Quality of data on subsequent events in a routine medical birth register. *Med Inform Internet Med*. 2002;27(1):33-38.
12. Teperi J. Multi method approach to the assessment of data quality in the Finnish medical birth registry. *J Epidemiol Community Health*. 1993;47(3):242-247.
13. Daud ANA, Bergman JEH, Bakker MK, et al. P-glycoprotein-mediated drug interactions in pregnancy and changes in the risk of congenital anomalies: a case-reference study. *Drug Saf*. 2015;38(7):651-659.
14. Daud ANA, Bergman JEH, Oktora MP, Kerstjens-Frederikse WS, Groen H, Bos JH, et al. (2017 Maternal use of drug substrates of placental transporters and the effect of transporter-mediated drug interactions on the risk of congenital anomalies. *PLoS ONE*. 12(3):e0173530. https://doi.org/10.1371/journal.pone.0173530
15. Greenlees R, Neville A, Addor MC, et al. Paper 6: EUROCAT member registries: organization and activities. *Birth Defects Res a Clin Mol Teratol*. 2011;91(Suppl 1):S51-S100.
16. Bhuiyan M, Petropoulos S, Gibb W, Matthews SG. Sertraline alters multidrug resistance Phosphoglycoprotein activity in the mouse placenta and fetal blood–brain barrier. *Reprod Sci*. 2012;19(4):407-415.
17. Kapoor A, Iqbal M, Petropoulos S, Ho HL, Gibb W, Matthews SG. (2013 Effects of sertraline and fluoxetine on P-glycoprotein at barrier sites: In Vivo and In Vitro Approaches. *PLoS ONE*. 8(2):e56525. https://doi.org/10.1371/journal.pone.0056525
18. Saruwatari J, Yasui-Furukori N, Niioka T, et al. Different effects of the selective serotonin reuptake inhibitors fluvoxamine, paroxetine, and sertraline on the pharmacokinetics of fexofenadine in healthy volunteers. *J Clin Psychopharmacol*. 2012;32(2):195-199.
19. Damkier P, Brønniche LMS, Korch-Frandsen JFB, Broe A. In utero exposure to antibiotics and risk of congenital malformations: a population-based study. *Am J Obstet Gynecol*. 2019 Jun 28;221(6):648.e1-648.e15. https://doi.org/10.1016/j.ajog.2019.06.050
20. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370(25):2397-2407.
21. Namazy JA, Schatz M. Management of Asthma during pregnancy: optimizing outcomes and minimizing risk. *Semin Respir Crit Care Med*. 2018;39(1):29-35.
22. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med*. 2010;363(22):2114-2123.
23. Källén B, Danielsson BR. Fetal safety of erythromycin. An update of Swedish data. *Eur J Clin Pharmacol*. 2014;70:355-360.
24. Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol*. 2011;118(1):111-120.
25. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA. Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. *BMJ*. 2015;351:h3190.
26. Danielsson BR, Danielsson C, Nilsson MF. Embryonic cardiac arrhythmia and generation of reactive oxygen species: common teratogenic mechanism for IKr blocking drugs. *Reprod Toxicol*. 2007;24(1):42-56.
27. Sari Y, Zhou FC. Serotonin and its transporter on proliferation of fetal heart cells. *Int J Dev Neurosci*. 2003;21(8):417-424.
28. Romøren M, Lindbæk M, Nordeng H. Pregnancy outcome after gestational exposure to erythromycin – a population-based register study from Norway. *Br J Clin Pharmacol*. 2012;74(6):1053-1062.
29. Kim RB, Wandel C, Leake B, et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharm Res*. 1999;16(3):408-414.

30. Anger GJ, Cressman AM, Piquette-Miller M. (2012) Expression of ABC efflux transporters in placenta from women with insulin-managed diabetes. *PLoS ONE*. 7(4):e35027. https://doi.org/10.1371/journal.pone.0035027
31. Mason CW, Buhimschi IA, Buhimschi CS, Dong Y, Weiner CP, Swaan PW. ATP-binding cassette transporter expression in human placenta as a function of pregnancy condition. *Drug Metab Dispos*. 2011;39(6):1000-1007.
32. Lye P, Bloise E, Dunk C, et al. Effect of oxygen on multidrug resistance in the first trimester human placenta. *Placenta*. 2013;34(9):817-823.
33. Wang C, Li H, Luo C, et al. The effect of maternal obesity on the expression and functionality of placental P-glycoprotein: implications in the individualized transplacental digoxin treatment for fetal heart failure. *Placenta*. 2015;36(10):1138-1147.
34. Mathias AA, Hitti J, Unadkat JD. P-glycoprotein and breast cancer resistance protein expression in human placentae of various gestational ages. *Am J Physiol Regul Integr Comp Physiol*. 2005;289:R963-9.
35. Sun M, Kingdom J, Baczyk D, Lye SJ, Matthews SG, Gibb W. Expression of the multidrug resistance P-glycoprotein, (ABCB1 glycoprotein) in the human placenta decreases with advancing gestation. *Placenta*. 2006;27(6-7):602-609.
36. Yeboah D, Sun M, Kingdom J, et al. Expression of breast cancer resistance protein (BCRP/ABCG2) in human placenta throughout gestation and at term before and after labor. *Can J Physiol Pharmacol*. 2006;84(12):1251-1258.
37. Sieppi E, Vähäkangas K, Rautio A, Ietta F, Paulesu L, Myllynen P. The xenoestrogens, bisphenol a and Para-nonylphenol, decrease the expression of the ABCG2 transporter protein in human term placental explant cultures. *Mol Cell Endocrinol*. 2016;429:41-49.
38. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ*. 2015;350:h1035.
39. Lee MS, Hekimian A, Doctorian T, Duan L. Statin exposure during first trimester of pregnancy is associated with fetal ventricular septal defect. *Int J Cardiol*. 2018;269:111-113.
40. Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM. Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol*. 2010;203:52.e1–52.e6. e1–6
41. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007;16(5):474-484.
42. Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. *Pharmacoepidemiol Drug Saf*. 2014;23(10):1066-1075.
43. THL. Congenital Malformations 2015: Statistical Report and appendices. In, https://thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/congenital-anomalies: National Institute of Health and Welfare, 2015.
44. Finnish Statistics on Medicines 2003: National Agency for Medicines Social Insurance Institution (Kela), 2004.
45. Finnish Statistics on Medicines 2007: National Agency for Medicines Social Insurance Institution, 2008.
46. Finnish Statistics on Medicines 2009: Finnish Medicines Agency Fimea Social Insurance Institution, 2010.
47. Finnish Statistics on Medicines 2012: Finnish Medicines Agency Fimea Social Insurance Institution, 2013.

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