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Effects of preconceptional paternal drug exposure on birth outcomes: cohort study of 340 000 pregnancies using Norwegian population-based databases

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Only a few (and small) studies have been able to include data related to drug ingestion by fathers prior to conception.
- About one quarter of fathers is dispensed prescribed drugs during the last 3 months prior to conception.

WHAT THIS STUDY ADDS

- This unique study exploring the impact of paternal drug use in a short time period (3 months) prior to conception in an unselected population did not indicate that paternal drug exposure is an important risk factor for adverse pregnancy outcomes.
- We have used data from 340 000 pregnancies. The large amount of material made it possible to explore how paternal drug use affected the offspring in more detail than previously.
- In the present study population, however, the frequency of prescription of drugs suspected to be teratogenic was low.

AIMS

We aimed to explore associations between drugs dispensed to the father prior to conception and pregnancy outcomes, such as pre-term birth, perinatal mortality, foetal growth retardation and birth defects.

METHODS

In this cohort study, two population-based registries, the Medical Birth Registry of Norway and the Norwegian Prescription Database, were linked. The study cohort consisted of 340 000 pregnancies in 2004–10. The association between specific drugs dispensed to the fathers during the last 3 months prior to conception and pregnancy outcomes was explored by estimating odds ratios (ORs) using multivariate logistic regression.

RESULTS

About one quarter (26%) of the fathers were dispensed at least one drug during the last 3 months prior to conception and 1.3% were dispensed at least one drug requiring special attention. Overall, the odds of different adverse pregnancy outcomes were not increased when the father had been dispensed drugs, i.e. the OR and 95% confidence intervals (CIs) for any birth defect when the fathers had been dispensed any drug were 0.99 (0.94, 1.0). When the fathers had been dispensed diazepam we found increased risk of perinatal mortality and growth retardation, with OR and 95% CIs of 2.2 (1.2, 3.9) and 1.4 (1.2, 1.6), respectively.

CONCLUSIONS

Large studies are necessary to reveal increased risk of rare outcomes as specific birth defects. Our study did not indicate that paternal drug exposure is an important risk factor for adverse pregnancy outcomes.

Introduction

The effects of maternal exposures on birth outcomes have been extensively examined [1]. Regarding paternal exposures, several studies have explored effects of sperm characteristics on birth outcomes [2]. Focus has been on paternal exposures to environmental and chemical factors, especially occupational exposures [3] and cancer treatments [4]. Also paternal drug exposures prior to conception may cause adverse effects on pregnancy outcomes, but knowledge of such possible effects is limited [5]. Previous studies on possible adverse effects of paternal drug exposure have usually been hampered by small study populations, since information on the fathers is seldom available in large databases.

Schirm *et al*. [6] described drug use among fathers during the last 6 months prior to conception in cohorts (consisting of about 60 000 fathers) in Denmark and the Netherlands. They found that one third of the fathers were dispensed drugs during the half year prior to conception. Information on pregnancy outcomes was not available.

Based on two population-based registries, the Medical Birth Registry of Norway (MBRN) and the Norwegian Prescription Database (NorPD), we have previously [7] reported the frequency of prescribed drugs dispensed to fathers the last 3 months prior to conception for 100 000 births in Norway during 2004–6. One fourth of the fathers were dispensed drugs, receiving on average two different drug substances.

Potential adverse effects due to paternal drug exposure may be mediated through direct mutagenic actions, disturbances in spermatogenesis or the transfer of drugs to the female via semen. The extent to which paternal exposures to drugs prior to conception contribute to pregnancy loss or birth defects is still not clear, and there is a need for more information on the effects of paternal drug exposure [8].

The aim of our study was to explore possible associations between drugs dispensed to the father in the last 3 months prior to conception and adverse pregnancy outcomes such as spontaneous abortion, pre-term birth, perinatal mortality, foetal growth retardation and birth defects in a large population-based study. Associations between paternal exposure to drugs prior to conception [6] evaluated to need special attention, and adverse outcomes were particularly explored.

Methods

Data sources

NorPD [9] is a research database which contains information on all prescribed drugs, reimbursed or not, dispensed at pharmacies to individual patients treated in ambulatory care from January 1 2004. NorPD covers the entire population of Norway (approximately 5.0 million). Data on use in institutionalized patients in nursing homes and hospitals are also collected, but these figures are only registered at an institutional level. Therefore, drugs dispensed at institutions are not included in our study. For each prescription, the gender and age of the patient, demographic information, dispensing date and detailed drug information are registered. Classification of drugs is based on the Anatomical Therapeutic Chemical (ATC) classification system [10].

The MBRN is a population-based registry containing information on all births in Norway since 1967 (about 2.6 million births) [11]. The MBRN is based on compulsory notification of births or of pregnancies from 12 completed weeks of gestation onwards, and includes identification on the parents by their personal identity numbers, demographic information on the parents, length of pregnancy as well as information on the infant, including birth defects and other adverse pregnancy outcomes [11]. All pregnancies terminated due to suspected birth defects or health problems for the child are also registered, but for these pregnancies information on the fathers are not recorded.

The MBRN records birth defects that have been diagnosed at the time of delivery or during the initial hospitalization [11]. Also foetal diagnoses and diagnoses obtained at the paediatric departments are reported separately. In this study, data on birth defects included the ICD-10 codes Q00-Q99 and P835, and the defects were grouped by organ system.

Study subjects

Data in the MBRN were linked to NorPD using the unique 11-digit personal identity number, assigned to all individuals living in Norway after 1960.

In our study, all singleton pregnancies, with known pregnancy-length of at least 12 weeks, registered in the MBRN were included, with estimated time of conception April 1 2004 or later and birth prior to January 1 2011 (n = 349 020). Pregnancies with registered length of 45 completed weeks or more were excluded. Using previously published data on birth weight by gestational age [12], we excluded pregnancies ending in a foetus with weight ± 4 SDs away from the published weights by gestational age for pregnancies with gestational age 23–44 completed weeks, since the gestational age for these pregnancies probably were wrong. In addition, pregnancies of less than 23 weeks of gestation with foetuses with weight 1000 g or more were excluded (probably wrong gestational age and/or weight). Terminated pregnancies were excluded from the main analysis, since we did not have information on the father in these pregnancies. In total, the identity of the father was reported in 97% of the pregnancies. A total of 336 893 pregnancies were included, birth defects were registered only for children born 2004–9, resulting in 279 796 pregnancies.

In the analyses, the fathers were followed with regard to prescriptions during the last 3 months prior to conception.

Outcomes

The following outcomes were studied:

1 *Spontaneous abortion* defined as pregnancies lasting less than 22 completed weeks (based on ultrasound when available (97%) or the last menstrual period).
2 *Pre-term birth* defined as live births after at least 22 and prior to 37 completed weeks.
3 *Perinatal mortality* defined as all foetuses, with pregnancy length of at least 22 completed weeks and dying within the first 7 days after birth [13].
4 *Small for gestational age* (*SGA)*, or growth retardation, defined as those 10% having lowest weight compared with all foetuses of the same sex and gestational week [13]. This variable was restricted to those with gestational age of 22–44 weeks.
5 *Birth defects*: All kinds of birth defects and birth defects in some major organ systems, classified according to ICD-10:
   a. Nervous system (Q00-07)
   b. Eye, ear, face and neck (Q10-18)
   c. Heart and blood vessels (Q20-28)
   d. Respiratory organs (Q30-34)
   e. Lip/palate (Q35-37)
   f. Digestive system (Q38-45)
   g. Genitalia (Q50-56, P835)
   h. Urinary organs (Q60-64)
   i. Musculoskeletal system (Q65-79)
   j. Down's syndrome (Q90)
   k. Other chromosomal abnormalities (Q91-99)
   l. Other and unspecified (Q80-89)
   m. Multiple defects (birth defects in at least two of the groups above)
   n. Any birth defect
   o. Serious birth defect as defined by the MBRN (http://www.mfr.no)

Exposures

In addition to all prescribed main ATC groups and all prescribed drugs combined, we focused on prescribed medicines regarded as drugs needing special attention by Schirm *et al*. [6]. This list, consisting of 20 drugs, was constructed after a literature review based on theoretical, experimental and epidemiological results. In the analyses, prescriptions during the last 3 months prior to the estimated time of conception were included, and only the most common drugs were analyzed separately. The frequency of adverse pregnancy outcomes were analyzed for the two most frequent/common drugs in the list by Schirm *et al*. in addition to paternal use of any of these drugs and any drugs at all. Also analyses for paternal use of selective serotonin re-uptake inhibitors (SSRIs) were performed [14].

Methodology

Odds ratios (ORs) of spontaneous abortions, pre-term births, perinatal mortality, SGA and birth defects were estimated with multivariate logistic regression models. Pregnancies lasting less than 22 completed weeks were excluded when analyzing pre-term births, perinatal mortality and SGA. The analysis of birth defects included births up to 2009. Adjustments were made for maternal and paternal ages as categorized variables (younger than 20 years, 20–39 years and at least 40 years of age) in all models. These variables were categorized because non-linear associations between these variables and some of the outcomes explored here have been reported [15]. Also, it was explored whether maternal smoking during pregnancy and maternal diabetes or epilepsy, which has been associated with increased risk of birth defects [16, 17], influenced the results by adjustments for these variables. Smoking habits for the mothers were available both at the beginning and at the end of pregnancy for 80% of the pregnancies. Also maternal consumption of the same drug as the father was exposed to was adjusted for. We also confined the adjustment for maternal drug use to use in the last 3 months prior to conception and the trimesters of pregnancy.

Data handling and analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL).

Ethics

The Norwegian Data Inspectorate was notified before the MBRN and NorPD were linked, as required by the Norwegian law for national health registries. The study was entirely register-based, and we did not contact the study subjects and no active participation was required of them.

Results

In total, 337 000 births during 2004–10 were included in our study (Table 1). There were almost 1500 perinatal deaths and more than 17 000 pre-term births. More than a quarter of the fathers (26%) were dispensed at least one prescribed drug during the last 3 months prior to conception (Table 2). During the last 6 months prior to conception, 39% of the fathers were dispensed at least one prescription. The frequency of use of the selected drugs requiring special attention is given in Table 3. A total of 4266 (1.3%) of the fathers were dispensed at least one of these drugs.

Overall, the odds of adverse pregnancy outcomes were not increased when the father had been dispensed drugs (Table 4). The odds of adverse pregnancy outcomes was not increased when the father had been dispensed drugs in any of the main ATC groups (data not shown), except for medications for the nervous system where increased odds for pre-term birth, perinatal mortality and birth defects of the urinary system were seen, with ORs (95% CI) of 1.2 (1.1, 1.3), 1.3 (1.1, 1.5) and 1.5 (1.2, 2.0), respectively.

A two-fold increased odds of perinatal mortality was observed when the father was dispensed diazepam prior

Table 1

Characteristics of the births included in analyses of dispensed drugs to fathers the last 3 months prior to conception

	n	%
Year of childbirth		
2004	497	0.15
2005	53 063	16
2006	55 522	16
2007	55 263	16
2008	57 261	17
2009	58 190	17
2010	57 097	17
Pregnancy length (completed weeks)		
<22	775	0.23
22–32	3 818	1.1
33–39	151 152	45
40–44	181 148	54
Birth weight (g)		
Missing	561	0.17
<500	657	0.20
500–2499	11 968	3.6
2500–2999	34 345	10
3000–3499	105 933	31
3500–3999	119 558	35
4000–4499	52 058	15
4500–6300	11 813	3.5
Paternal age (years)		
<20	2 162	0.64
20–49	330 690	98
50+	4 041	1.2
Maternal age (years)		
Missing*	11	0.00
<20	7 348	2.2
20–39	320 090	95
40+	9 444	2.8
Spontaneous abortion†	775	0.2
Pre-term birth‡	17 300	5.1
Perinatal mortality§	1 461	0.43
Small for gestational age¶	33 600	10
Total number of births	336 893	

*Maternal age was set to the mean maternal age (30 years) for these foetuses in the analyses. †Pregnancy length less than 22 completed weeks. ‡Live births after at least 22 but prior to 37 completed weeks. §All foetuses with pregnancy length of at least 22 completed weeks and deaths within 7 days after birth. ¶Small for gestational age was defined as those 10% having lowest weight compared with all foetuses of the same sex and gestational week for those with gestational week 22–44.

Table 2

Number of fathers who were dispensed drugs during the last 3 months prior to conception (n = 336 893)

Drug (main groups) (ATC code)	*n*	%
Alimentary tract and metabolism (A)	10,185	3.0
Blood and blood forming organs (B)	1,760	0.52
Cardiovascular system (C)	6,637	2.0
Dermatologicals (D)	10,737	3.2
Genito urinary system and sex hormones (G)	2,454	0.73
Systemic hormonal preparations, excl. sex hormones and insulin (H)	3,882	1.15
Antiinfectives for systemic use (J)	21,924	6.5
Antineoplastic and immunomodulating agents (L)	823	0.24
Musculo-skeletal system (M)	19,258	5.7
Nervous system (N)	21,572	6.4
Antiparasitic products, insecticides and repellents (P)	1,312	0.39
Respiratory system (R)	23,894	7.1
Sensory organs and various (S + V)	8,683	2.6
Any drug	87,847	26

ATC, Anatomical Therapeutic Chemical.

Table 3

Number of fathers who were dispensed drugs requiring special attention (according to Schirm *et al.* [6]) during the last 3 months prior to conception (n = 336 893)

Drug (ATC code)	*n*	%
Cimetidine (A02BA01)	82	0.02
Prednisolone (H02AB06)	1,477	0.44
Indomethacin (M01AB01)	183	0.05
Valproic acid (N03AG01)	347	0.10
Diazepam (N05BA01)	1,354	0.40
Sulfasalazine (A07EC01)	117	0.03
Morphine (N02AA01)	38	0.01
Azathioprine (L04AX01)	268	0.08
Furosemide (C03CA01)	122	0.04
Isotretinoin (systemic) (D10BA01)	80	0.02
Androgens (G03B)	121	0.04
Phenytoin (N03AB02)	31	0.01
Phenobarbital (N03AA02)	21	0.01
Ergotamine (N02CA02)	0	0.00
Spironolactone (C03DA01)	44	0.01
Lithium (N05AN01)	159	0.05
Methotrexate (L01BA01)	5	0.00
Daunorubicin (L01DB02)	0	0.00
Acitretin (systemic) (D05BB02)	44	0.01
6-Mercaptopurine (L01BB02)	3	0.00
One or more of these drugs	4,266	1.30

ATC, Anatomical Therapeutic Chemical.

to conception (Table 4), and this group also had increased odds of being small for gestational age (growth retardation). In the present study, there were 1354 pregnancies where the father had used diazepam and 13 of these ended in a perinatal death. Only two of these cases were exposed to maternal use of diazepam, and in five cases the mothers were not smoking in pregnancy (six of the cases had missing on maternal smoking).

Among the births in 2004–9, 13 073 (4.7%) foetuses had at least one birth defect (Table 5). Among these, 3684 had fathers who had been dispensed drugs in the last 3 months prior to conception. There was an increased odds of birth defects of the urinary system when diazepam had been dispensed to the father (Table 6). However, there were only six foetuses with these birth defects (three with congenital hydronephrosis (ICD-10: Q620), two with unilateral renal agenesis (Q600), one of whom also had renal dysplasia (Q614), and one with other congenital malformations of the bladder and urethra (Q647)) who were fathered by a man with a diazepam prescription. Adjustment for maternal diabetes mellitus or maternal epilepsy marginally influenced the results of paternal drug exposure (data not shown).

Table 4

Odds ratios (ORs) with 95% confidence intervals (CI) from multivariate logistic regression, including prescriptions during the last 3 months prior to conception, for spontaneous abortion*, pre-term birth†, perinatal mortality‡ and small for gestational age (SGA)§, adjusted for maternal and paternal age (n = 336 893)

	Spontaneous abortion (n = 775)*			Pre-term birth (n = 17 300)†			Perinatal mortality (n = 1 461)‡			SGA (n = 33 600)§		
Drug (ATC-code)	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI
Any drug	247	1.1	0.97,1.3	5 245	1.1	1.0,1.1	420	0.98	0.87,1.1	9 397	0.93	0.91, 0.96
Any drugs in Table **3**	12	1.2	0.69,2.1	237	1.1	0.95,1.2	24	1.3	0.87,2.0	470	1.1	1.0, 1.3
Prednisolone (H02AB06))	4	0.99	0.37,2.6	93	1.0	0.84,1.3	8	1.1	0.53,2.1	163	0.92	0.79, 1.1
Diazepam (N05BA01)	4	1.3	0.47,3.4	83	1.2	0.96,1.5	13	2.2	1.2,3.9	178	1.4	1.2, 1.6

*Pregnancy length less than 22 completed weeks. †Live births after 22 but prior to 37 completed weeks. ‡All foetuses with pregnancy length of at least 22 completed weeks and deaths within 7 days after birth. §SGA- small for gestational age was defined as those 10% having lowest weight compared with all foetuses of the same sex and gestational week for those with gestational week 22–44. ATC, Anatomical Therapeutic Chemical.

Table 5

Number of subjects with registered birth defects in 2004–9 (n = 279 796). Terminated pregnancies are not included

Birth defect	ICD-10	n	%
Nervous system	Q00-07	236	0.10
Eye, ear, face and neck	Q10-18	494	0.20
Heart and blood vessels	Q20-28	3,013	1.1
Respiratory organs	Q30-34	234	0.10
Lip/palate	Q35-37	528	0.20
Digestive system	Q38-45	1,644	0.60
Genitalia	Q50-56, P835	1,981	0.70
Urinary organs	Q60-64	587	0.20
Musculoskeletal system	Q65-79	4,631	1.7
Down's syndrome	Q90	345	0.10
Other chromosomal abnormalities	Q91-99	111	0.00
Other and unspecified	Q80-89	554	0.20
Multiple defects*		1,018	0.40
Any birth defects		13,073	4.7
Serious birth defects		7,185	2.6

*Defects included in more than one of the main categories listed above.

Due to the effect of diazepam on outcomes (Tables 4 and 6) we did different sub analyses. The same analyses performed for the broader group anxiolytics, revealed about the same ORs as for diazepam. Excluding pregnancies with a father who also had been dispensed opioids (N02A) and/or hypnotics (N05C), reduced the number of exposed cases, and the ORs (95% CI) for perinatal mortality and birth defects of the urinary system were 1.6 (0.65, 3.8) and 2.4 (0.78, 7.6), respectively. When the fathers had been dispensed anxiolytics we found about similar odds of perinatal mortality, and growth retardation (SGA). Paternal use of diazepam was associated with maternal use of diazepam (8% *vs*. 0.7% in pregnancies with and without paternal use, respectively), and maternal smoking both at the beginning and at the end of pregnancy (25% *vs*. 8%) (Table 7). Adjusting for maternal use of diazepam in the last 3 months prior to conception and the trimesters of pregnancy did not, however, change the ORs of perinatal mortality for paternal use of diazepam. The ORs (95% CI) for perinatal mortality by maternal use of diazepam during the 3 months prior to conception and the trimesters of pregnancy were 0.92 (0.44, 1.9), 2.0 (0.94, 4.3), 1.3 (0.39, 4.1) and 2.1 (0.75, 6.0), respectively, when adjusting for paternal use of diazepam.

The fathers using diazepam seemed to be somewhat older than those not using diazepam, and there was more maternal smoking in pregnancies with paternal use of diazepam (Table 7). Among the 13 perinatal deaths in pregnancies with paternal diazepam use, information on maternal smoking habits was missing in six cases. Due to the low number of outcomes and missing data, analyses with adjustment for maternal smoking habits were performed both with categories for missing maternal smoking included (OR 2.1, 95% CI 1.2. 3.6) and without pregnancies with unknown maternal smoking (OR 1.4, 95% CI 0.66. 3.0).

The list of drugs in Table 3 included cimetidine from the group of histamine$_2$-receptor antagonists. The whole group of histamine$_2$-receptor antagonists (A02BA) was used by only 993 (0.3%) of the fathers. Indomethacin was included from the group of NSAIDs (M01A), Too few of the fathers used indomethacin to examine this drug, but paternal use of drugs in the larger group NSAIDs did not increase the risk of adverse outcomes. There was no increased risk of adverse outcomes after paternal use of anti-epileptics (N03).

Only 80 of the fathers had used isotretinoin during the last 3 months prior to pregnancy. Seven of the 80 pregnancies ended in a pre-term birth (OR = 1.8; 95% CI 0.81, 3.8). One of the foetuses had serious birth defects (ICD-10: Q25.0 (patent ductus arteriosus) and Q90.9 (Down's syndrome)). Five of the fathers used methotrexate, but none of the outcomes studied here occurred in the corresponding pregnancies. None of the fathers had used thalidomide.

More than 3000 of the fathers had used SSRIs during the last 3 months prior to pregnancy. A modest increased risk of pre-term birth was observed in these pregnancies

Table 6

Odds ratios (ORs) with 95% confidence intervals (CI) from multivariate logistic regression, of dispensed drugs to fathers during the last 3 months prior to conception, for birth defect in some major organ systems, adjusted for maternal and paternal age ($n = 279\,796$)

	Drug (ATC-code)											
	Any drug			Any drugs requiring special attention [6]			Prednisolone (H02AB06)			Diazepam (N05BA01)		
Birth defect	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI	Exposed cases	OR	95% CI
Nervous system	73	1.1	0.86, 1.5	2	0.69	0.17, 2.8	1	0.88	0.12, 6.3	1	1.1	0.15, 7.7
Eye, ear, face and neck	126	0.86	0.70, 1.0	7	1.1	0.53, 2.4	4	1.6	0.61, 4.4	2	0.98	0.25, 4.0
Heart and blood vessels	833	0.96	0.88, 1.0	25	0.65	0.44, 0.97	11	0.74	0.41, 1.3	10	0.81	0.44, 1.5
Respiratory organs	60	0.86	0.64, 1.1	1	0.33	0.05, 2.4	0	–		1	1.0	0.14, 7.3
Lip/palate	156	1.0	0.87, 1.3	6	0.89	0.40, 2.0	3	1.2	0.37, 3.6	2	0.92	0.23, 3.7
Digestive system	486	1.1	0.95, 1.2	25	1.2	0.82, 1.8	16	2.0	1.2, 3.3	8	1.2	0.60, 2.4
Genitalia	569	1.0	0.92, 1.1	32	1.3	0.92, 1.9	12	1.2	0.70, 2.2	10	1.3	0.68, 2.4
Urinary organs	176	1.1	0.90, 1.3	14	1.9	1.1, 3.3	6	2.1	0.94, 4.7	6	2.6	1.2, 5.8
Musculoskeletal system	1 249	0.93	0.87, 0.99	63	1.1	0.85, 1.4	26	1.1	0.78, 1.7	21	1.1	0.73, 1.7
Down's syndrome	114	1.2	0.97, 1.5	3	0.68	0.20, 22.1	0	–		2	1.4	0.35, 5.6
Other chromosomal abnormalities	30	0.92	0.60, 1.4	2	1.4	0.36, 5.8	0	–		1	2.2	0.31, 16
Other and unspecified	179	1.2	1.0, 1.4	6	0.85	0.38, 1.9	0	–		3	1.3	0.43, 4.1
Multiple defects*	286	0.98	0.86, 1.1	11	0.86	0.48, 1.6	3	0.60	0.19, 1.9	5	1.2	0.51, 3.0
Any birth defect	3 684	0.99	0.95, 1.0	174	1.1	0.91, 1.2	75	1.2	0.93, 1.5	62	1.2	0.92, 1.5
Serious birth defect	2 035	0.99	0.94, 1.0	85	0.94	0.76, 1.2	35	0.99	0.71, 1.4	30	1.0	0.72, 1.5

*Defects included in more than one of the main categories listed above.

(OR = 1.3, 95% CI 1.1, 1.5). There was also an increased risk of birth defects in the digestive system (OR = 1.8, 95% CI 1.2, 2.6), but no increased risk for serious birth defect or for birth defects in total.

Discussion

In this population-based study with almost 340 000 births, there were basically no increased risks of adverse outcomes after paternal drug use just before conception. However, there were indications of increased odds of perinatal mortality and growth retardation when the father was dispensed diazepam during the last 3 months prior to conception. This may be explained by inadequate adjustment for confounders.

As far as we know, this is the largest study on adverse effects connected to paternal drug use prior to conception. We used two nationwide registries, the MBRN and the NorPD, and linkage of these two registries was performed using the personal identity number. The registries were based on compulsory registrations of all births in Norway and all prescribed drugs dispensed to individuals from all Norwegian pharmacies. The data were collected prospectively from the total population. Therefore, selection and recall bias were eliminated in contrast to most studies on paternal factors which have relied on the mother as a proxy reporter [18].

All pregnancies terminated due to suspected birth defects or health problems for the child are also registered, but for these pregnancies information on fathers are not recorded.

We had no information on the fathers in the pregnancies ending in termination of pregnancy due to suspected birth defects or health problems for the child (n = 1285). About 81% of these children had serious birth defects. Hence, these pregnancies were excluded from the main analyses. Assuming that the mothers in these pregnancies had another pregnancy fathered by the same man prior to or after this pregnancy, we could find an assumed father in terminated pregnancies in 76% of the cases. Analyses performed including the terminated pregnancies with the assumed fathers gave similar results.

Date of dispensing medications is known, but we did not know whether the dispensed drugs were actually used or not, or eventually when they were used. However, because only information about drugs dispensed and purchased by patients is entered into the databases, primary non-compliance is not an issue [19]. Further, we were not able to link medications used by the fathers if hospitalized.

Maternal diabetes and maternal epilepsy have been shown to increase the risk of adverse pregnancy outcomes [16, 17]. Including adjustments for maternal diabetes or epilepsy, however, did not change the results.

We had no other information on the fathers apart from their age and which drugs they were dispensed prior to conception, i.e. no medical information on the fathers or information on the indication for their drug use was available. Since we did not have information on sexual habits, we decided not to look at possible influence of paternal exposure during pregnancy.

Table 7

Characteristics of the births by paternal use of diazepam (n = 336 893)

	Paternal use of diazepam	
	No (%)	Yes (%)
Maternal use of diazepam	0.73	8.0
Prior to	0.45	6.2
First trimester	0.26	4.7
Second trimester	0.11	1.5
Third trimester	0.10	1.3
Maternal smoking		
At the beginning of pregnancy	18	39
At the end of pregnancy	8.6	25
Maternal parity		
0	42	44
1	36	33
2	16	15
3	4.5	5.4
4+	2.1	2.7
Pregnancy length (completed weeks)		
<22	0.23	0.30
22–32	1.1	1.6
33–39	45	49
40–44	54	49
Paternal age (years)		
<20	0.64	0.15
20–49	98	95
50+	1.2	4.8
Maternal age (years)		
<20	2.2	2.8
20–39	95	93
40+	2.8	3.8
Birth weight <1500 g	0.89	1.3
Birth weight <2500 g	3.7	5.0
Small for gestational age*	10	13

*Small for gestational age was defined as those 10% having lowest weight compared with all foetuses of the same sex and gestational week for those with gestational week 22–44.

Paternal drug use may influence male fertility [14, 20]. However, no information on male fertility was available.

The grouping of birth defects used should have been more detailed, i.e. serious and less serious birth defects should have been separated within these major groups. However, the number of exposed foetuses/children with these groups of birth defects was too small for a further division. However, we made calculations for the whole group of serious birth defects.

Even though the study cohort was relatively large, the number of specific birth defects was limited in pregnancies with fathers being dispensed specific drugs. Hence, our results are encumbered with large uncertainties.

Possible effects of maternal and paternal use of azathioprine and other anti-rheumatic drugs on birth defects were explored in a recent publication [21]. Even though we had twice as many pregnancies included in our study, the exposures were still too rare (number of exposed foetuses/children) to be examined further, e.g. only nine of the foetuses/children with any birth defect were exposed to paternal use of azathioprine (OR = 0.83, 95% CI 0.43, 1.6).

While Schirm *et al*. [6] found that one third of the fathers had received drugs in the 6 months prior to conception, we found that one quarter of all fathers were dispensed at least one prescription during the last 3 months prior to conception, and 39% of the fathers were dispensed at least one prescription during the last 6 months prior to conception.

Concerns have been made that paternal drug exposure prior to conception contributes to changes in fertility, adverse pregnancy outcomes or birth defects [20]. Fortunately, the use of highly teratogenic drugs such as isotretinoin and thalidomide is very low in the Norwegian population. Hence, we do not have data to explore the effect of paternal use of these drugs.

Even though our study is the largest study on paternal drug exposure we are aware of, larger studies are necessary to explore possible adverse effects on pregnancy outcomes of specific drugs. We studied pregnancy outcomes associated with dispensed specific prescribed drugs to fathers in the last 3 months prior to conception and included almost 340 000 pregnancies with information on the fathers. There were indications of increased risk of perinatal mortality and growth retardation when the father was dispensed diazepam. However, this finding may be due to confounding since, for example, maternal smoking, maternal use of diazepam and maternal age seem to differ from other pregnancies. Maternal use of diazepam has previously been linked to higher incidence of orofacial clefts [22].

In conclusion, overall the odds of adverse pregnancy outcomes were not increased when the father had been dispensed drugs. Indications of increased risk of some adverse birth outcomes were observed when the fathers had been dispensed diazepam. However, since a large number of associations were examined, we cannot disregard the possibility of chance findings. Even though this is a relatively large study, it is still too small to further explore possible adverse effects of paternal exposure prior to conception, effects that, if present, probably are small.

Conflict of Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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