Research protocol

Title: Safety of the second generation antipsychotics during pregnancy

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List of abbreviations

ATC = Anatomic Therapeutic Classification

ETOPFA = Elective Termination of Pregnancy for Fetal Anomaly

Kela = Social Insurance Institution in Finland

MCA = Major Congenital Anomaly

THL = National Institute for Health and Welfare

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Research synopsis

Study title. Safety of the second generation antipsychotics during pregnancy.

Background. Second generation antipsychotics have largely replaced first generation antipsychotics but little is known about their safety during pregnancy.

Methods. This is a population-based cohort study based on the Drugs and Pregnancy project database in Finland. This database includes data from national health registers: the Medical Birth Register, the Register on Induced Abortions, the Malformation Register (all maintained by the National Institute for Health and Welfare), and the Prescription Register and Special Refund Entitlement Register (both maintained by the Social Insurance Institution). Data have been collected during Jan 1st 1996 - Dec 31st 2010 and include all births (live and still births), pregnancy terminations due to major congenital anomaly, and information on drug purchases during pregnancy and 3 months before pregnancy. For this study, we collect from the Drugs and Pregnancy project database all women with one or more purchase(s) of the second generation antipsychotics during pregnancy or one month before pregnancy. There are 55,000-60,000 births per year in Finland, and the total study population includes nearly 880,000 pregnancies. In Finland, 0.3% of pregnant women have a diagnosis of psychosis as a chronic disease. As several of the second generation antipsychotics have only been introduced recently to the market, we expect to include 1,300 – 1,500 pregnancies exposed to second generation antipsychotics at some stage of pregnancy.

Objectives. The primary objectives of the study are i.) to assess the risk of major congenital anomalies after first trimester exposure to second generation antipsychotics and ii.) to investigate the prevalence of other perinatal outcomes, including small or large for gestational age, preterm birth, low birth weight, and perinatal mortality. The exposed group is compared i) to women and their offspring exposed to first generation antipsychotics during the period of

three months prior to pregnancy until the end of pregnancy to control for maternal illness, and ii) to unexposed women.

Timelines. Data collection for the study will start in November 2013, and final results with manuscript submission are expected in fall 2015.

Background and significance

In Finland, 0.3% of pregnant women have a chronic psychotic illness (Artama *et al*. 2011). During the last two decades, use of the second generation antipsychotics (atypical antipsychotics) has increased. This tendency is evident not only on population level but also within the pregnant population; in 2006, 0.2% of pregnant women used second generation antipsychotic drugs and the use increased up to 0.6 % in 2010, while during the same period the use of first generation antipsychotics increased from 0.1 % to 0.2 % (National Institute for Health and Welfare, THL, unpublished statistics 2012). While the relatively abundant experience of first generation antipsychotic use during pregnancy does not suggest increased risk for the fetus, much less experience for use during pregnancy is available for the second generation antipsychotics. The increased use of second-generation antipsychotics may to some extent be related to the argued but not uniformly proven better tolerability, and a more favorable side-effect profile when compared to the first generation antipsychotics (Tandon *et al.* 2011). Further, off-label use, including use as hypnotics and sedatives, may also play a role.

Several second generation antipsychotics have less effect on prolactin secretion than first-generation antipsychotics (Henderson and Doraiswamy 2008) and consequently, pregnancies may occur more easily also during treatment. Further, as maternal psychiatric well-being is a prerequisite for fetal well-being and favorable pregnancy outcome, changing effective medication because of pregnancy is seldom possible. Several second generation antipsychotics, especially olanzapine and clozapine, may predispose to hyperglycaemia (Henderson and Doraiswamy 2008, American Diabetes Association 2004), which as such may increase the risk for pregnancy complications including congenital anomalies and being born large for gestational age. Randomized, controlled studies are rarely possible to perform in pregnant

women, and data on safety of the second generation antipsychotic drugs are based on observational data including case reports, case series, and small cohort studies including studies based on follow-up data from teratology information services. Data gathered from these various sources have not suggested an increased risk of major congenital anomalies after second generation antipsychotic drug use on drug class level or on individual drug level, but the numbers included in the published studies have been too small for reliable risk assessment. Further, antipsychotics are often used together with other psychiatric drugs, making evaluation of individual drug-associated risks difficult. Individual studies have suggested an increased risk for being born large for gestational age (Newham *et al.* 2008) but this association has not been observed in other studies (Lin *et al.* 2010). We plan to investigate the effects of second generation antipsychotic use during pregnancy on pregnancy outcome, including major congenital anomalies (MCA), pregnancy complications, and peri- and neonatal complications. Due to the increasing use of second generation antipsychotics also among pregnant women, the results will have important implications for pregnant women themselves and for prescribing practices for clinicians who treat pregnant women with psychiatric disorders.

As the group of second generation antipsychotics consists of individual, structurally different chemical compounds, we also intend to perform analyses on MCAs on individual drug level.

While limited data are available, there is no suggestion of a markedly increased risk for malformations or other adverse perinatal outcome. We therefore hypothesize that second generation antipsychotics are not major teratogens.

Objectives

The objectives of the planned study are to:

1. Examine the association between second generation antipsychotic use during the first trimester of pregnancy and MCAs, including pregnancies ending in birth or in elective termination of pregnancy for fetal anomaly (ETOPFA).

2. Examine the association between second generation antipsychotic use during pregnancy and pregnancy complications and peri- and neonatal outcome.

Methods

The data for this study are extracted from the existing database of 'Drugs and Pregnancy' project in Finland for the years 1996-2010 (Artama *et al*. 2011). This project has been established by three governmental organizations: The National Institute for Health and Welfare (THL), the Social Insurance Institution in Finland (Kela) and the Finnish National Medicines Agency (Fimea). The objective of the project is continuing surveillance of drug-related safety during pregnancy. Several studies on drug use and safety have already been carried out using this continuously growing project material (Kieler *et al.* 2012, Artama *et al.* 2011, Malm *et al.* 2011, Malm *et al.* 2005). Data from births and terminations of pregnancy have been gathered since Jan 1st 1996 and are currently available until Dec 31st 2010 for study purposes. In that project, the Medical Birth Register, the Abortion Register, the National Register of Congenital Malformations, and the Prescription Register, including also the Special Refund Entitlement Register, have been linked by the personal identification number (PIN) assigned to all citizens and permanent residents (Artama *et al*. 2011). In this study we use a cohort study design and include i) births (the Medical Birth Register and the National Register of Congenital Malformations), and ii) fetuses from ETOPFAs (the National Register of Congenital Mal-

formations). Women and their offspring exposed to second generation antipsychotics and the non-exposed controls will be collected from this database.

Description of the registers included in the study

The national Medical Birth Register was established in 1987 and is maintained by the National Institute for Health and Welfare (THL) (THL 2013*a*). This computerized register collects data on maternal demographic characteristics, medical history including reproductive history, smoking, diagnoses during pregnancy and delivery, and neonatal outcome data up to six days' age. Data in the MBR includes all live births and stillbirths with gestational age of 22 weeks or more or birth weight of 500 grams or more, and their data are collected in a standard form from all maternity hospitals and include all births, including the occasional homebirths. All infants are examined in the hospital by a paediatrician. 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. Extensive review of the data, including cross-checking with the data from the Finnish Population Register and Cause-of-Death Register at Statistics Finland indicate that the data are virtually complete (THL 2013a; Gissler and Shelley 2002, Teperi 1993).

The national Register of Congenital Malformations, maintained by THL, receives comprehensive data on MCAs including live births, stillbirths and ETOPFAs, all with at least one detected major congenital anomaly including major structural anomalies, chromosomal defects, teratomas and congenital hypothyroidism, classified and coded according to the extended 9th version of the ICD classification. Minor anomalies are excluded principally according

to the exclusion list of the European Surveillance of Congenital Anomalies, EUROCAT (www.eurocat-network.eu). Data are collected from hospitals, health-care professionals and cytogenetic laboratories as well as from the Medical Birth Register, the Register of Induced Abortions, the Register of Visual Impairment and the Care Register for Health Care (including Information on Outpatient Services in Specialised Health Care), all maintained by THL, as well as from the National Supervisory Authority for Welfare and Health (Valvira) and from the Cause of Death Statistics maintained by Statistics Finland. Diagnoses obtained from these data sources are confirmed by contacting the hospitals concerned. Although the register mainly collects data from the first year of the child's life, it also includes subsequently detected congenital anomalies. The validity of the RCM is considered good and has been ascertained in several studies (Leoncini *et al.* 2010, Pakkasjärvi *et al.* 2006, THL 2013*b*).

The Prescription Register is maintained by the Social Insurance Institution in Finland (Kela) since 1995. The register contains data on 99% of reimbursed prescription drug purchases (Finnish Statistics on Medicines, 2010). Prescription-only medicines 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 three months at a time. Data in the register include the date of the purchase, the International Anatomic-Therapeutic-Chemical (ATC) classification code indicating the generic name of the drug and the dose prescribed. Over-the-counter drugs or medications given to institutionalized persons are not included in the register (Kela 2012). Kela also maintains the Special Refund Entitlement Register since 1964 with data on patients holding entitlement for higher reimbursement for several chronic illnesses requiring continuous drug treatment. The entitlement for special reimburse-

ment has to be shown by doctor's certificate and the register includes information about indications for prescription.

Definition of exposed and unexposed cohorts

Exposed. The definition of exposure includes pregnancies where the woman has purchased second generation antipsychotics (4^{th} level ATC code N05AE, N05AH, N05AL, N05AX) at any time during pregnancy and/ or one month before pregnancy. Major congenital anomalies will be analyzed in the cohort with purchase(s) during one month prior to pregnancy or during the first trimester (Table 1). The beginning of pregnancy has been calculated from the best clinical estimation of gestational age at birth (primarily based on ultrasound) as registered in the MBR. Length and timing of exposure is defined by evaluating second generation antipsychotic use during different trimesters. The length of pregnancy is divided into first (days 0 - 84 after last menstrual period), second (days 85 - 182), and third trimester (days 183 until birth). With the annual rate of 55,000 - 60,000 births and the average annual rate of 260 ETOPFAs during years 1996-2010, the total Drugs and Pregnancy database counts up to nearly 880,000 pregnancies (872,036 live births, 3,126 stillbirths and 3,886 ETOPFAs). In Finland, 0.3% of pregnant women have a diagnosis of psychosis as a chronic disease (Artama et al. 2011). As several of the second generation antipsychotics have only been introduced recently to the market, we expect to include 1,300 – 1,500 pregnancies exposed to second generation antipsychotics at some stage of pregnancy.

We will perform subanalyses including only women with $\geq$2 second generation antipsychotic drug purchases to confirm exposure. Further, we will perform subanalyses to assess the effects of chronic exposure (second generation antipsychotic drug purchases in each trimester) on perinatal outcome (Table 1).

The two *unexposed reference groups* consist of:

- 1. All pregnant women and their offspring not exposed to second generation antipsychotics during pregnancy and three months before pregnancy, but exposed to first generation antipsychotics (ATC codes N05AA, N05AB, N05AC, N05AD, N05AF) at any time during the period of three months before pregnancy until the end of pregnancy. The purpose of this reference group is to control for maternal illness. In Finland, appr, 0.1% - 0.2% of pregnant women use first generation antipsychotics (THL, unpublished statistics) and we expect to include appr. 1,000 -1,500 women in this group. Because first generation antipsychotics are often used in small doses for nausea and vomiting in pregnancy, we will perform subanalyses including only women with entitlement to special reimbursement due to severe psychotic or other severe mental disorder in the exposed and in this reference group.
- 2. Pregnant women and their offspring unexposed to second generation antipsychotics during the period of three months prior to pregnancy until the end of pregnancy. This reference group is exclusive from the first reference group and serves as the background population reference group. Referents in this group are matched for year of birth of child (+/- 1month) and will be randomly selected as 5 referents for one exposed (5:1).

Definition of outcomes

1. Major congenital anomalies. These analyses include all pregnancies ending in birth or ETOPFA (Table 1).
2. Pregnancy complications, in all pregnancies ending in delivery and including
    - multiple pregnancy
    - gestational diabetes

- gestational hypertension
- breech presentation
- mode of delivery (instrumental delivery or Caesarean section)
- diagnosis of shoulder dystocia

3. Perinatal complications are analysed in singleton pregnancies ending in birth and include (Table 2):
    - preterm birth (< 37 gestational weeks)
    - moderately preterm birth (<32 gestational weeks)
    - low birth weight (< 2,500 g)
    - very low birth weight (<1,500g)
    - small for gestational age (according to age specific national standards, Sankilampi et al. 2013)
    - large for gestational age (according to age specific national standards, Sankilampi et al. 2013)
    - perinatal death
4. Neonatal outcomes are analysed in singleton, full-term live born infants and include
    - low Apgar score
    - hypoxia (umbilical artery pH < 7.20)
    - need for respirator treatment
    - need for treatment in neonatal (intensive) care unit
    - need for care outside home at the age of one week (Table 2).

The comparisons between exposure groups will be made according to timing of gestational exposure (Table 1).

Covariates and possible confounders to be considered for adjustment in the analyses are presented in Table 3. Pregnancies in women with psychiatric diagnosis are high risk pregnancies due to greater consumption of psychotropic drugs in general as well as smoking and alcohol use. Data on prescribed psychotropic drug use are virtually complete, while data on smoking are missing in 3% of the study material (Table 3). Alcohol use is not routinely collected in any of the registers and data on alcohol use are only available occasionally and therefore cannot be included in analyses. Data on alcohol exposure are available in the Register of Congenital Malformations for all cases with a diagnosis of fetal alcohol spectrum defects.

Statistical analyses

All data are anonymized and coded prior to statistical analysis. The prevalence of specific outcomes is compared between exposed and unexposed pregnant women and their offspring. Univariate analyses are used to study demographic differences between the study cohorts, and logistic regression to assess the association between second generation antipsychotic use during pregnancy and MCAs and other perinatal outcomes. In subanalyses, exposed women will be stratified according to entitlement to special reimbursement due to severe psychiatric disorder. Covariates will be tested using a P -value of < 0.1 to detect associations with exposure and outcome. If associated with both exposure and outcome, the covariate will be included as a true confounder in the analysis. With 1,300 exposed births and fetuses from ETOPFAs, the study has a 87.9% power to detect a 60% relative increase (1.8% absolute increase) in the prevalence of MCAs presuming a baseline prevalence of 3% in the control cohort (alpha = 0.05, two-sided), and for perinatal complications that have a prevalence of 6% (as preterm birth) we have a 87.4% power to detect a 40% relative risk increase (2.4% absolute risk increase).

Study timelines

This study has been registered in the ENCePP Register of Studies. Data extraction will start on November 30th[t], 2013 and end by February 2014. Analyses of data will start during spring 2014, and an interim report of preliminary results is to be expected during fall 2014. Final results and manuscript for submission in an international, peer-reviewed scientific journal are expected during 2015.

Approval

The utilization of sensitive health register data for scientific research and the data linkages in the 'Medicines and Pregnancy' -project has been approved by the register administrators and the national data protection authority. Since the study subjects are not contacted, according to the Finnish legislation informed consent is not required.

Implications of the study

Using national, population-based register data for 15 years enables us to have a large enough material to obtain a reasonable number of exposed pregnancies for studying rare outcomes, such as major congenital anomalies. The quality and coverage of the registers included in the study material are considered excellent. Register-based studies are free of recall bias but limitations include to possible bias of drug compliance. However, non-compliance is likely to occur with short-term drug therapies and for fear of teratogenicity, while drug therapies for treating chronic diseases, including antipsychotics, are usually not given up during pregnancy (Malm *et al.* 2003). This study will provide epidemiologic evidence on the safety of second generation antipsychotics on pregnancy outcome, including major congenital anomalies, pregnancy complications and perinatal outcomes. As the use of second generation antipsychotics for different indications has been increasing, the results will have important implica-

tions for pregnant women with psychiatric disorders needing drug treatment, and for prescribing practices for clinicians who treat these pregnant women.

Data protection and storage

The Drugs and Pregnancy database contains anonymized data, maintained in the THL in locked-up location and accessible only to researchers with permission and guarded by institutional and personal passwords. The research data extracted from this database are similarly secured and accessible only for persons with researcher status in the THL. The research data will be stored in this location for 10 years.

Possible amendments and deviations

Thorough reasons will be given for possible amendments and deviations from the research protocol and, if realized, will be documented and made publicly available in the ENCePP forum.

Independent review of study results

According to the national data protection legislation, the research data are available only for those researchers who have applied for and granted permission to data access. In case of a justified reason for outside review, permission to check the data can be applied from the National Institute for Health and Welfare.

Communication of results to regulatory authorities

The study results are communicated at each phase of analyses directly to the representative of the Finnish National Medicines Agency, a member of the study group (M-L N).

Author contribution

All authors have contributed substantially to the planning and writing of the study protocol.

Review of the literature

First trimester exposure and MCAs

Clozapine. Animal studies have not demonstrated an increased risk of birth defects with clozapine. The manufacturer database includes over 500 exposed pregnancies without a suggestion of an increased rate in congenital anomalies (Einarson and Boskovic 2009). Further, data based on the Swedish Medical Birth Register included nearly 20 exposed pregnancies, among them one MCA (ectopic anus) (Reis and Källen 2008). A small prospective study with 6 exposed pregnancies indicated no specific risks (McKenna *et al.* 2005). There are also several individual case reports with successful use of clozapine during the first trimester or throughout pregnancy (Duran *et al.* 2008, Gupta and Grover 2004, Karakula *et al.* 2004, Mendekhar 2003, Yogev *et al.* 2002), In one case report, neonatal outcome was normal but speech delay was suspected to be associated with prenatal exposure to clozapine (Mendekhar *et al.* 2007).

Olanzapine. Animal studies have not demonstrated an increased risk of MCAs with olanzapine. The Swedish Medical Birth Register data included 80 exposed pregnancies with three MCAs (craniocynostosis and ureteral reflux, limb reduction defect, and ventricular septal defect with undefined upper alimentary tract anomaly) (Reis and Källen 2008). The diversity of MCAs observed in that study is not suggestive of a causal association. A prospective follow-up study reported 60 first trimester exposures including one infant with cleft lip and encephalocele (McKenna *et al*. 2005). The manufacturer has reported nearly 150 olanzapine-exposed pregnancies with prospective follow up and no increased risk (Einarson and Boskovic 2009). There are also several case reports reporting normal infant outcomes after olanzapine exposure during the first trimester (Aichorn *et al*. 2008, Malek-Ahmadi 2001, Neumann and Frasch 2001, Kirchheiner *et al.* 2000, Lim 2001), but also one case report with cardiac and musculoskeletal birth defects (Yesayahu 2007) and one with meningocele (Arora and Praharaj 2005).

Quetiapine. Animal studies have not demonstrated an increased risk of MCAs. The manufacturer's database includes nearly 300 pregnancies with known outcome, but including also retrospective cases. Among the 14 reports of offspring with congenital anomalies, no pattern of defects was seen and no increased risk was suspected based on that material (Einarson and Boskovic 2009). The Swedish Medical Birth Register includes 41 exposed infants, including one with gastroschisis and one with an undefined oral cavity malformation (www.janusinfo.se). Further, a prospective study including follow up of 36 quetiapine-exposed pregnancies observed no cases with congenital anomaly among the exposed offspring (McKenna *et al.* 2005). There are also individual case reports of first trimester exposure with normal outcome (Rampono *et al.* 2007, Gentile 2006, Tenyi *et al.* 2002).

Risperidone. Animal studies have not observed teratogenicity. No increased risk of MCAs was observed in a prospective study based on teratology information services' follow-up data and including 49 exposed pregnancies (McKenna *et al.* 2005). The manufacturer has data on 68 prospectively collected pregnancies with known outcome with no indication of elevated risk (Coppola *et al.* 2007). The Swedish Medical Birth Register includes 82 early exposures with three infants with different congenital anomalies (pes equinovarus, polydactyly, ventricular septal defect) and no pattern to suggest a causal relationship (www.janusinfo.se). Individual case reports have also been published with normal outcome (Mendekhar and Lohia 2008, Rodriguez-Salgado 2008).

While there are no data suggesting a major teratogenic risk associated with clozapine, olanzapine, quetiapine or risperidone use, the limited experience related to first trimester use does not allow reliable risk evaluation.

Ziprasidone. Animal studies have demonstrated a decrease in fetal viability in rats and possible teratogenic effects at ziprasidone doses corresponding to human therapeutic doses. Little information in humans is available. The manufacturer has collected data on nearly 60 exposed cases with known outcome, including one case with unspecified congenital anomaly (Einarson and Boskovic 2009). Three infants exposed in early pregnancy with no congenital anomalies have been collected in the Swedish Medical Birth Register (www.janusinfo.se), and single case reports with normal outcome have been published (Werremeyer 2009). Additionally, one infant with cleft palate has been described (Peitl *et al.* 2010).

Sulpiride. While animal studies have not suggested teratogenicity, human reports on sulpidire exposed pregnancies are lacking.

Aripiprazole. Animal studies have demonstrated possible teratogenic effects presented as increased rates of diaphragmatic hernia in offspring of treated pregnant rats. Human experience on first trimester exposure is limited on 19 cases reported in the Swedish Medical Birth Register, including one infant with congenital anomaly (oral cleft) (www.janusinfo.se), and two case reports with normal outcome (Lutz *et al*. 2010, Mendekhar *et al*. 2006).

Paliperidone. Paliperidone is the active metabolite of risperidone and therefore probably comparable to risperidone in terms of teratogenicity. Experimental animal studies have not suggested teratogenic potential with paliperidone. No data on human pregnancy exposure has been published.

Pregnancy complications and perinatal outcome

Caesarean section is more common in women using antipsychotics than in non-users (Reis and Källen 2008). This may partly be due to the overall health status of antipsychotic users and associated pregnancy complications. Second generation antipsychotic use is known to be associated with weight gain, possibly mediated by increased insulin resistance. This is most evident for clozapine, olanzapine and risperidone (Simon *et al.* 2010, Henderson and Doraiswamy 2008). High blood sugar levels in early pregnancy increase the risk for MCAs and obesity per se has been associated with an increased risk for neural tube defects (Dixit and Girling 2008). Individual case reports have described second generation antipsychotic use during pregnancy and gestational diabetes, but large studies are lacking. Pre-pregnancy and gestational diabetes increase the risk for being large for gestational age, predisposing to peri- and neonatal complications including shoulder dystocia and asphyxia. One study based on small numbers (n=25) observed an increased risk for being born large for gestational age when compared to infants exposed prenatally to first generation antipsychotics or those not exposed to antipsychotics (Newham *et al.* 2008). Obesity may further predispose to gestational hypertension.

Use of the second generation antipsychotic by the mother has not been associated with an increased risk for preterm birth (Lin *et al.* 2010) but data are few. One prospective cohort study including 150 pregnancies observed a small increased risk for low birth weight but this difference was not statistically significant (McKenna *et al.* 2005).

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Table 1. Definition of exposed and unexposed cohorts.

Outcome	Study material	‡Exposure	‡Unexposed reference group (1)	‡Unexposed reference group (2)
Major congenital anomalies	All births and elective terminations of pregnancy for major fetal anomaly	Second generation antipsychotic drug purchase(s) during one month before pregnancy and/ or during first trimester -analyses on individual drug level (ATC code level 5) -subanalyses including women with purchases during the first *and* second trimester to confirm exposure -stratified analyses including women with entitlement to special reimbursement due to severe psychotic or other severe mental disorder	No second generation antipsychotic drug purchases during three months before pregnancy and during pregnancy but one or more first generation antipsychotic drug purchase(s) during three months before pregnancy or during pregnancy	No second generation antipsychotic drug purchase(s) during three months before pregnancy or during pregnancy ('general controls') -collected exclusively from Comparison cohort (1)
Pregnancy outcome	All pregnancies ending in birth	One or more purchases of second generation antipsychotic drugs during the period of one month before pregnancy or during pregnancy; analyses on drug group level (ATC code level 3)		
Perinatal outcome	All pregnancies ending in birth			

	-Subanalyses including only singleton births	-subanalyses including women with ≥2 purchases to confirm exposure -subanalyses including women with purchases in each trimester to assess the effects of chronic exposure
Neonatal outcome	All pregnancies ending in *live* birth -Subanalyses including only singleton births	-stratified analyses including women with entitlement to special reimbursement due to severe psychotic or other severe mental disorder

Table 2. Outcome variables.

Major congenital anomalies	Analyses of malformations according to the EUROCAT subgroups
Pregnancy complications	Multiple pregnancy Gestational diabetes Gestational hypertension Breech presentation Mode of delivery Diagnosis of shoulder dystocia
Perinatal outcome	Preterm birth < 37 gestational weeks Moderately preterm birth < 32 gestational weeks Low birth weight (< 2,500g) Very low birth weight (<1,500g) Small for gestational age Large for gestational age Perinatal death
Neonatal outcome	Apgar score 1 minute (≤6; >6) 5 minute (<7; ≥7) Need for respirator treatment Need for treatment in neonatal (intensive) care unit Hypoxia (umbilical arterial pH < 7.20) Need for hospitalization at the age of 7 days

Table 3. Covariates to be tested

Covariate	**Availability in register data**
Year of birth of child	Virtually complete
Maternal age at the end of pregnancy (25-29 = ref/ <25 or ≥30)	Virtually complete
Parity (one or more previous deliveries = ref/ no previous deliveries)	Virtually complete
Marital status (married or co-habiting = ref/ single)	95%
Smoking (no = ref/ yes)	97%
Socio-economic status based on maternal occupation at birth (upper white collar = ref/ lower white collar/ blue collar/ other)	82%
Exposure to drugs, including other psychiatric drugs, antiepileptics, and other suspected or established teratogens (no = ref/ yes)	Virtually complete
Entitlement to special reimbursement due to pre-pregnancy diabetes (no = ref/ yes)	Virtually complete
Entitlement to special reimbursement due to other chronic disease than psychosis or pre-pregnancy diabetes (no = ref/ yes)	Virtually complete