**First trimester exposure to methylphenidate:   
a population based cohort study**

Study Protocol

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**Introduction**

[New version pending!]

**Method**

The analysis was constructed as a controlled cohort-study, using the single pregnancy as the unit of analysis. We compared the prevalence proportion of malformations in a cohort of pregnancies exposed to MPH in the first trimester to a cohort of pregnancies where the mother had never used any psychostimulant.

We used data from four Danish nationwide registries: the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry and the Danish Civil Registration System. Virtually all medical care in Denmark is furnished by the public health authorities, whereby these data resources allow true population-based studies, covering all inhabitants of Denmark.

Data was obtained for the period of 1 January 1995 to 31 December 2012.

**Registries**

The Danish National Patient Register (1) contains data on all hospitalizations in Denmark since 1977 and out-patient visits since 1995. Discharge diagnoses are coded according to ICD-10 since 1994. Virtually all medical care in Denmark is furnished by the national health authorities, whereby this data resource allows true population-based studies, covering all inhabitants of Denmark.

The Medical Birth Registry (2) contains information on all pregnancies in Denmark, both hospital- and homebirths. Information stored in the registry include basic data on the children (gestational age, weight, height, apgar score, referral to neonatal care unit etc.), complications and procedures performed during the delivery. Until 1997 data were collected through birth reports sent to the National Board of Health. From 1997 the registry is primarily based on the Danish National Patient Registry, but supplied with birth reports on home births and stillborn children.

The Danish National Prescription Registry (3) contains data on all prescription drugs redeemed by in Denmark since 1995. Prescription data includes the date of dispensing, the substance, brand name, and quantity. The dosing information and the indication for prescribing are not recorded. Drugs are categorized according to the Anatomic Therapeutic Chemical code, a hierarchical classification system developed by the WHO for purposes of drug use statistics WHO (4).

The Danish Civil Registration System (5) contains data on vital status (date of death) and migration to and from Denmark, which served as census data.

All data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish residents since 1968 that encodes gender and date of birth. All linkage was performed anonymously within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes (6;7).

**Pregnancies**

Pregnancies were identified using the Medical Birth Registry. As this registry only includes pregnancies resulting in births, either stillborn or live born, pregnancies terminated prior to birth, i.e. both spontaneous and elective abortions, were not included in our material. As malformations are incompletely registered in stillborn children, we only included pregnancies resulting in live births (the infant survived ≥1 day).

Exploratory analysis showed that maternal use of MPH was very rare (one subject) prior to 1 January 2005. Also, we required at least six months of follow-up for the child after birth, to be able to assess malformations that were not detected at birth. Therefore we only included pregnancies terminated after 1 January 2005 and before 1 July 2012.

To be able to assess drug exposure, we defined a period corresponding to the first trimester for each pregnancy. We did so using information from the Danish Birth Registry: We took the date of termination of the pregnancy and subtracted the gestational age at termination as estimated in the registry. The resulting date estimates the date of the end of the last menstruation. We therefore defined the first trimester as an interval from the 15th day to the 84th day from this date.

We excluded multiple pregnancies, pregnancies where the mother migrated to or from Denmark within five years prior to the initiation of the pregnancy or where the child migrated from Denmark within the six months after being born. Furthermore, we excluded pregnancies where the mother had used certain drugs that are rarely used but known to be highly teratogenic. These drugs were vitamin K-antagonists (B01AA), tetracyclines (J01AA), ACE-inhibitors (C09A and C09B), retinoids (D05BB, D10AD and D10BA) and selected antiepileptic drugs: carbamazepine (N03AF01), oxcarbazepine (N03AF02), phenytoin (N03AB02), valproic acid (N03AG01) and phenobarbital (N03AA02) (8). Use of these drugs was defined as having redeemed a prescription within a time window defined as 180 days prior to the first trimester up to the end of the pregnancy.

**Cohorts**

To be included in the exposed cohort, consisting of pregnancies exposed to MPH in the first trimester, the mother was required to redeem one or more prescriptions for MPH (ATC, N06BA04) within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester.

The unexposed cohort included pregnancies where the mother had never redeemed any prescription for any psychostimulant (ATC, N06BA) at any time point prior to the end of the pregnancy.

Using the above definitions, some pregnancies failed to be included in either cohort. This was intentional, as to avoid bias from misclassification, and was subject to sensitivity analyses (see below).

**Matching**

The limiting factor in terms of statistical precision would be the number of first-trimester exposed women. From preliminary analyses of age-specific MPH user prevalences and age specific birth rates, we had calculated the expected number of exposed women to be in the order of 400. As the expected number of outcomes therefore would be low, we chose to analyze the data by use of propensity scores (PS) (9), which estimates the likelihood of being treated similarly to those entering the exposed cohort.

For each pregnancy in the exposed cohort, we matched 10 pregnancies from the unexposed cohort. We used sequential balanced nearest-neighbor matching (10) to match exposed and unexposed on propensity score (max caliper 0.01). In brief, this ensures that for each exposed subject, half of the matched unexposed have PS above the index subject and half will have a PS below.

The following variables were included in the calculation of the propensity score: Maternal age, maternal smoking status during first trimester, maternal body mass index (BMI) (≈5% missing values handled by imputation of mean value), calendar year of termination of pregnancy, length of education (grouped into 7-10 years, 11-12 years, ≥13 years and unknown) and concomitant use of each of the following drugs: Antipsychotics (N05A), antidepressants (N06A), antiepileptics (N03A), anxiolytics (N05B), and NSAIDs (M01A excluding M01AX). Concomitant use of these drugs was defined as one or more prescriptions for the given drug within 40 days before the beginning of the first trimester up to the end of the first trimester.

**Endpoints**

The two study endpoints were major malformations and major cardiac malformations respectively. Classification of malformations happened according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system guide 1.3 (11).

Furthermore, we calculated the mean gestational age and birth weight of live births.

**Analysis**

Our main outcome measure was the prevalence proportion ratio (PPR), equivalent to the risk ratio, for major malformations and major cardiac malformations comparing the exposed to the unexposed pregnancies.

We furthermore applied a range of supplementary/sensitivity analyses.

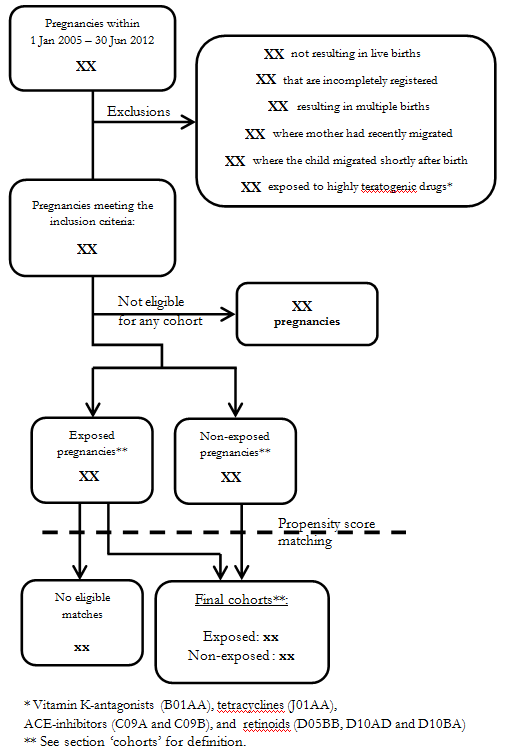
Firstly, we performed subgroup analyses, stratifying by maternal age and by excluding pregnancies with concomitant use of other psychostimulants than MPH (ATC, N06BA) or any of the abovementioned confounder drugs.

Secondly, we changed the eligibility criteria for entering the unexposed cohort from never-use to previous use of MPH. This was defined as having redeemed two or more prescriptions for MPH prior to 180 days before the beginning of the first trimester, but no prescriptions for any psychostimulant (ATC, N06BA) within a time window defined as 180 days before the beginning of the first trimester up to the end of the pregnancy. In this analysis, we only matched exposed to unexposed in a ratio of 1:1.

Lastly, we applied alternative criteria to define pregnancies that entered the exposed cohort: A) A more restrictive criteria, requiring one or more prescriptions within the first trimester, and B) a less restrictive criteria, requiring one or more prescriptions for MPH within 40 days before the beginning of the first trimester up to the end of the first trimester.

**Figures**

**Figure 1: Flowchart over included pregnancies**

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**Tables**

**Table 1: Basic characteristics of included pregnancies.**

|  |  |  |
| --- | --- | --- |
|  | **Exposed** | **Unexposed** |
|  | **(n=)** | **(n=)** |
| Maternal age, median (IQR) |  |  |
| Maternal BMI, median (IQR) \* |  |  |
| Maternal smoking status |  |  |
| Yes |  |  |
| No |  |  |
| Unknown |  |  |
| Maternal length of education |  |  |
| 7-10 years |  |  |
| 11-12 years |  |  |
| ≥13 years |  |  |
| Unkown |  |  |
| Drug exposure\*\* |  |  |
| Antipsychotics |  |  |
| Antidepressants |  |  |
| Anxiolytics |  |  |
| NSAIDs |  |  |
| Gestational age at birth, mean (CI) |  |  |
| Birth weight, mean (CI) |  |  |
| Low Apgar score\*\*\* |  |  |
| Endpoints |  |  |
| Major malformations |  |  |
| Cardiac malformations |  |  |
| IQR = Interquartile range; CI = confidence interval  \* xx (xx%) missing values.  \*\* Defined as having redeemed ≥1 prescription within 40 days prior  to the first trimester up to the end of the first trimester  \*\*\* Defined as Apgar < 7 after 5 min | | |

**Table 2: Fetal outcomes and Prevalence Proportion Rates (PPR)   
comparing the exposed to the unexposed cohort, overall and by subgroup.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Sub-group** | **Exposed**  Events / no. pregnancies | **Unexposed**  Events / no. pregnancies | **PPR (95% CI)** |
| All |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| Maternal age < 30 |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| Maternal age ≥ 30 |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| No use of confounding drugs\* |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| \* Atomoxetine (ATC, N06BA09), Modafinil (N06BA07), Dexamphetamine (N06BA02), Antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and NSAIDs (M01A excluding M01AX). | | | |

**Table 3: Sensitivity analyses**

|  |  |  |  |
| --- | --- | --- | --- |
| **Sensitivity analysis** | **Exposed**  Events / no. pregnancies | **Unexposed**  Events / no. pregnancies | **PPR (95% CI)** |
| Comparing to previous users |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| More restrictive entry criteria |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
| Less restrictive entry criteria |  |  |  |
| Major malformations |  |  |  |
| Cardiac malformatios |  |  |  |
|  | | | |

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