

First Trimester *In Utero* Exposure to Methylphenidate

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Abstract: Methylphenidate is a centrally acting sympathomimetic used for the treatment of attention deficit/hyperactivity disorder in children and adolescents and for narcolepsy in adults. Despite the growing use among adult women, no reliable data on the prevalence of use during pregnancy have been published, and safety during pregnancy has not been established. We systematically reviewed available data on birth outcome after human *in utero* exposure to methylphenidate. Systematic searches in PubMed/Embase were performed from origin to August 2012, and data from Michigan Medicaid recipients, The Collaborative Perinatal Project and the Swedish Birth Registry were evaluated. Excluding three case reports, a total of 180 children exposed to methylphenidate *in utero* during first trimester were identified, among whom, four children with major malformations were observed. Methylphenidate exposure during pregnancy does not appear to be associated with a substantially (i.e. more than two-fold) increased risk of congenital malformations.

Methylphenidate is a centrally acting sympathomimetic used in the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents and against narcolepsy in adults. Methylphenidate is not approved for treatment of ADHD in adults due to lack of data on safety and effect [1]. In Denmark, there are no clinical guidelines on the treatment of adults with ADHD. Nevertheless, methylphenidate is increasingly prescribed to adults, and the number of adults treated with methylphenidate and other centrally acting sympathomimetics for ADHD has increased dramatically during the last 10 years (fig. 1). A recent study characterised the use of ADHD medication in Denmark from 1995 to 2011; methylphenidate accounted for 89% of the prescribed centrally acting sympathomimetics for ADHD [2]. In 2001, about 180 adults aged 20–40 years were prescribed ADHD drug. In 2010, this figure had risen to nearly 10,000 [3]. About half of all ADHD drug users are above 18 years of age corresponding to a prevalence rate by late 2011 of about 0.5%. Among adults, the prevalence rate does not differ significantly between genders, resulting in roughly 25% of ADHD drug users being adult women of the child-bearing age [2]. In general, ADHD is considered to be a persisting disorder, and available data suggest that between 30% and 70% of children with ADHD continue to have symptoms in adulthood [4]. Despite the fact that methylphenidate does not have a United Kingdom marketing authorisation for the treat-

ment of adults with ADHD, the National Institute for Health and Clinical Excellence (NICE) considers methylphenidate the first-line drug in clinical guidelines of the treatment of adults with ADHD [5]. The American Academy of Child and Adolescent Psychiatry has concluded that stimulant medication (including methylphenidate) can be used to treat adults who have been carefully evaluated [6]. Despite the growing use among adult women, no reliable data on the prevalence of use during pregnancy have been published.

The safety of methylphenidate during pregnancy has not been established. Animal studies have shown that methylphenidate is not teratogenic in mice [7,8]. No teratogenic effects were observed in rats, but a dose seven times the maximum recommended human dose (MRHD) caused maternal toxicity and foetal skeletal variations. In rabbits, doses about 40 times the MRHD were teratogenic (increased incidence of spina bifida). The no-effect dose for embryo-foetal development was about 11 times the MRHD [7].

With the steeply increasing use in the fertile age, *in utero* exposure, either as clinically indicated treatment or, more commonly, accidental exposure during unrecognised early pregnancy, is becoming a subject of controversy. We thus present this systematic MiniReview of available data on birth outcome after human *in utero* exposure to methylphenidate.

Methods for Review

PubMed/Embase searches were performed from origin to August 2012, using keywords shown in fig. 2. Retrieved papers were cross-checked for additional references of interest. Additional data on *in ute-*

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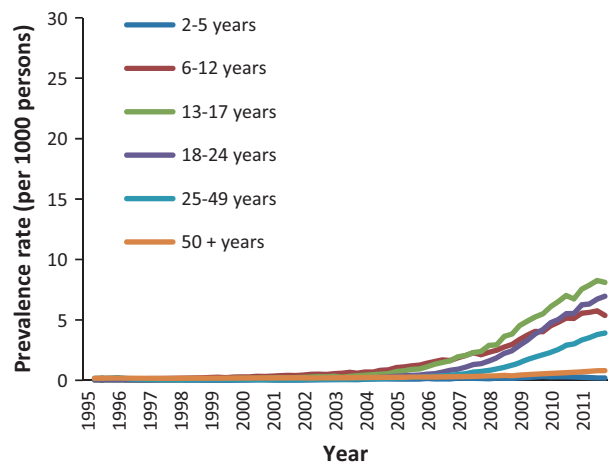


Fig. 1. Prevalence rates of Danish women treated for attention deficit/hyperactivity disorder (prevalence per 1000 persons) per quarter from January 1997 to September 2011, specified by age. Reproduced from [2] with permission.

ro exposure and pregnancy outcome were extracted from other available sources: The Michigan Medicaid Cohort [7], The Swedish Medical Birth Registry [9] and The Danish Ministry of Health (adverse reaction database) [10]. This MiniReview was conducted in accordance with PRISMA guidelines [11].

Results

The results from the literature search and overview of the review process including reasons for exclusion are displayed in fig. 2. A total of 52 potentially relevant references were identified during the database searches and reference screenings. Forty-six studies were excluded after screening of abstracts. Four studies were excluded as they did not contain safety data on methylphenidate during pregnancy, contained no original data or dealt with intravenous abuse of methylphenidate during pregnancy. The study dealing with intravenous abuse examined the effects of intravenous methylphenidate and pentazocine among 38 pregnant women. Among the 39 children (one set of twins), 21% were born prematurely, 31% had growth retardation and 28% had symptoms of withdrawal. The twins had malformations compatible with foetal alcohol syndrome, and major malformations were recorded in two other infants. This study was confounded by the concurrent abuse of cigarettes, alcohol, other drugs and concurrent diseases, and therefore was excluded [12]. Lastly, four papers were identified from the reference lists. Eventually, six articles reporting data from methylphenidate exposure during pregnancy were retrieved for full-text review.

Case Reports

An infant with microtia after *in utero* exposure to methylphenidate from the third to the sixth week of pregnancy was reported in a study from 1962 (using material from the Liverpool abnormalities registry 1962) [13].

Cohort Data

Four cohorts were identified describing birth outcome after *in utero* exposure to methylphenidate (table 1).

Eleven mother–child pairs with first-trimester exposure to methylphenidate were monitored as part of The Collaborative

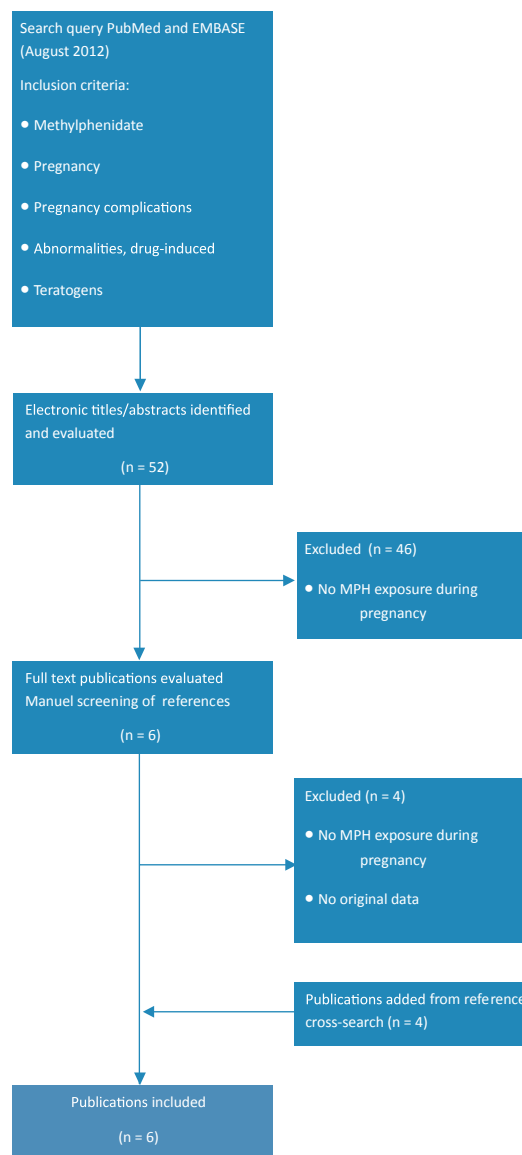


Fig. 2. Selection tree for the literature search.

A case report from 1975 described an infant delivered at 30 weeks' gestation, with multiple limb malformations. The infant had been exposed to haloperidol, methylphenidate and phenytoin during the first 7 weeks of pregnancy. The infant died at 2 hr of age of a subdural haemorrhage [14].

Pregnancy-related adverse effects reported to the Danish Medicines Agency include one congenital malformation (myelomeningocele), three spontaneous abortions, one pre-eclampsia and one unintended pregnancy during administration of an oral contraceptive [15].

Table 1.

Source, exposure and congenital malformations in four cohort studies.

Ref. no.	Country	Source	Years	No. of first trimester exposed	No. of malformations observed	Type of malformations
16	USA	The Collaborative Perinatal Project	1959–1974	11	0	–
7	USA	Michigan Medicaid	1985–1992	13	1	Cardiovascular defect (unspecified)
17	Israel	Israeli Teratology Information Services	2005–2009	52	0	–
18	Sweden	Swedish Birth Registry	1994–2012	104	3	2 ventricular septal defects 1 univentricular heart
Total	–	–	–	180	4	–

Perinatal Project including 50,282 women. The methylphenidate exposure was analysed as a part of 96 pregnancies exposed to ‘other sympathomimetics’, which included 16 different agents. No significant increase in malformations was observed for this group. There were seven children with malformations in the ‘other sympathomimetics’ group, yielding a crude relative risk of 1.13 (95% CI not provided). There is no information on the specific nature of the malformations and which specific medications these seven children had been exposed to [16].

A surveillance study of Michigan Medicaid recipients involving 229,101 pregnancies between 1985 and 1992 reported 13 newborns exposed to methylphenidate during the first trimester of pregnancy. Among these, one major malformation (a cardiac defect) was found [7].

Recently, a prospective comparative cohort study was reported as an abstract [17]. Fifty-four methylphenidate-exposed pregnancies [52/54 (96%) in the first trimester] were followed. The outcome was compared with that of 54 pregnancies who contacted the Israeli Teratology Information Service concerned of exposure to a drug not known to be teratogenic, matched by maternal age, gestational age at initial contact and year. No children with malformations were observed in the cohort exposed to methylphenidate in the first trimester. There were no significant differences in the rate of live-births, miscarriages or elective terminations of pregnancy between the groups. The median gestational age at delivery and birth weight were also comparable.

The latest data from the Swedish Birth Register holds 104 reports on children exposed to methylphenidate *in utero* in early pregnancy. Three children had congenital malformations (2–3 expected). Two children had ventricular septal defects and one child was born with a univentricular heart [18].

Four malformations among 180 exposed children yields a rate of 2.2% with 95% confidence limits of 0.6–5.6% (exact binomial distribution). Assuming a spontaneous malformation rate of 3.5% [19,20], this corresponds to a relative risk of 0.6 with confidence limits of 0.2–1.6.

Comment

A total of 183 children exposed to methylphenidate *in utero* during first trimester were identified, among which seven children with malformations were observed. Excluding case

reports, which do not contribute to a meaningful risk assessment, there were four cohorts totalling 180 first-trimester-exposed pregnancies with a total of four malformations reported. The data quantity and quality of these cohorts, as well as the level of confounder control is unimpressive. In fact, only one of these cohorts has been subject to a peer-reviewed publication process. However, taken at face value, the figures are reassuring; four malformations among 180 first-trimester-exposed children are slightly lower than expected, and the upper limit of the relative risk is below 2. One limitation of this MiniReview is the possibility of publication bias; very small cohort studies with few or no adverse birth outcomes are unlikely to be published. However, such publication bias would have the effect of elevating our risk estimate. As our combined estimate is already low, the possibility of publication bias does not imply a high risk.

In terms of overall safety evaluation, the EMA guidelines suggest that at least 1000 first-trimester-exposed pregnancies should be evaluated with no signs of excess risk before reassuring statements on use during pregnancy may be included in the Summary of Product Characteristics [21]. This is, however, a rather conservative regulatory approach that rarely provides the prescribing physician with meaningful help in terms of clinical decision-making and risk communication.

The more widespread use of methylphenidate in the adult population over the last decade should allow for more comprehensive, valid and generalisable pharmacoepidemiological data to be generated in the near future.

Conclusion

Methylphenidate exposure during pregnancy does not appear to be associated with a substantially (i.e. more than twofold) increased risk of congenital malformations. While to some extent reassuring in a clinical context, the quality and quantity of the available exposure data does not allow for a specific risk assessment.

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