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Methylphenidate use in pregnancy and lactation: a systematic review of evidence

Blanca M. Bolea-Alamanac,[1] Amy Green,[2] Gauri Verma,[3] Penelope Maxwell[4] & Simon J. C. Davies[5]

[1]Academic Unit of Psychiatry, University of Bristol, [2]Avon and Wiltshire Partnership Mental Health Trust, [3]F2 Doctor, University Hospitals Bristol, NHS Foundation Trust, Bristol, UK, [4]Specialist Pharmacist Child and Adolescent Mental Health, John Hunter Hospital, Newcastle, Australia and [5]Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Correspondence
Dr Simon J. C. Davies Assistant Professor, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, CAMH, 1001 Queen Street West, Toronto, ON, Canada M6G 1H4.
Tel.: +1(416) 535 8501
Fax: +1(416) 583 1272
E-mail: simon_davies@camh.net

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AIMS
The aims of this review were to summarize the scientific evidence about the risks of using methylphenidate for ADHD in pregnancy and lactation, to present a case in which interruption of treatment after delivery and during breastfeeding was harmful and to discuss the implications of treating or not treating ADHD in pregnancy and lactation.

METHODS
For the systematic review, databases searched included Pubmed, Psychinfo, Web of Science, Embase, Biosis and Medline.

RESULTS
Three articles were found with a total sample of 41 children exposed to methylphenidate in pregnancy. Malformations reported included congenital heart defects ($n = 2$), finger abnormalities (syndactyly, adactyly and polydactyly $n = 2$) and limb malformations ($n = 1$). Other problems included premature birth, asphyxia and growth retardation. One case report ($n = 1$) and one case series ($n = 3$) were identified regarding exposure to methylphenidate through breast feeding. In all cases, children developed normally and no adverse effects were reported. In our case report we describe an infant exposed to methylphenidate during pregnancy and breast feeding, who developed normally having no detectable congenital abnormalities.

CONCLUSIONS
The number and size of the studies found were small. Identified cases were not representative of the general adult ADHD population having methylphenidate as monotherapy during pregnancy as all the articles reported combinations of methylphenidate with either known teratogenic drugs or drugs of abuse. There is a paucity of data regarding the use of methylphenidate in pregnancy and further studies are required. Although the default medical position is to interrupt any non-essential pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk. Doctors need to evaluate each case carefully before interrupting treatment.

Introduction

Attention deficit and hyperactivity disorder (ADHD) is a clinical syndrome defined in the DSM-IV [1] by high levels of hyperactive, impulsive and inattentive behaviours, beginning in early childhood, persistent over time, pervasive across situations and leading to clinically significant impairments.

ADHD was classically described as a childhood condition. However 15% of children diagnosed with ADHD will still have symptoms by age 25 years and 65% of these will qualify for a diagnosis of ADHD in partial remission [2].

Fayyad *et al*. [3] reported an average prevalence rate of ADHD in adulthood of 3.4% across 10 countries. As awareness increases, more adult patients are being diagnosed with ADHD presenting new challenges for treatment.

Specific issues include treatment of co-morbid psychiatric illness and addiction, treatment in the presence of metabolic disorders (diabetes, obesity) and periods of physiological change (pregnancy and lactation).

Case report

BK is a 21-year-old mother of one (Baby K) and has a diagnosis of ADHD, recurrent depression and borderline personality disorder. She was first diagnosed and treated for ADHD at the age of 12 years. Trials without medication in her late adolescence were unsuccessful.

She was referred to Adult Mental Health Services at age 18 years and presented as anxious and depressed and she had also begun self-harming. BK was referred to the specialist Adult ADHD Service for advice. She responded well to 40 mg fluoxetine daily and continued to take methylphenidate (72 mg day^{-1} of the slow release formulation). During 2 years of regular contact with the ADHD service her mood improved, her self-harming behaviours reduced and her ADHD symptoms appeared well controlled.

When she was 20-years-old, she unexpectedly fell pregnant. This was her first pregnancy.

During the first trimester she continued to take 72 mg day^{-1} of slow release methylphenidate. BK felt that the significant risks of deterioration in her mental health outweighed the risks to the fetus. At week 13 of pregnancy, an informed decision to continue methylphenidate at a lower dose (54 mg day^{-1}) was made by BK and her consultant using updated information from the UK National Teratology Service.

Fluoxetine was reduced at the same time (without down-titrating the dose). Methylphenidate was titrated down to 18 mg 6 weeks before delivery with the plan to stop it completely 1 week before delivery to avoid discontinuation symptoms in the newborn. The last mental health review of the patient took place 1 month before the predicted date of delivery. Baby K was born at 38 weeks by ventouse delivery and weighed 8lb 12oz. His Apgar score was 6 at 1 min, 7 at 5 min and 8 at 10 min, the unusually slow increase being the result of inhaling a small quantity of meconium. He subsequently spent 6 h on the Neonatal Intensive Care Unit for ventilation and observation. There were no further perinatal complications.

BK was not prescribed stimulants during the postpartum period.

Approximately 5 weeks after delivery BK's mental health began to deteriorate. She found it difficult to bond with Baby K and to cope with motherhood. Concerns were raised about her ability to raise the baby and social services became involved. She was diagnosed with post-natal depression and started on 50 mg day^{-1} sertraline which had some benefit in treating her mood symptoms. However, she still expressed symptoms suggestive of ADHD which were resistant to treatment with antidepressants only and had a significant effect on her relationship and ability to care for the child. BK wanted to restart methylphenidate and continue to breastfeed. Following an informed discussion, methylphenidate was titrated slowly up to the pre-conception dose of 72 mg day^{-1}, starting at 10 mg day^{-1} (instant release) and later changed to the slow release preparation.

Baby K was examined by a paediatrician at 14 weeks and was assessed as developing normally with a good temperament and no feeding difficulties. Further medical reviews (6 months and 1 year) did not reveal any developmental problems in the child. No concerns were raised either by the health visitor or family doctor. In samples taken to ascertain methylphenidate exposure after different dosages, no methylphenidate was detected in either maternal milk or Baby K's blood. Regular psychiatric review established that BK's mood stabilized. At the time of the last review (2 years after delivery) BK had developed into an engaged and responsive mother who had bonded well with her child.

Pharmacokinetics and pharmacodynamics of methylphenidate in pregnancy

Methylphenidate, a stimulant drug derived from the amphetamine family is effective for the treatment of ADHD [4, 5], and is considered first line treatment for ADHD in the adult in European practice. Once in solution methylphenidate is rapidly and extensively absorbed from the small intestine and colon [6]. The main factor controlling absorption from immediate release preparations is probably gastric emptying time, whereas for slow release preparations it is the programmed drug release and solution pattern [7]. Prolongation of gastric emptying during pregnancy, could increase the time to peak plasma dose for the immediate release form. Methylphenidate is metabolized through esterification by gut enzymes. P450 enzymes have a minimal metabolizing role [8] and therefore increased activity of these enzymes in pregnancy is unlikely to cause any effect on methylphenidate plasma concentration. The drug is rapidly eliminated as ritalinic acid (alpha-phenylpiperidine acetic acid) in the urine [6, 9, 10] resulting in little or no accumulation of the active compound. Changes in volume of distribution during pregnancy may affect therapeutic effects of methylphenidate, and adjustment of dose may be necessary depending on clinical response. Animal studies have established that amphetamines are transferred across the placenta [11, 12] but there is no supporting human data concerning methylphenidate, which is a derivative of this family. Drugs that are more likely to

cross the placenta are not protein bound, have a molecular weight of less than 500 Daltons (Da), have a long half-life, are lipid soluble and weak acids [13]. Methylphenidate exhibits low plasma protein binding (approximately 15%) and, has a molecular weight of only 269.8 Da, but it has a short half-life (1.4–4.2 h) and is freely soluble in water. Overall the chemical characteristics of methylphenidate suggest some possibility that it may be able to cross the materno-fetal barrier and reach the fetal circulation.

Studies in animals (rats and rabbits) have shown a decrease in gestational weight of mothers exposed to methylphenidate. A low teratogenicity risk was found for rabbits and no teratogenic toxicity was observed in rats [14].

The neurobiology of ADHD is largely unknown. It is hypothesized that adults with ADHD have low tonic firing of dopamine and norepinephrine neurons particularly in the prefrontal cortex. Methylphenidate, acting as a re-uptake blocker of dopamine and norepinephrine, increases the bioavailability of these amines in the synaptic cleft, reducing the core symptoms of ADHD. Whether it has this effect in the developing brain is unknown.

Lactation and methylphenidate

Drug concentration in breast milk, and therefore its potential effect on the newborn, depends on maternal dosage, rate of absorption into the maternal circulation, maternal drug metabolism [15] and time from drug administration to breastfeeding. Methylphenidate's solubility and low molecular weight allow it to enter breast milk [13]. The relative infant dose (the ratio of the amount of drug ingested by the baby compared with the maternal dose) is 0.7% [16], suggesting little infant exposure via breast milk. Relative infant doses below 10% are considered safe in breastfeeding [13].

Systematic review

Methods

A systematic review was performed with the aim of obtaining data about the use of methylphenidate for the treatment of ADHD during pregnancy and lactation. Six medical databases were searched (Pubmed, Psychinfo, Web of Science, Embase, Biosis, Medline). Articles in English, Spanish, French and Italian published in the last 40 years and up to September 2012 were considered. Search terms included methylphenidate, ritalin, Concerta, amphetamine, pregnancy, lactation and other relevant terms (breastfeeding, sympathomimetic, stimulant, ADHD, ADD, hyperkinetic disorder). Mesh terms were also included (desmethylphenidate, ritalin, focalin, metadate, minimal brain dysfunction, hyperkinetic syndrome, etc). Of 73 abstracts identified, 11 fulfilled the review criteria (human studies, use of methylphenidate during pregnancy or/and lactation). Further examination of these articles revealed that five fulfilled the review criteria (three being in pregnancy and two in lactation). All articles were hand searched for additional studies. Studies were evaluated according to the Oxford Centre of Evidence Based Medicine levels of evidence criteria [17] and rated by three independent clinicians. Written consent was obtained from the patient to report the case in a scientific journal. The search strategy and systematic review protocol can be obtained by writing to the authors.

Results

Methylphenidate in pregnancy

No case control or cohort studies were found. Two case reports and a case series were identified (Table 1). The case series [18] described a sample of 38 mothers who were abusing methylphenidate and i.v pentazocine during pregnancy. There were increased rates of prematurity and growth retardation, and almost one third of the children had withdrawal symptoms at birth. Two congenital anomalies were found, polydactyly and a heart septal defect. Twenty-two of these children underwent cognitive testing 1 year after birth, three exhibited borderline normal development while the rest were within the normal range. The two case reports [19, 20] also involved exposure to methylphenidate with other drugs. Kopelman *et al*. described a case of a fetus exposed to prescribed haloperidol, phenytoin and methylphenidate having severe limb malformations (adactyly, syndactyly and deformed radius) and aortic valve defects [19]. In the report by Lundquest *et al*. the fetus was exposed to methylphenidate and pentazocine i.v, dextropropoxyphene and paracetamol in the context of drug misuse [20]. No malformations were found but the child suffered narcotic syndrome and asphyxia at birth. The mother died from pulmonary hypertension at delivery. This was the only case in which maternal outcomes were reported.

In our case, the child developed normally and no congenital malformations or other abnormalities were detected.

Lactation

Two articles were identified regarding exposure to Methylphenidate through breast feeding [16, 21] (Table 2). A case series ($n = 3$) and a case report ($n = 1$). In all cases, children were developing normally and no adverse effects were found. The relative infant doses were below the recommended <10%: 0.6%, 0.7% (no data on relative infant dose of the third infant was reported) and 0.16% respectively. In one case report the child was only breastfed sporadically [21], and in the other breastfeeding was combined with solid food [16]. No information was provided in the case series about frequency of breastfeeding. All four

Table 1

Summary of clinical studies of methylphenidate in pregnancy classified according to level of evidence (LOE)

Authors	LOE	Study type	*n*	Exposure	Dose	Summary
Kopelman *et al.* 1975 [19]	5	Case report	1	Haloperidol, phenytoin and methylphenidate	Methylphenidate 30 mg daily, haloperidol 15 mg daily, phenytoin 300 mg daily.	Syndactyly in hands, adactyly in one foot, deformed radius and aortic valve malformation. No information provided about maternal outcome.
Lundquest *et al.* 1987 [20]	5	Case report	1	Methylphenidate and pentazocine i.v, propoxyphene and paracetamol (route unknown)	Blood toxicology: methylphenidate 20 mg oral dose equivalent, pentazocine 5 ng ml^{-1}, propoxyphene 0.49 μg ml^{-1}/	Born with severe birth asphyxia and withdrawal syndrome. Mother died from pulmonary hypertension at delivery
Debooy *et al.* 1993 [18]	4	Case series	39	Methylphenidate and pentazocine i.v.	Unknown	21% premature, 31% growth retardation, 28% withdrawal syndrome.1 polydactyly, 1 congenital septal defect in heart. No information provided about maternal outcomes.

Table 2

Summaryof studies about methylphenidate and breastfeeding

Author	Study type	*n*	Exposure	Summary	LOE
Spigset *et al.* 2007 [21]	Case report	1	Methylphenidate instant release 15 mg daily	No adverse effects found in infant	5
Hackett *et al.* 2005 [16]	Case series	3	Methylphenidate 35–80 mg daily	No adverse effects found in infants	4

mothers were prescribed methylphenidate for therapeutic reasons narcolepsy ($n = 1$) and ADHD ($n = 3$). In one ADHD case, the mother omitted medication at weekends. In another the mother was taking a low dose of the instant release tablet (15 mg daily). No information was given regarding formulation in the other cases. Time of feeding was an important factor on the infant exposure. No traces of the drug were found at 5 h after administration of the first maternal dose in one of the infants, and again methylphenidate serum concentrations were undetectable on the first feed of the morning, suggesting careful co-ordination of dosing and feeding times would minimize effects on the child.

Discussion

Methylphenidate in pregnancy

Three articles encompassing 40 exposed mothers and 41 infants were identified. All children were assessed for malformations but follow-up information was only available for 32 of the initial sample. Only a single case report involved methylphenidate as a prescribed drug, the remainder being fetal exposures to methylphenidate as a drug of abuse. In populations of drug misusers neglect of pregnancy care, poly-drug abuse, infection and poor general maternal health are all factors which may impact on pregnancy outcomes. Therefore these cases are not representative of methylphenidate exposure in the general population, and information and selection biases are inherent to case series and case reports. The case where methylphenidate was used under medical prescription also included haloperidol and phenytoin. The mother who was taking these medications during pregnancy died shortly after delivery. It is difficult to ascertain the role methylphenidate might have had in this case, as the teratogenic effect can be attributed to phenytoin which is well recognized as a human teratogen [22].

Lactation

The two articles found on methylphenidate and breastfeeding did not report any adverse effects in the infants. These results should be interpreted with caution as the sample size was very small ($n = 4$). Our case report adds to

this evidence and suggests that, conversely, withdrawal of medication for ADHD in the post-natal period may have risks. In the case presented methylphenidate concentrations in the child's blood were not detectable. The other cases reported some evidence that careful dosing of methylphenidate combined with timing of breastfeeding can limit the amount passed on to the child. Early morning feeds before the first maternal dose did not contain quantifiable amounts of the drug, and in one of the cases no methylphenidate was found in the child after 5 h of the maternal dose. No studies were found on the differences in breast milk excretion of instant release formulations *vs.* slow release. Research is needed in this area.

Conclusions

Although methylphenidate may theoretically cross the placenta, the effect on the developing brain of the unborn child is unknown. The three papers identified were not representative of the population taking methylphenidate by physician prescription for a diagnosis of ADHD, and only one of them referred to therapeutic use of methylphenidate. Therefore, the risk to the unborn fetus of methylphenidate remains undetermined. When making a therapeutic decision this risk needs to be balanced against that of withdrawing medication. In our case further harm arose from sudden interruption in treatment. However, the patient had other comorbidities (borderline personality disorder and recurrent depression) which may confound the interpretation of the effects of methylphenidate. The child was healthy at the time of his last review (age 1 year) but the effects of exposure to the drug may not be evident in the first years of life.

Our case and the systematic literature review suggest that breastfeeding whilst taking methylphenidate results in little exposure to the infant. This exposure can be further reduced by co-ordinating dosing and feeding times.

Women with ADHD face many challenges during pregnancy and lactation such as attending physician appointments, following a childcare routine and balancing the needs of the newborn child with their own symptoms and physical health. Additionally mental illness is an important factor in maternal mortality and infant/child outcomes [23]. All these factors need to be considered when making therapeutic decisions for ADHD in this population. Though the default position for many physicians is to interrupt any non-essential pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk. As more adults are being treated and diagnosed with ADHD, the continuation of treatment during pregnancy will become a pressing issue. More studies are required to elucidate the safety of this drug during pregnancy and lactation. Pharmacokinetic profiling of these drugs would be particularly useful to assess the exposure to the child through pregnancy and breastfeeding. Until such studies are performed, clinicians need to assess each case individually and make informed decisions about the risk of continuing or stopping ADHD treatment during pregnancy and breastfeeding.

Competing Interests

Blanca Bolea has received speaker fees and travelling expenses on one occasion from Janssen Pharmaceuticals. Amy Green, Gauri Verma, Penelope Maxwell and Simon Davies have no conflicts of interest to declare. No external funding was required for this work.

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