Pharmacokinetics, safety and efficacy of methylphenidate during pregnancy in women with Attention-Deficit (Hyperactivity) Disorder

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Primary objective is assessment of the pharmacokinetic profile of MPD in pregnancy. Secondary objectives are the safety and efficacy of any use of MPD during pregnancy.

Ethical review	Approved WMO
Status	Completed
Health condition type	Maternal complications of labour and delivery
Study type	Observational invasive

Summary

ID

NL-OMON49916

Source
ToetsingOnline

Brief title
Methylphenidate during pregnancy

Condition

- Maternal complications of labour and delivery
- Cognitive and attention disorders and disturbances

Synonym
Attention deficit hyperactivity disorder

Research involving
Human

Sponsors and support

Primary sponsor: Isala Klinieken

Source(s) of monetary or material Support: Isala

Intervention

Keyword: AD(H)D, methylphenidate, pregnancy

Outcome measures

Primary outcome

Serum levels methylphenidate

(Immediate release: 2-3 hours after intake,

extended release: 7 hours after intake)

Secondary outcome

Secondary outcomes:

• Birth weight

• Apgar score at 1 and 5 minutes

• Score list withdrawal symptoms

• Miscarriage

• Major congenital malformations

Explorative outcome:

AD(H)D symptom severity; Weis functional impairment rating scale - self report

(WFIRS-S)

Study description

Background summary

Although Attention-Deficit Disorder with or without hyperactivity (AD(H)D) is a neurodevelopmental disorder originally diagnosed during childhood, it persists into adulthood in 65% of cases. AD(H)D is characterized by two different types of symptoms: attention-deficit and hyperactivity-impulsivity and the estimated prevalence among adults in the Netherlands is about 2-5%.

In order to warrant a diagnosis, AD(H)D-symptoms must be severe and cause clinically significant impairment persistently in at least two domains of an individual*s life. At the age of 17 and older, five examples of inattentiveness and five examples of hyperactivity or impulsivity have to be present. Likewise, symptoms have to be present before the age of 12. The classification of AD(H)D is based on the occurrence of attention deficit and hyperactivity-impulsivity. ADD is mainly characterized by attention deficit while ADHD-patients often suffer from a combination of attention deficit and hyperactivity-impulsivity. This combination of symptoms often occurs in children, giving them the diagnosis ADHD. In adulthood, the hyperactivity decreases but inattention, disorganization and impulsivity leads to difficulties in functioning, both at home and at work.
AD(H)D-symptoms in adulthood (depression, anxiety, substance misuse, and impairment across different domains of functioning) are often attributed to depression, anxiety or personality disorder, which may explain a delayed diagnoses of AD(H)D. However, both the number of adults diagnosed with AD(H)D and the number of adults treated with AD(H)D medication are on the rise during the past years.
The initial treatment of AD(H)D consists of (cognitive) behavior therapy and coaching. Medication should only be prescribed to patients showing a severe disorder and who do not respond sufficiently to the non-medical treatment. Next to this, the risk-benefit balance is of great importance while choosing for medical treatment. First choice of pharmacological treatment in the Netherlands is methylphenidate (MPD). MPD is a central nervous system (CNS) stimulant drug with therapeutic effects of which adults with AD(H)D can benefit with acceptable side effects.

Methylphenidate during pregnancy
MPD is an amphetamine which influences the sympathetic nerve system.10 During pregnancy, amphetamines may be associated with an abruptio placentae, pre-eclampsia and intra uterine growth retardation.3,11 Because there is insufficient information available on the use of MPD after the first trimester, MPD is discommended in the 2nd and 3rd trimester until more data on the safety of the (unborn) child is available. The use of MPD during early pregnancy seems unlikely to increase the risk of birth defects.3

In practice, pregnant patients are off label treated with benzodiazepines, haloperidol or antidepressants in order to alleviate symptoms of AD(H)D.

However, this alternative way of symptom reduction is often not satisfactory. Difficulties in organizing, impulsivity and hyperactivity tend to remain present. Studies show that these symptoms are associated with depression, physical strain, less eating, the use of caffeine, smoking and poor vitamin intake.12,13 AD(H)D symptoms and stress that comes with discontinuing MPD could therefore place both mother and child at risk.9,13

The assumption is that MPD use is increased during fertile phase of life to alleviate disruptive symptom in several domains, for example domestic and professional. Therefore, the number of pregnancies exposed to MPD will increase.14

Recent studies suggested a possible relationship between the use of AD(H)D-medication during pregnancy and miscarriage, preterm birth, increased risk of caesarian delivery and 1 minute APGAR <7. 15,16,17,18 However, these studies did not distinguish between different types of ADHD-medication, so it is unclear whether these effects are due to MPD. In addition, most of these associations can not be confidently attributed to stimulant treatment; in these cases, the diagnosis ADHD or correlates of it seems to be responsible for the association. Therefore, confounding by indication must be taken into account.

In a recent meta-analysis of Jiang et al., eight cohort studies that estimated adverse maternal or neonatal outcomes associated with exposure to ADHD medication during pregnancy were included. No association of MPD was found with pre*eclampsia, diabetes, post*partum haemorrhage, placental abruption, spontaneous abortion, preterm birth, small for gestational age (SGA), low birth weight, low Apgar scores, stillbirth and major congenital malformations. Exposure to ADHD medication was associated with an increased risk of neonatal intensive care unit (NICU) admission compared with no exposure at any time (RR 1.88; 95% CI, 1.7-2.08) and compared with women with exposure either before or after pregnancy (RR 1.38; 95% CI, 1.23-1.54; P < 0.001). However, only two studies contributed to these pooled estimates and no distinction was made between type of ADHD-medication.19 Another meta-analysis (Lin Li et al.) included the same eight studies as Jiang et al. and demonstrated that the absolute RDs were overall small in magnitude, particularly for studies using alternative comparisons groups to rule out confounding. Because of the limited number of studies and control for confounding, Lin Li et al. stated it is currently unclear whether these small associations are due to a causal effect of prenatal exposure to ADHD medication or confounding.20
In the meta-analysis of Jiang et al., it was found that methylphenidate is marginally associated with cardiac malformations in the neonate (RR 1.27; 95% CI, 0.99*1.63; P = 0.065) compared to no exposure. This correlation was also found in the meta-analysis of Koren et al. (OR 1.59; 95% CI, 1.02-2.49), which focused on congenital malformations including only MPD-exposed infants. This study also yielded an OR of 1.26 (95% CI, 1.05-1.51) for major malformations.21 More research on the possible association between MPD use during pregnancy and (cardiac) malformations in the neonate needs to be conducted.

Pharmacokinetics of MPD during pregnancy
In general, during pregnancy the aim is to determine the lowest but effective dose of psychotropic drugs. MPD is a short-acting stimulant with a duration of action of 1 to 4 hours and a pharmacokinetic half-life value of 2 to 3 hours, and with a maximum exposure at two hours. It is an indirect acting epinephrine like drug, which does not influence the epinephrine receptors directly, but inhibits the reuptake of dopamine and norepinephrine. MPD is quickly and completely absorbed by the intestines. The blood brain barrier is passed easy as a result of high lipophilicity and low protein binding. MPD are 50-90 % excreted in urine as ritalinic acid. Only 1.5-3.3 % is excreted by faeces. A marked individual variability in the dose-response is observed, dosage has to be titrated for optimal therapeutic effect with minimal toxicity.
Carboxylesterase 1 (CES1A1) is the major enzyme responsible for the first pass, stereoselective metabolism of MPD.22,23 Several physiological changes occur in the pregnant state, affecting the pharmacokinetics of many drugs, especially psychotropics.24 It is not clear yet how and if CES1A1 enzymes change during pregnancy. Therefore, it is not clear if MPD serum levels change during pregnancy. This possible change in MPD serum levels may be relevant in the treatment of pregnant women.

Study objective

Primary objective is assessment of the pharmacokinetic profile of MPD in pregnancy. Secondary objectives are the safety and efficacy of any use of MPD during pregnancy.

Study design

This study compromises a prospective cohort study in a level II and III obstetrical setting in a pregnant population with AD(H)D and their offspring. We will measure drug concentration levels in the mother during pregnancy and after birth in both the mother and the neonate to assess the pharmacokinetic profile of MPD in pregnancy. Furthermore, we will look at the effect of (dis)continuing MPD during pregnancy on birth weight, miscarriages, APGAR score, Finnegan score, major congenital malformations and maternal AD(H)D symptom severity. We will follow AD(H)D-patients included in the Isala Psychiatry-Gynaecology-Pediatrics (PGP) protocol during their pregnancy by taking blood samples and conducting WFIRS-S at different moments in pregnancy. The exact number of blood samples and WFIRS-S assessments will depend on the stage of pregnancy the patient is in when she is included in the study. All other parameters will be determined after birth.

Study burden and risks

The risks of participation in this study compromises extra blood sampling for patients and the newborn attending the study programme. Blood sampling can

cause infections in exceptional cases. Only qualified personnel will draw blood samples according to standard procedures in the Isala Klinieken. APGAR score, birth weight and major congenital malformations are part of the regular control performed after giving birth. The Finnegan score is validated for opiate-exposed infants. Because there is no scoring system for the measurement of withdrawal symptoms in MPD-exposed infants, this score list is used. The WFIRS-S is the only measure of functional impairment that looks at 7 specific domains and has been psychometrically validated in the AD(H)D population. This rating scale is already part of the regular care of AD(H)D-patients. The blood sampling and WFIRS-S administrations will be combined with visits to the psychiatrist already planned. In this way, the burden for the patients will be minimal. The patients decide for themselves whether they want to continue, adjust or stop using AD(H)D-medication during their pregnancy. All medical treatment decisions will be made between the participant and her treating provider, independent of study participation. By assessing the different endpoints in women during pregnancy with or without the use of MPD, the effect of MPD on both mother and child can be determined. This information is valuable for AD(H)D-treatment in pregnant women in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns

Inclusion criteria

Pregnant with a singleton
Diagnosed with AD(H)D
Age 18 years or older

Exclusion criteria

Declared unfit by a psychiatrist
Juridical status (care authorization)
Prisoners

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-08-2022
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	04-11-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL78291.075.21