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REVIEW ARTICLE

The Effects of Drugs used for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) on Pregnancy Outcome and Breast-feeding: A Critical Review

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Abstract: Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral condition found in 5-10% of school-age children and in 2-5% of adults. Stimulants affecting the dopaminergic, noradrenergic and/or serotonergic systems are commonly used for treatment in children and adults, including women of childbearing age. The data on the effects of stimulants (methylphenidate and amphetamines) in pregnancy are generally reassuring, but methylphenidate might slightly increase the rate of cardiac malformations and of spontaneous abortions, while amphetamines might slightly increase the risk for premature birth, low birth weight and other pregnancy complications. Bupropion, a dopamine and norepinephrine reuptake inhibitor, when used as an antidepressant, appears to be safe in pregnancy. The data on the use of atomoxetine, guanfacine and clonidine in pregnancy are scarce**.** Importantly, there are practically no data on the long-term neurodevelopmental effects of most of these drugs. The published data on the development of children born to methamphetamine-abusing women may be misleading since these women generally use other drugs, including alcohol, and the home environment where the child is raised may not be optimal. The treating physician should judge the need for treatment during pregnancy in relation to the severity of the clinical symptoms. If needed, methylphenidate is preferred over amphetamines because breast feeding is possible. If one uses non-stimulant medications, bupropion seems to be the preferred drug.

Keywords: ADHD, pregnancy outcome, drugs, stimulants, complications of pregnancy, non-stimulant drugs, lactation.

1. INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral disorder characterized by inattention, poor self-control, disorganization, impulsivity and often motor over-activity and restlessness. Symptoms typically appear at early school age but may be first manifested up to 12 years of age [1-6]. Common comorbid states are learning difficulties and underachievement as well as difficulties in interpersonal relations and a variety of behavioral and psychiatric conditions. About half of these children will continue to have the symptoms in adulthood [2-6]. Adults with ADHD, if untreated, are often unable to maximize their potential. They might experience difficulties at work and unemployment, social dysfunction, increased risk of antisocial behavior and an increased tendency towards substance abuse, problems to obey laws and an increased rate of car and other accidents [3-8]. The economic burden of ADHD, especially if untreated, is very high [9, 10]. Hence, optimal pharmacologic treatment at adolescence and adulthood is generally advised (4-6), increasing the number of women with ADHD that receive treatment during childbearing age and specifically pregnancy.

Of special importance is the fact that adolescents and young adults with ADHD have an increased tendency towards substance abuse, and pharmacologic treatment of ADHD may reduce that tendency [4]. This association of ADHD and substance abuse was the trigger for a recently published consensus paper [3] to screen adolescents in substance abuse clinics for ADHD and use long-acting stimulants for their continuous treatment, further increasing the use of ADHD medications by adults.

The rate of ADHD among school-age children is 5-10%, and among adults, it is 2-5% [10-12]. The DSM 5 [1] proposed specific clinical diagnostic criteria based on behavioral findings. These and other diagnostic criteria are increasingly used for the diagnosis of ADHD in adults [4-6]. There are also specific questionnaires for children and for adults. Various computerized attentional performance tests (CPTs) might also help in the diagnosis, but they are only adjunct means to the clinical diagnosis. With the improvement of the diagnostic means, suggestions for pharmacological treatment

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in adults with ADHD became more common [3-6], further increasing the number of women treated during childbearing age.

Treatment, in both children and adults, is primarily pharmacological; various stimulants being the first-line treatment, or non-stimulant drugs given to those that do not respond well or do not tolerate stimulants [4-6, 13-15]. These various drugs are as follows: Stimulants: Methylphenidate, dexmethylphenidate, amphetamine combinations: dextroamphetamine and lidexamfetamine. Non-stimulant drugs include atomoxetine (norepinephrine reuptake inhibitor), clonidine (alpha2 norepinephrine agonist) and guanfacine (alpha 2 norepinephrine agonist). Rarely, especially with depression as a comorbid state, antidepressants (mainly bupropion) are effective treatments.

Generally, all drugs used for the treatment of ADHD cross the placenta, hence the developing embryo and fetus are exposed to the drugs if taken by the mother during pregnancy. Despite the significant increase in the use of ADHD medications by pregnant women [11, 12], the data available on the possible effects of these drugs during pregnancy are still inadequate [17, 18].

Stimulants increase the synaptic dopamine concentrations while other drugs increase the synaptic concentrations of norepinephrine (*i.e*., atomoxetine) or serotonin (tricyclic antidepressants - TCAs) or exert the beneficial effects by interference with alpha-adrenergic substances [16-18].

One of the problems in the assessment of the possible effects of stimulants in pregnancy is the fact that some of these drugs are used recreationally and, as such, may also cause addiction. Moreover, the data accumulated are, to a large extent, obtained from addicted mothers or from mothers using occasionally high doses. This is especially relevant to our data on the effects of amphetamines and non-stimulant drugs.

In view of the increased number of women of childbearing age diagnosed with ADHD, there is a need to bring to the attention of the medical community the possible effects of drugs used for the treatment of ADHD on the developing embryo and fetus. Special emphasis is given to stimulants that are generally preferred over non-stimulant drugs. Table **1** summarizes the data related to the effects of these drugs on the embryo/fetus, course of pregnancy and development.

2. METHODS

We searched the English literature related to pharmacological treatment of ADHD in pregnancy in PubMed and EMBASE. Since most of the non-stimulant drugs used for the treatment of ADHD are used for other indications (*i.e*., their use as anti-hypertensives, for mood disorders, or for the cessation of smoking), we searched the specific literature related to the outcome of pregnancy following the use of these specific drugs for the different clinical indications using the name of the specific drug, pregnancy outcome, or the specific drug and embryo, fetus, development. In addition, we searched the literature related to the use of amphetamines as recreational drugs. We also searched the literature specifically describing the effects of drugs in pregnancy and lactation such as REPROTOX (www.reprotox) or books (*i.e*., "Drugs in pregnancy and lactation" edited by C. Schaefer, P. Peters and R.K. Miller, third edition), for any relevant and updated data on each one of these drugs related to pregnancy and lactation.

3. STIMULANTS FOR THE TREATMENT OF ADHD

The more commonly used stimulants for the treatment of ADHD and narcolepsy are amphetamines and methylphenidate**.** Amphetamines are also used for recreational purposes. Both drugs bind to the dopamine transporter, inhibiting dopamine reuptake, thus reducing the breakdown of synaptic dopamine. There are a number of different preparations of

Table 1. The effects of ADHD drugs on the developing embryo/fetus and on the course of pregnancy.

Drug	Congenital Malformations	Complications of Pregnancy	Neurodevelop-mental Outcome	Comments
Methylphenidate	Apparently increased cardiac malformations	Possibly increased spontaneous abortions, preterm birth, preeclampsia, perinatal complications	Probably normal development- only one small study	specific effects of ADHD cannot be ruled out
Amphetamines and methamphetamine	Probably not; some abnormalities in brain imaging following methamphetamine exposure	Reduced birth weight and gestational age at delivery, reduced fetal growth, small head circumference, Withdrawal symptoms	Increased ADHD, increased behavioral problems and aggression normal cognition	Most data from recreational abuse of methamphetamine
Bupropion	Possibly increased cardiac anomalies, in debate	Withdrawal symptoms	No data	Data from treatment of depression and smoking cessation
Atomoxetine	Insufficient data	No complications insufficient data	No data	Data from treatment of hypertension
Clonidine	Probably not	-	No data	Data from treatment of hypertension
Guanfacine	No data	No data	No data	-

both amphetamines and methylphenidate differing in the length of time they are effective (*i.e*. immediate release, extended-release long-acting ext.) and chemical configuration (*i.e*., focalin, which is the d-enantiomer of methylphenidate).

3.1. Methylphenidate (Ritalin) and Dexmethylphenidate

3.1.1. Congenital Malformations

Methylphenidate is a piperidine derivative structurally related to amphetamine. There seem to be no human data regarding the placental transfer of methylphenidate, but its molecular weight of 269.8 Dalton is sufficiently low to suggest transfer. Moreover, methylphenidate was found to cross the mouse placenta and concentrate in the fetal brain [19-21].

Data on the possible effects of methylphenidate and amphetamines in human pregnancy was summarized in 2005 by the expert panel on the evaluation of risks to human reproduction as being insufficient [19], but since then, several important studies have been published, including several meta-analyses [20-24].

Several case reports and case series reviewed by Bolea - Alamanac *et al*., [20] reported no significant teratogenicity. Similarly, in a case series of 38 pregnant mothers (39 infants) who were abusing methylphenidate [21], there was only an increased rate of Small for Gestational Age (SGA) infants, prematurity and withdrawal symptoms, the latter being observed in 28% of the newborns.

Dideriksen *et al*. [22] found 4 cohort studies, including 180 first trimester exposures to methylphenidate, with only 4 malformed infants; all 4 had congenital heart defects, two of them having ventricular septal defects (VSD). This study from the Swedish birth registry was extended to include 208 first- trimester and 98 second and third-trimester pregnant women that filled out prescriptions for methylphenidate [23]. Five infants had cardiac anomalies, 4 of them VSD (27). The rate of cardiac anomalies among all cases from both studies was increased (9/486 -1.85%). Although this finding is in line with several later studies also demonstrating increased cardiac malformations, we should remember that there were no control groups for comparison.

In a Danish cohort study of prescriptions of methylphenidate from 222 pregnancies exposed, compared to 2,220 controls, there was no increase in the rate of major anomalies or of cardiac malformations [24].

In another Danish study on the outcome of 480 pregnancies in which the mothers were prescribed different medications for ADHD [25], there was an increase in miscarriage and induced abortions. There were 3 malformed infants. The authors described a constant annual increase in the use of these medications in pregnancy. However, there was no data for individual medications.

A relatively recent cohort study evaluated the outcome of 382 pregnancies exposed to methylphenidate (343 with first-trimester exposure) and 382 pregnancies exposed to non-teratogenic agents (controls). In this multicenter study from several Teratogen Information Services [26], there was no increase in the rate of major congenital anomalies (10/309 methylphenidate *vs*. 13/358 controls), but there was an increase in spontaneous and induced abortions and a reduction in live-born infants. The higher rate of spontaneous abortions was also associated with a high rate of previous spontaneous abortions. In addition, there were more perinatal complications among those who took methylphenidate until delivery, including poor neonatal adaptation (13/55 *vs*. 48/355). It is, however, possible that some of the data are confounded by indication.

Increased spontaneous abortion was also observed by Bro *et al*. [27] in 186 women who were treated during pregnancy with methylphenidate or atomoxetine (adjusted Relative Risk 1.55, 95% CI 1.03-2.36), but such an increase was also observed in 275 women with ADHD without treatment. Thus, the increase may be confounded by indication.

In a recent large population study by Huybrechts *et al*. [28], the investigators used both the US Medicaid Analytic extract data and the data from the Nordic Health registries with a total population of 4.3 million pregnancies of whom 3474 had prescriptions for methylphenidate during the first 90 days of pregnancy. Treatment with methylphenidate during pregnancy was associated in both the American and the Nordic populations with a small increase in the rate of congenital cardiac malformations. In the American registry, the adjusted relative risk was 1.28, (95% CI 0.94-1.74), and in the Nordic registry, it was also 1.28 (95% CI 0.83-1.97) with a pooled RR estimate from both registries of 1.28 (95% CI 1.00-1.64). There was no significant increase in the general rate of congenital malformations. It is interesting to note that no increase in the rate of cardiac or other malformations was observed among the children of 5662 mothers prescribed amphetamines during pregnancy (only 99 from the Nordic registry). While the data are convincing, we should remember that this study used prescriptions the women received during the first trimester of pregnancy, and there is no confidence that the women indeed took the medications.

In a recent meta-analysis carried out by us on 4 cohort studies with about 3,000 exposures only to methylphenidate during pregnancy, we found an OR of 1.59 (95% CI 10.2-2.49) for cardiac malformations [29]. There was no significant increase in the general rate of congenital malformations (OR of 1.26, 95% CI 1.05-1.51). An increased rate of cardiac malformations was also reported by Andrade [30] in his commentary on stimulants during pregnancy.

3.1.2. Other Complications of Pregnancy

Cohen *et al*. [31] studied the possible effects of treatment on a relatively large population of pregnant women (1515 women) with ADHD, comparing the outcome of pregnancies in women treated with stimulants (amphetamine, dextroamphetamine or methylphenidate) after 20 weeks of pregnancy to a very large group of women not treated with stimulants (and not having ADHD). They found a small increase in rates of preeclampsia and preterm births, but no effects on the rate of placental abruption or SGA. The authors did not evaluate spontaneous abortions.

A similar study was published by Poulton *et al*. [32] using health records from Australia. The authors compared women treated with stimulants (before or during pregnancy) to untreated women with ADHD and found a small increase

in the rate of cesarean deliveries, preeclampsia and preterm birth. The authors agree that their study, however, does not necessarily reflect the effects of a stimulant treatment since women in the treated group were either treated before or during pregnancy and the group was small - only 175 pregnant women.

Maternal use of stimulants in pregnancy (90% used methylphenidate) increased the rate of admission to neonatal intensive care units by 50% [33]. However, the mothers using stimulants had a higher rate of smoking, alcohol use, overweight and the use of psychotropic drugs. Hence it is difficult to decide that stimulants are responsible for these complications.

It can therefore, be concluded that there is inadequate proof that stimulants increase the rate of pregnancy complications, and the slight increase observed may be a result of ADHD.

3.1.3. Breast Feeding

There is relatively little data. Methylphenidate is secreted in small to moderate amounts in milk, but the infant receives less than 1% of the maternal dose corrected for body weight and methylphenidate is generally undetected in the infant's blood [34-36]. Hence, there is no contraindication to breast feeding.

3.1.4. Neurodevelopmental Outcome

Debooyi *et al*. [21] examined the development of 21 children born to mothers who abused methylphenidate at one year of age and found that 4 of them functioned below normal. However, since alcohol abuse was so common among these women, it is difficult to decide what was responsible for the low neurodevelopmental abilities of these 4 children. We found no other published data.

3.1.5. In Summary

The current data on more than four thousand first trimester methylphenidate exposures suggests that methylphenidate is not a major human teratogen. However, methylphenidate may slightly increase the rate of cardiac malformations. Pregnant women taking methylphenidate in the first trimester of pregnancy might be advised to undergo fetal echocardiography. There might also be an increased rate of spontaneous abortions, prematurity, SGA and perinatal complications, but the data are still insufficient. We could find no studies on the long-term neurodevelopment of the exposed children. Hence, depending on the clinical picture, it is for the treating physician to decide whether to stop methylphenidate treatment once pregnancy is known.

3.2. Amphetamines, Methamphetamines (Adderall) and Lisdexamphetamine (Vyvanse)

3.2.1. Congenital Malformations

Amphetamines, of which methamphetamine is a - known drug of abuse, increase the synaptic dopamine. The data on their possible effects in pregnancy are scarce, and many of the published studies report the outcome of pregnant women abusing amphetamines [19].

Case reports and retrospective studies reported increased rates of cardiac anomalies, limb reduction defects and exencephaly associated with amphetamine exposure during pregnancy [19, 37, 38]. However, later prospective studies failed to confirm any associations with cardiac or other malformations [28, 39, 40].

A prospective study on 228 amphetamine-exposed pregnancies used as a recreational drug did not find an increase in major malformations [39]. Kallen *et al*. [23] described the outcome of 132 women prescribed amphetamines in the first trimester of pregnancy with 4 children (3%) having congenital malformations

3.2.2. Effects on the Course of Pregnancy and Maternal Complications

Several retrospective studies found a higher rate of prematurity and SGA among women using amphetamines recreationally. A reduction in birth weight and increased rate of prematurity was reported in a retrospective study of 141 infants exposed during different times of pregnancy to amphetamines. The study was carried out on amphetamine addicted mothers [41]. Eriksson *et al*. compared the outcome of 69 pregnancies of amphetamine-addicted mothers; 17 of them stopped amphetamine, and the others continued to use these drugs throughout pregnancy [42]. There was an increased rate of prematurity, maternal hypertension, postpartum hemorrhage, and retained placenta in those using amphetamines throughout pregnancy.

In a prospective cohort study of 204 infants born to methamphetamine abusing mothers [43] as compared with unexposed infants, the infants exposed to methamphetamine had a higher rate of growth restriction and earlier delivery. If the drug use is discontinued sometime before delivery, these complications normalized.

Smith *et al*. [44] found in a retrospective study that methamphetamine exposure reduced fetal growth in utero as observed even in term infants. The association with smoking further reduced fetal growth.

Kalaitzopoulos *et al*. [45], in their meta -analysis of 8 studies involving 626 women taking methamphetamine during pregnancy, as compared to 2626 controls, found lower gestational age at birth, lower birth weight and head circumference, birth length and Apgar scores. These reinforce the findings described above.

It can be summarized that perinatal complications include higher rates of gestational hypertension, preeclampsia, placental abruption, intrauterine fetal death, preterm birth, neonatal death, and infant death.

We should, however, remember that a major problem in many of these studies lies in the fact that the pregnancies are of mothers addicted to methamphetamines. Many of these women also used other psychotropic drugs, including opioids and/or alcohol. Hence, these important confounders should be considered in the evaluation of the above-described data. In addition, the possible effects of ADHD on these parameters have not been adequately studied. It is therefore difficult to assess from these data the possible adverse effects of am-

phetamines used for the treatment of ADHD or narcolepsy on the course of pregnancy.

3.2.3. Withdrawal Symptoms

Withdrawal symptoms were described in newborn infants prenatally exposed to methamphetamine, manifested by jitteriness, drowsiness, and respiratory distress [46].

3.2.4. Abnormalities in Brain Imaging Studies

Several brain imaging studies have shown distinct long-term morphologic changes in the brain structure of children born to mothers who abused amphetamines during pregnancy using diffusion tension imaging, proton magnetic resonance imaging H-MRI or fMRI [47-49].

Abnormalities in white matter microstructure [47] including motor pathways (corona radiata and corticospinal tract) were demonstrated by diffusion tension imaging (DTI); Sex-dependent structural differences in striatal, parietal, and temporal areas compared to controls was found by MRI as well as a reduction in cortical thickness and in the size of subcortical nuclei including the caudate nucleus, striatal, frontal and limbic white matter [47-49].

3.2.5. Neurodevelopmental and Behavioral Studies

In contrast to the lack of studies on the neurodevelopmental outcome of children prenatally exposed to methylphenidate, there are many studies on the neurodevelopmental outcome of children born to amphetamine abusing mothers. A high proportion of these mothers also abused other drugs, cigarettes and alcohol.

In contrast to the above-mentioned descriptions of changes in brain structure evidenced from different imaging studies [47-49], some of the neurodevelopmental studies on children born to methamphetamine addicted mothers showed only few neurodevelopmental abnormalities. For example, Chang *et al*. [50] evaluated 49 children exposed during pregnancy to methamphetamine and examined at 3-4 years of age, in comparison to 49 control children. There was no difference in their cognitive abilities compared to sex-matched controls, but there were differences in visual-motor integration. In addition, the investigators found several changes in the composition of neuro-metabolites in the brain of the children prenatally exposed to methamphetamine, as evidenced by proton magnetic resonance spectroscopy [50].

The most important data on neurodevelopmental abilities of children from birth to 7.5 years of age come from the IDEAL (Infant Development, Environment and Lifestyle) study on neurodevelopmental follow-up of children born to mothers who were addicted to methamphetamines [51-54].

The multicenter controlled prospective IDEAL study recruited at delivery methamphetamine-exposed infants born in the US and New Zealand between 2002 and 2004 in comparison to socio-demographically matched control infants. The methamphetamine addicted mothers had also been exposed to factors common to methamphetamine abusers, including alcohol, tobacco, marijuana, and maternal depression. The study cohorts consisted of 412 mother-infant pairs (204 with prenatal methamphetamine exposure and 208 unexposed controls) that were recruited in the US and of 223 (108 exposed to methamphetamine and 115 controls) that were recruited in New Zealand. Findings regarding motor, cognitive, behavioral, and emotional development for the children followed from birth to 7.5 years of age have been published in several studies and summarized in 2015. As children of addicted parents also suffer from postnatal neglect and sometimes even child abuse, one has to remember that the neurodevelopmental data is a result of the interaction between prenatal exposure and postnatal environmental deprivation.

3.2.5.1. Data on Neonates

Prenatal methamphetamine exposure in the IDEAL cohort was associated in the neonatal period with a greater likelihood of admission to the neonatal intensive care unit, reduced birth weight, slightly smaller head circumference and shorter body length. The infants also had poor suck, decreased arousal, increased physiological stress, and low tone [51].

3.2.5.2. Developmental Data at the Age of 3-5 Years

No differences were found between the exposed and control children in mental development, expressive and receptive language and gross motor skills. There were some differences in fine motor skills and a higher rate of behavioral problems and language delay. However, these were attributed to adverse home environments rather than methamphetamine [52, 53].

In an additional study at the same age, prenatal methamphetamine exposure was associated with behavioral and attentional problems and with some increase in anxiety/depression. These deviations, including attentional problems and decreased inhibitory control, seemed to be more prominent at 5-6 years [52-54].

3.2.5.3. Data at 7.5 Years of Age

There was a higher rate of aggressive and rule-breaking behavior among the exposed children, a higher rate of externalizing problems in the Child Behavior Checklist (CBCL) and a higher number of children with some cognitive impairment [54, 55]. There was also a higher rate of ADHD among the prenatally exposed children. It should again be noted that their mothers were addicted to amphetamines and ADHD is more prevalent in addicted persons [1, 4, 10]. Hence, the higher rate of ADHD might be related to the genetic predisposition rather than to the action of amphetamines.

We found no other neurodevelopmental studies in children born to mothers with ADHD treated with low doses of amphetamines during pregnancy.

3.2.6. Breast Feeding

Amphetamines are excreted in human milk and may also be found in the urine of nursing infants [36, 56-58]. Poor sleeping and irritability have been described in some nursing infants, but long-term adverse effects were not described, and the data are insufficient. Due to the relatively high milk levels and possible effects on the nursing infant, such as irritability and agitation, breast-feeding is contraindicated by some sources [36, 58].

3.2.7. In Summary

Prenatal exposure to amphetamines does not seem to increase the rate of major congenital malformations, but there seems to be a small increase in various perinatal complications suggesting some interference with intrauterine growth. The data on the neurodevelopmental outcome is also reassuring. Most studies were carried out on children born to mothers who were addicted to amphetamines, and were therefore exposed to high levels of the drug. The observed neurobehavioral changes, including a high rate of ADHD (observed in one study), may also be confounded by exposure to other substances such as alcohol or other drugs. Pregnant women with ADHD who are in need of amphetamine treatment might be able to continue treatment during pregnancy, trying to use the smallest effective dose. It is for the treating physician to consider the necessity of treatment and if treatment is not absolutely needed, it may be advisable to stop treatment during pregnancy. Breast feeding is contraindicated.

4. BUPROPION

Bupropion is a non - stimulant drug acting as a norepinephrine-dopamine reuptake inhibitor (NDRI), primarily affecting the reward-pleasure mesolimbic dopaminergic system [59, 60]. In the last several years, it is also used for the treatment of ADHD [59]. It is marketed as an immediate release (IR), sustained-release (SR) and extended-release (XR) product.

Chemically, bupropion has some similarities to stimulant drugs as it belongs to the class of aminoketones [60]. Since bupropion is mainly used as an antidepressant or for smoking cessation, most data are from pregnant women taking bupropion for these indications. We found no studies on the effects of bupropion on pregnancy in women with ADHD.

4.1. Effects on Pregnancy

Much of the data on its safety in pregnancy come from the pregnancy registry organized by the manufacturer [61]. According to their report on a prospective study of 806 first trimester exposures, there were 651 normal liveborn infants and 18 malformed infants in a cohort of first trimester exposures, a rate not different from the general population. The manufacturer also conducted a retrospective cohort study and a nested case-control study and reached similar conclusions.

Cole *et al*. [62] studied the outcome of 1,213 infants from the GlaxoSmithKline bupropion pregnancy registry exposed in utero to bupropion during the first trimester of pregnancy and found a rate of 2.3% malformations including cardiac anomalies among first trimester exposures [aOR of 0.95 (95% CI 0.62-1.45) and 1.0 (95% CI 0.57-1.73)] compared to the control groups. The rate of cardiovascular anomalies was also similar among the groups [62].

In a smaller prospective cohort study of 136 women who used bupropion in the first trimester of pregnancy for smoking cessation or depression, infants were followed up to the first year after delivery [63]. There were no major malformations in the bupropion-exposed group and no increase in preterm birth or low birth weight compared with two control groups of non-teratogenic exposures or of administration of other antidepressants. An additional study from the same group on 113 pregnant women with first trimester exposure to bupropion [64] also did not find any increase in major congenital anomalies.

In a population-based case control study from the National Birth Defects Prevention Study in the United States, the authors found that more mothers of infants with left outflow tract cardiac anomalies were taking bupropion compared to mothers of infants without congenital anomalies or with non-cardiac anomalies. However, exposure was based on maternal retrospective recall and some of the mothers taking bupropion had also taken other antidepressants which might have contributed to the increased cardiac anomalies [65].

Moreover, another case-control study from the Slone Epidemiology Center Birth Defects Study [66] found increased rate of ventricular septal defects (VSD) with the use of bupropion as an antidepressant, but not if used with other antidepressants. Here, too, maternal self-report was used to determine first trimester drug exposure.

The issue of increased cardiac malformations related to bupropion use in pregnancy is still in debate. In that context it is worth mentioning that a study using US Medicaid data from 2000-2007 [67] with 8,856 pregnancies prescribed bupropion - 6,691 in the first trimester of pregnancy, did not find an increase in any cardiac malformation including right ventricular outflow tract obstruction, or ventricular septal defect.

Figueroa found an increased rate of ADHD among 114 children at 5 years of age that were born to depressed mothers who were given prescriptions for bupropion, especially during the second trimester of pregnancy [68]. No such increase was found in depressed mothers treated with SSRI or untreated. A positive association still remained after adjustment for several confounders including parental ADHD. However, the small size of the group, the fact that the study was based on prescriptions and the relatively low rate cases (5/114) weaken these results.

4.2. Breast Feeding

Bupropion is secreted in human milk in concentration higher than the maternal blood level [36, 69, 70]. However, in a study on 2 infants nursed by mothers taking bupropion, bupropion or its metabolite hydroxybupropion were not detected in infants' blood and there were no side effects in the infants [69]. The nursing infants are expected to be exposed to about 2% of maternal dose-corrected dose [70] thus reducing the fear of side effects. In spite of reported transient side effects [71], depending on the dose, nursing is generally not contraindicated [36].

We found no studies on neurodevelopmental outcome of prenatally exposed children, except for the data on the prevalence of ADHD that may be confounded by maternal disease or other factors.

4.3. In Summary

Bupropion, similar to other antidepressants [36, 72], is not associated with an increased rate of congenital anoma-

lies. Thus, pregnant women treated with bupropion can continue treatment during pregnancy. Practically, there is no data on long-term development.

5. ATOMOXETINE

Atomoxetine (Strattera) is a norepinephrine reuptake inhibitor often used in the pharmacological treatment of ADHD. It inhibits the reuptake of norepinephrine by selectively inhibiting the presynaptic norepinephrine transporter [73, 74]. It was also the first non-stimulant drug approved in the US for the treatment of ADHD. It is marketed as an extended-release drug active for 10-12 hours [16-18]. There are only few case reports on the possible effects of atomoxetine on human pregnancies and several cohort studies.

5.1. Effects on Pregnancy

Kallen *et al*. [23], in their comprehensive data from the Swedish registry on the effects of psychotropic drugs in pregnancy, described the outcome of 450 women that were prescribed (treated) with stimulants, of which 34 used atomoxetine. Of the 34 women, 22 were prescribed atomoxetine in the first trimester of pregnancy. No congenital anomalies were reported in these pregnancies. Cohen *et al*. [32] evaluated the outcome of pregnancies in 453 women who used atomoxetine during pregnancy and did not find any increase in congenital malformations or in pregnancy complications. There are no data on the neurodevelopmental outcome of children prenatally exposed to atomoxetine or on the possible transfer to the nursing infant. There seems to be no data regarding its safety during breastfeeding.

5.2. In Summary

No additional conclusions can be drawn from the human studies on the safety of atomoxetine in pregnancy. Due to the lack of data, the treating physician should consider the clinical value of atomoxetine treatment in women with ADHD during pregnancy.

6. CLONIDINE

Clonidine is being used for many years for the treatment of hypertension. Clonidine is an alpha 2 adrenergic agonist that may regulate norepinephrine release from the Locus Coereleus in the brainstem, having similar effects to atomoxetine. It is known to cross the human placenta, and is cleared more rapidly from the blood during pregnancy [75, 76]. No data could be found on possible effects of clonidine on pregnancy in women treated for ADHD, and all data are therefore derived from the use of clonidine as an antihypertensive agent. Generally, the doses used for the treatment of hypertension are higher than those used for the treatment of ADHD.

6.1. Effects on Pregnancy

Generally, the studies on the treatment of hypertension during pregnancy by clonidine demonstrated the safety of this drug in pregnancy. There are several case reports on malformed infants prenatally exposed to clonidine, but this may be a coincidence. Rothberger *et al* [76] studied 72 hypertensive pregnant women treated with clonidine during pregnancy and found that fetal growth was reduced in the pregnancies of women who respond to clonidine treatment by reduced cardiac output, but not in women who responded to clonidine by reduced vascular resistance. Hence, reduced fetal weight was related to specific effects of clonidine on maternal hemodynamics.

In a prospective study on 100 hypertensive pregnant women [77] half treated with clonidine hydrochloride and half with methyldopa, there was no increase in malformations rate. Similarly, Tuimala *et al* [78] studied the outcome of pregnancies in 82 hypertensive women treated with clonidine during pregnancy and found no malformed infants.

In spite of the fact that the data on the safety of clonidine in pregnancy stems from the treatment of hypertension, they can also be applied to the treatment of ADHD. The indication for what a drug is given makes little differences regarding teratogenicity, unless the doses are significantly different or the underlying disease directly affects the developing embryo/fetus, as known for diabetes [79].

6.2. Breastfeeding

Clonidine is secreted in human milk in relatively large amounts, and the milk concentrations are higher than in maternal blood. The concentrations in the infants' blood were found to be half of those in the mother [80]. There are also several reports on cases of complications of maternal clonidine administered for the treatment of hypertension-induced in breast-fed infants (*e.g*., hypotonia, drowsiness, episodes of apnea and seizure -like episodes). In spite of the fact that these adverse effects disappeared after nursing was stopped [36, 81], breastfeeding is contraindicated [81].

6.3. Neurodevelopmental Outcome

Huisjes *et al*. [82] examined 22 children born to hypertensive mothers treated during pregnancy with clonidine compared to 22 children born to hypertensive mothers not treated with clonidine. They found at early school age a slightly higher rate of hyperactivity and sleep disorders compared to those not treated with clonidine. No other neurodevelopmental studies were found.

6.4. In Summary

From the little data available on the possible effects of clonidine treatment for hypertension on the developing human embryo and fetus, it seems that clonidine is not teratogenic. If needed, clonidine can be used in pregnant women with ADHD. Due to high milk concentrations, it is preferable to avoid breastfeeding.

7. GUANFACINE

Guanfacine is an alpha 2 adrenergic agonist with an action similar to that of clonidine and is used as an antihypertensive agent and in the last years as a non -stimulant treatment for ADHD, especially in cases of stimulant failure [82, 83]. The little data on its possible effects in pregnancy comes from its use as an anti-hypertensive drug where it seems to be well-tolerated and safe for treatment during pregnancy for both the mother and fetus. Although guanfacine might de-

crease serum prolactin levels, it does not seem to interfere in the course of pregnancy [84].

7.1. Effects on Pregnancy

No studies were found regarding the use of guanfacine in the first trimester of pregnancy. Phillip *et al*. [85, 86] studied the pregnancy outcome of 30 women with preeclampsia treated with guanfacine in the second half of pregnancy and only for 16-68 days. There were no malformed infants, but 20% had low birth weight. This could also be attributed to maternal preeclampsia. The newborn infants were reported to have normal heart rates and had no specific complications. In addition, we could find no data on the development of offspring exposed in utero to guanfacine or on guanfacine treatment and breastfeeding.

7.2. In Summary

As long as there is no additional data on the safety of guanfacine in pregnancy, it may be advisable to discontinue treatment when pregnant.

CONCLUSION

From the currently available data from prospective, retrospective and case-control studies, it can be concluded that none of the drugs used for the treatment of ADHD is a major human teratogen. There are only very few long-term neurodevelopmental studies on the offspring. Hence, it is advisable that women with ADHD will plan their pregnancies and if possible, depending on the severity of their symptoms, it is preferable to stop treatment before or at the beginning of pregnancy. If treatment is needed, one should prefer methylphenidate or amphetamines over other drugs, with a slight preference to methylphenidate, to enable breastfeeding. If they are treated with non-stimulant medications, bupropion is the preferred drug since there is more reassuring data on this drug in pregnancy.

LIST OF ABBREVIATIONS

ADHD	=	Attention deficit/hyperactivity disorder
aOR	=	Adjusted odds ratio
CI	=	Confidence interval
CPTs	=	Computerized attentional performance tests
DSM 5	=	Diagnostic statistical manual 5
DTI	=	Diffusion tensor imaging
MDMA	=	Methylenedeoxymetamphetamine
MRI	=	Magnetic resonance imaging
NDRI	=	Norepinephrine-dopamine reuptake inhibitors
OR	=	Odds ratio
Ritalin IR	=	Ritalin immediate release
Ritalin LA	=	Ritalin long acting
Ritalin SR	=	Ritalin sustained release
SGA	=	Small for gestational age
SSRIs	=	Serotonin reuptake inhibitors
VSD	=	Ventricular septal defect

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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