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REVIEW ARTICLE

ADHD Treatment and Pregnancy

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Abstract There is increasing recognition that ADHD is a common condition, not only in children and teenagers but also in adults. This has led to a rapid rise in the number of women of childbearing age who are being treated for this condition. Against the background of concerns about the use of medication of any kind during pregnancy and breastfeeding, it is remarkable that there is so little information available on the effects of ADHD medication on the fetus and newborn. The impulsivity associated with ADHD might lead to an increased rate of unplanned pregnancy. Although treating ADHD during pregnancy and lactation might have negative effects on the baby, suspension of treatment or inadequate treatment could also place both mother and baby at risk. Pharmacodynamic and pharmacokinetic changes during pregnancy could affect both the efficacy and the concentration of medication. Again, there is almost no guidance available. The US Food and Drug Administration has classified ADHD medications as being "pregnancy category C", implying that there is insufficient information to confirm either harm or lack of harm. From the limited information that has been published, it would appear that the risk of fetal malformation, at least with methylphenidate, is very low and that the amounts of medication excreted in breast milk and consumed by the infant are very small. Three questions that both clinicians and patients are likely to ask are the following. Should ADHD medication be stopped before, during or after pregnancy, or should it be continued throughout? Should ADHD medication doses be adjusted during the course of the pregnancy or after delivery? Should breastfeeding be encouraged or discouraged? Discontinuing ADHD treatment could put both mother and baby at risk. This has to be balanced against the possible risks to the baby of continuing treatment. Although the data remain inadequate, the risk of the latter appears to be quite small, at least for methylphenidate. However, there is recent evidence that the rates of fetal loss both through abortion and through miscarriage are increased with methylphenidate. Discussions about ADHD treatment with women of childbearing age should be balanced, open and honest, acknowledging the lack of information on the possible risks to the offspring of continuing treatment, while also drawing attention to the possible risks to both mother and child of discontinuing treatment.

Key Points

The documented rise in ADHD treatment in pregnancy has been marked in recent years and shows signs of continuing to increase

There is a striking lack of information on the effect of ADHD treatment in pregnancy

There is currently no evidence of an increased malformation risk with methylphenidate in pregnancy, but atomoxetine has been available for a relatively short time, implying that information is particularly sparse

1 Introduction

ADHD is a common condition in children, teenagers and adults [1, 2]. The growing recognition that this condition

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often continues through the late teenage years and into adulthood has led to a rapid increase in the numbers of patients in this age group who are being treated for it [3]. Both clinicians and women of childbearing age rightly have concerns about the use of medication of any type during pregnancy and lactation, because of possible adverse effects on the fetus and newborn child. Against this background, it is of great interest to know whether medication used to treat ADHD crosses the placenta, is associated with fetal malformations and is transferred into breast milk in clinically significant amounts. Concerns about the possible adverse effects on the child might lead the pregnant female to stop ADHD treatment, with potential consequences for her own wellbeing. The situation might be complicated further by both pharmacokinetic and pharmacodynamic changes affecting the efficacy of ADHD treatment during the course of the pregnancy and after delivery. Females of childbearing age should be fully informed of the practical implications of ADHD treatment during pregnancy and in the postpartum period, for both their own wellbeing and that of the offspring. However, the information currently available is very limited. The US Food and Drug Administration (FDA) has classified ADHD treatments as being "pregnancy category C" [4, 5], which implies that either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Effectively, this means that there is inadequate evidence either for harm or lack of harm. In the UK, the National Institute for Health and Care Excellence (NICE) guideline CG72 on ADHD in children, young people and adults [6] draws attention to a number of factors in pregnancy that may increase the risk of ADHD in the offspring, but it makes no recommendations with regard to the management of pregnancy or breastfeeding in women with ADHD.

2 Search Strategies

The MEDLINE/PubMed databases from 1946 to week 4 of March 2014, with no language or other restrictions, were initially searched using the term "(ADHD or attention deficit hyperactivity disorder) and pregnancy". This yielded a surprisingly small number of references (455), most of which referred to the risks of offspring developing ADHD after having been exposed to environmental factors such as smoking in pregnancy, rather than the risks associated with treating mothers who have ADHD. All of these titles/abstracts were assessed for relevance. Thirty-four were selected as being of possible relevance, of which only five were strictly relevant, i.e. dealt with the effects of medication taken for ADHD on the fetus or baby. Google Scholar and the reference lists of the few key papers that were found were also searched, and relevant papers were obtained. Additional, more specific search strategies were used for breastfeeding, fetal malformations and pharmacokinetics. The search strategies were as follows: "(breastfeeding or breast feeding) and (methylphenidate or dexamfetamine or Adderall or lisdexamfetamine or atomoxetine)", "(malformation) and (methylphenidate or dexamfetamine or Adderall or lisdexamfetamine or atomoxetine)" and "pregnancy and (methylphenidate or dexamfetamine or lisdexamfetamine or atomoxetine or Adderall) and (levels or pharmacokinetic or concentration)", respectively. All these searches revealed remarkably small numbers of references, several of which were not relevant.

3 Epidemiology

International studies indicate that the prevalence of ADHD in children is approximately 5 %, and in adults it is about 3 or 4 % [1, 2, 7]. Treatment with medication is recommended for severe ADHD. Milder forms of ADHD should be managed, at least initially, with non-medical strategies; the UK NICE Guideline CG72 recommends the use of medication as first-line treatment in adults with moderate or severe impairment [6]. The Centers for Disease Control and Prevention (CDC) in the USA have estimated that approximately 3.5 million of a total population of around 74 million children in the USA are treated for ADHD [8]. Reliable figures for treatment of adult ADHD worldwide are not readily available, but there is a growing recognition that this condition has been under-recognized and under-treated in adults. The implication of this is that the numbers of adults who will be treated for ADHD are expected to increase greatly over the next few years. The number of recorded births in the USA in 2011 was 3,953,590 [9]. On the basis of the US National Comorbidity Survey Replication [7], the estimated prevalence of ADHD in adults (aged 18–44 years) in the USA was 4.4 %, of whom 38.4 % were female, implying that approximately 1.7 % of the adult female population had a diagnosis of ADHD. Of these females, 12.1 % had received ADHD treatment within the previous 12 months. If the fertility rate in females with ADHD is the same as that in the general population, and if the proportion of females treated for ADHD in 2011 was no less than that in 2006, this would imply that more than 8,000 females who were receiving treatment for ADHD gave birth in the USA within 1 year. It has been stated that adults with ADHD are under-recognized and under-treated, although this situation is being addressed. The implication is that the proportion of females receiving treatment for ADHD is likely to increase, and the

numbers may already be considerably higher than these figures. This emphasizes the importance of having accurate information to provide to prospective parents about the risks and benefits of ADHD treatment during pregnancy.

4 Health Considerations for the Mother

The core features of ADHD are developmentally inappropriate and impairing levels of overactivity, inattention and impulsivity [6]. The overactivity tends to wane over the teenage years and into adulthood, sometimes being replaced with internal feelings of restlessness and a desire to move, which the individual may be able to control. The absence of obvious overactivity in the adult may lead to the failure to diagnose and consequently to treat ADHD. The implications of failing to treat ADHD in adulthood can be profound [10]. Poor concentration is usually prominent and is liable to affect performance in training and employment. Impulsivity, often associated with emotional instability, can have major effects on an individual's personal and professional life, and is one of the reasons for the high rate of ADHD in the prison population [11]. Impulsivity might also lead to an increased rate of unplanned pregnancies. The expectations of motherhood may be much more difficult to fulfil in someone who has poor concentration and is impulsive, with implications both for the mother's wellbeing and for that of the baby. Untreated or inadequately treated ADHD can result in risk-taking, which could place the mother and child at risk, both prenatally and postnatally. In severe cases, a mother with ADHD may be deemed to lack the skills required to care effectively for young children, and this may become a child protection matter. Among the factors that need to be considered is the association between ADHD and substance misuse [12]. Although there continues to be debate on this subject, there is some evidence to indicate that adequate treatment of ADHD might decrease substance misuse [13, 14] rather than leading to it, as was previously suggested. If this is the case, then there would be a strong argument for ensuring adequate treatment of ADHD in the mother, not only for her own health but also because substance misuse is clearly associated with problems in offspring. Mothers who take alcohol or illicit drugs such as heroin or cocaine, or who smoke during pregnancy, are more likely to have children with ADHD [15]. Because mothers with ADHD are more prone to substance misuse, their offspring—in addition to being subject to any genetic factors increasing the likelihood of ADHD—might, as a result of such substance misuse, be more likely to develop ADHD. However, the need for continued treatment during pregnancy has to be weighed against the risks of the medication to both mother and child. There are very few data on treatment during pregnancy, implying that a reliable analysis of risks to the mother's health cannot easily be performed. The data on the risks of ADHD treatment in the general population are reassuring; in particular, much has been published on the cardiovascular risks, which appear to be low [16, 17]. How well these data apply to pregnant women remains uncertain.

5 Pharmacokinetic and Pharmacodynamic Considerations for ADHD Treatment During Pregnancy

Pharmacokinetic and pharmacodynamic changes during pregnancy can have a considerable influence on potential drug efficacy and toxicity in general [18, 19]. These considerations are likely to be of importance with regard to ADHD treatment during pregnancy.

Gastric emptying may be prolonged during pregnancy, and this could influence the timing/speed of action, especially for immediate-release preparations of methylphenidate and for dexamfetamine.

The volume of distribution of drugs used to treat ADHD is also likely to be altered during the course of the pregnancy, and this could result in changes in efficacy.

Published research on medication used to treat other conditions—notably, antiepileptic medication—has indicated that blood levels can be affected profoundly by pregnancy. For example, the serum level of the antiepileptic drug lamotrigine falls markedly in the first trimester of pregnancy, falling to a minimum during the second and third trimesters [20], and rises rapidly after delivery of the baby [21]. If similar changes were to occur with medications used to treat ADHD, this would have implications for control of symptoms of this condition during pregnancy, when higher drug doses might be required. There would also be implications for management after delivery of the baby, when the blood levels might rise sharply, with the risk of toxicity to the mother together with increased transfer into breast milk and possible consequences to the baby. There is clearly a need for carefully designed research into the effects of pregnancy and delivery on the pharmacokinetics of ADHD medications, so as to inform decisions on drug adjustments over this period. Because methylphenidate and dexamfetamine are not primarily metabolized by cytochrome P450 isoenzymes, changes in these enzymes are unlikely to have a significant effect on the concentrations of these drugs. The same might not, however, hold for atomoxetine, which is metabolized in the liver. The situation for atomoxetine is further complicated by the difference between extensive and poor metabolizers; the effect of pregnancy on atomoxetine blood levels in these two groups has yet to be determined.

Because of the major hormonal changes that occur during pregnancy, it would not be surprising if there were pharmacodynamic implications for ADHD treatment. In other words, the treatment might be more effective or less effective at various stages during the pregnancy and postpartum period. As far as the author is aware, no studies on these issues have been carried out.

6 Fetal Malformations and Other Health Considerations for the Fetus

6.1 Methylphenidate

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR), from their 2005 evaluation of the potential for methylphenidate to cause adverse effects on reproduction and development in humans [22], concluded that there were insufficient data to draw conclusions on (i) an association between methylphenidate therapy in pregnant women and pregnancy loss; and (ii) possible reproductive effects of methylphenidate in humans.

Dideriksen et al. [23] carried out a recent "mini review" of the effects of first-trimester in utero exposure to methylphenidate. They commented that the safety of methylphenidate during pregnancy has not been established. Their review of animal studies indicated that methylphenidate is not teratogenic in mice or in rats. However, in rats, a dose of seven times the maximum recommended human dose (MRHD) resulted in both maternal toxicity and fetal skeletal variations. The authors also commented that in rabbits, doses of about 40 times the MRHD were teratogenic, resulting in an increased incidence of spina bifida. There were no apparent effects on the development of the embryo or fetus at doses of around 11 times the MRHD. The authors searched PubMed/Embase and examined data from Michigan Medicaid recipients, the Collaborative Perinatal Project and the Swedish Birth Registry. Their search in August 2012 identified 52 titles/abstracts, but only six relevant publications were examined. A total of 183 children exposed to methylphenidate in the first trimester were reported in these publications, including three case reports. Excluding the case reports, there were four malformations in the 180 remaining children, resulting in a rate of 2.2 % (95 % confidence interval [CI] 0.6–5.6 %). On the basis of a spontaneous malformation rate in the general population of 3.5 %, the authors calculated a relative risk of 0.6 (95 % CI 0.2–1.6). The malformations in the four cohort studies were cardiac/cardiovascular: one unspecified cardiovascular defect, two ventricular septal defects and one univentricular heart. The authors acknowledged that the information was limited but concluded that methylphenidate exposure during pregnancy did not appear to be associated with a substantially (i.e. more than two-fold) increased risk of congenital malformations.

Pottegard et al. [24] recently reported a carefully conducted population-based cohort study of the effects of first-trimester exposure to methylphenidate, using Danish nationwide register data covering the years from 2005 to 2012. However, the data did not include pregnancies that were terminated, either spontaneously or electively prior to birth. The authors also did not analyse the results from stillbirths, because information on malformations in this group was incomplete. They included only pregnancies in which the infant survived for at least 1 day. It is interesting to note that they identified only one subject who took methylphenidate before 1 January 2005, which they chose as their start date for the data collection. To ensure that malformations that were not immediately evident were also recorded, the authors included only patients for whom 6 months of follow-up after birth was available. If the baby died within this time, the results were still included. They excluded pregnancies during which mothers took drugs that were known to be teratogenic. Mothers were required to have redeemed one or more prescriptions for methylphenidate within a time window from 14 days before the beginning of the first trimester to the end of the first trimester. The comparison group did not redeem a prescription for methylphenidate during this period. A total of 240 exposed pregnancies were identified, of which 222 met the inclusion criteria. Each of these was matched, using extensive matching criteria, to 10 control subjects who did not redeem prescriptions for methylphenidate (2,220 subjects). The exposed and unexposed cohorts were well matched, apart from a slightly higher prevalence of antipsychotic drug use in the exposed group. These groups were also compared with a random sample of 10,000 unexposed pregnancies; the cohorts were significantly younger, were less educated, smoked more and had a substantially higher consumption of drugs, which included antipsychotics, antidepressants, anxiolytics and non-steroidal anti-inflammatory drugs. In the exposed cohort, there were seven major malformations (3.2 %), of which three (1.4 %) were cardiac. In the unexposed cohort, the results were 86 (3.9 %) and 32 (1.4 %), respectively. These rates were also comparable to those in the random sample of unexposed pregnancies—namely, 3.7 and 1.1 %, respectively. The point prevalence ratios (exposed/unexposed cohorts) were 0.8 (95 % CI 0.3–1.8) for all major malformations and 0.9 (95 % CI 0.2–3.0) for cardiac malformations. The authors pointed out that the number of first-trimester exposed pregnancies (222) fell short of European Medicines Agency guidelines, which have suggested that at least 1,000 first-trimester exposed women should be found with no sign of excess risk before a

reassuring statement can be included in the summary of product characteristics. The authors concluded that use of methylphenidate in the first trimester of pregnancy did not appear to be associated with a substantially (more than twofold) increased overall risk of congenital malformations. They pointed out that the data were insufficient to allow risk estimates of specific malformations or other unwanted pregnancy outcomes, including excess risks of miscarriage, preterm birth, low birth weight, neonatal complications or postnatal neurodevelopmental issues.

Haervig et al. [3] recently reported a study of ADHD medication exposure in pregnancy from 1999 to 2010 in Denmark. A total of 1,054,494 pregnancies were registered, of which 480 were exposed to ADHD medication, which included methylphenidate (81.9 %), atomoxetine (9.4 %) and modafinil (8.8 %). All pregnancies ending in either a live birth or stillbirth registered in the Medical Birth Registry, miscarriage or pregnancy termination registered in the National Patient Registry or the Register of Legal Induced Abortions were identified. Carrying out this study in Denmark had the advantage that extensive medical information is recorded in nationwide registries. Unlike the study of Dideriksen by al., which examined only first-trimester exposure to ADHD medication (methylphenidate), the "exposure of interest" in this study was defined as the period of redeemed prescription of ADHD medication from 28 days before the first day of the last menstrual period, estimated from the gestational age recorded in the registry, until the end of pregnancy. Outcomes of pregnancy were categorized as induced abortion on maternal request (at $<$12 completed weeks), induced abortion on special indication (at $\geq$12 completed weeks), miscarriage (fetal loss at $<$22 completed weeks), stillbirth (fetal loss at $\geq$22 completed weeks) and live birth (child with any signs of life at $\geq$22 completed weeks). The authors included any congenital malformations diagnosed within the first 12 months of life. For any woman who had pregnancies with and without ADHD medication, the authors also conducted a case-crossover analysis, comparing exposed and unexposed pregnancies in the same woman. There were several notable findings from the study. First, the incidence of pregnancies exposed to ADHD medication increased from 5 to 533 per 100,000 person-years between 2003 and the first quarter of 2010. This was confirmed by a similar increase in ADHD prescribing in the general population of females in Denmark. Second, compared with the general population of women without a diagnosis of ADHD, those who were exposed to ADHD medication were, on average, more likely to be younger, single, less well-educated and receiving social security benefits. They were also more likely to be taking other medication. Third, both the abortion and miscarriage rates were increased in women exposed to ADHD medication (odds ratio [OR] adjusted for age, region and ethnicity: 4.70, 95 % CI 3.77–5.85; abortion "on maternal request": OR 2.99, 95 % CI 1.34–6.67; abortion "on special indication" and miscarriage: OR 2.07, 95 % CI 1.51–2.84). The stillbirth odds ratio of 2.38 (95 % CI 0.59–9.55) was not statistically significant, reflecting the fact that the numbers were too small to allow any conclusion to be drawn. Fourth, and of particular interest, was the finding that the adjusted odds ratios in the crossover study both for induced abortion on maternal request and for stillbirth were not statistically significantly increased. The odds ratios were 1.34 (95 % CI 0.90–2.00) for induced abortion on maternal request and 1.30 (95 % CI 0.69–2.47) for miscarriage. The numbers for abortion on special indication were too small to provide meaningful data. Finally, the adjusted odds ratio for congenital malformations was 0.48 (95 % CI 0.15–1.53), and the unadjusted figures were 0.50, with a similar confidence interval, providing no evidence for an increase in congenital malformations in babies born alive to mothers taking ADHD medication. This last finding is remarkable, since the women with ADHD were—regardless of whether or not they were exposed to ADHD medication—apparently more socially disadvantaged. However, this might, in part, reflect an increase in the pregnancy loss, leading to a reduction in congenital malformations in those born alive, again regardless of whether the women were taking medication or not; no definite conclusions can be drawn relating to this, because no information was provided on any malformations in the pregnancies that did not result in live births. Although this paper provided some very valuable findings, some key information was not available, as is often the case with studies from databases. For example, as the authors acknowledged, the "exposure" to ADHD medication was based on prescriptions redeemed, but there could be no guarantee that the subjects actually took the medication. Most of the mothers were exposed to methylphenidate; the results did not allow analysis of individual medications, but the numbers exposed to other medications for ADHD were small.

Earlier studies of methylphenidate in pregnancy included single case reports by Kopelman et al. [25] and Lundquest et al. [26], and a case series of 39 mothers reported by Debooy et al. [27]. In the first of these cases, the mother was also taking haloperidol and phenytoin, and in the second case, the mother was taking methylphenidate and pentazocine intravenously, as well as paracetamol. The series of 39 cases reported by Debooy et al. [27] was of mothers taking methylphenidate and pentazocine intravenously. Because all of these mothers were taking other medication, and the majority of the cases were individuals who were misusing drugs—and who might, in addition, have been taking other substances of misuse—no conclusions can be drawn about the role of methylphenidate in

Table 1 Reports of fetal malformations with methylphenidate (adapted from Bolea-Alamanac et al. [28])

Authors	Number of patients	Drugs recorded	Pregnancy outcome
Kopelman et al. [25]	Single case report	Haloperidol 15 mg daily, phenytoin 300 mg daily, methylphenidate 30 mg daily	Syndactyly of fingers, adactyly of one foot, deformed radius, aortic valve malformation
Lundquest et al. [26]	Single case report	Methylphenidate and pentazocine intravenously, propoxyphene and paracetamol; doses not known	Severe birth asphyxia and withdrawal syndrome; the mother died: pulmonary hypertension at delivery
Debooy et al. [27]	39	Methylphenidate and pentazocine intravenously; doses not known	21 % were premature, 31 % had growth retardation, 28 % had withdrawal syndrome, one had polydactyly, one had congenital cardiac septal defect
Bolea-Alamanac et al. [28]	Single case report (see text for details)	Methylphenidate slow-release 72 mg daily, reduced to 54 mg daily at 13 weeks gestation, subsequently titrated down to 18 mg daily 6 weeks before delivery with a plan to stop it 1 week before delivery; fluoxetine 40 mg daily	Delivered at 38 weeks by ventouse extraction; inhaled a small amount of meconium; 6 h in neonatal intensive care unit for ventilation and observation; no further complications; no abnormalities when examined at 14 weeks by a paediatrician

causing the malformations that were reported. These cases were summarized in a recent publication by Bolea-Alamanac et al. [28]. Table 1 in the current article draws on data from their paper and provides information on these cases. Bolea-Alamanac et al. also presented a detailed new case report. The patient, who had a history of depression treated with fluoxetine 40 mg daily and ADHD treated with slow-release methylphenidate 72 mg daily, became pregnant unexpectedly at 20 years of age with her first pregnancy. She continued to take the methylphenidate in the same dose during the first trimester because she felt that the risks of deterioration in her mental health outweighed the risks to the fetus. The dose was decreased to 54 mg daily in the 13th week of pregnancy, and the fluoxetine was reduced at the same time. The methylphenidate was titrated down to 18 mg at 6 weeks before delivery, with a plan to stop it completely 1 week before delivery to avoid discontinuation symptoms in the newborn. The baby was born at 38 weeks gestation by ventouse delivery, with Apgar scores of 6 at 1 min, 7 at 5 min and 8 at 10 min. There was minor meconium aspiration, and the baby was admitted to the neonatal intensive care unit for ventilation and observation for 6 h. There were no further perinatal problems. The mother was not prescribed stimulants postpartum, but her mental health began to deteriorate 5 weeks after delivery and did not respond satisfactorily to sertraline. She expressed the wish to recommence methylphenidate and to continue to breastfeed. The methylphenidate was increased slowly to the original dose of 72 mg of the slow-release preparation daily. No methylphenidate was detected either in the breast milk or in the baby's blood. Examination of the baby by a paediatrician at 14 weeks of age, with further reviews at 6 months and 1 year, revealed no developmental problems. Although it would be unwise to draw any conclusions from a single case report, this case might be viewed as being reassuring, both in terms of breastfeeding and with regard to the baby of a mother taking methylphenidate during pregnancy.

6.2 Amphetamines

As Humphreys et al. [29] have pointed out, most of the information on prenatal amphetamine exposure is from illicit drug use or use of these drugs to suppress appetite. Although abuse of amphetamines in pregnancy has been associated with low birth weight, pre-term birth and problems with the fetus, the confounding factors—particularly misuse of alcohol and other drugs—imply that it would be difficult to be certain about attribution of these findings to the amphetamines [30].

Oei et al. [31] have reviewed the general subject of the effects of amphetamines on the pregnant woman and her children. They have drawn attention to a number of publications reporting adverse effects in amphetamine users, including psychosis, increased libido, tachycardia, tachypnoea, ischaemic heart disease, acute myocardial infarction, Parkinson disease and neurological deficits, including short-term memory, executive function and manual dexterity problems. There have been other interesting reports showing an association between the use of amphetamines and fetal malformations. For example, Elliott et al. [32] reported a cluster of gastroschisis cases in Nevada. Fourteen cases were compared with 57 controls. The odds ratios for the use of methamphetamine or any vasoconstrictive recreational drug (methamphetamine, amphetamine, cocaine, ecstasy) were 7.15 (95 % CI

1.35–37.99) and 4.46 (95 % CI 1.21–16.44), respectively. However, it should also be noted that there were high odds ratios for gastroschisis associated with self-reported illnesses during pregnancy, including chest cold (OR 8.20, 95 % CI 1.54–43.5) and sore throat (OR 15.94, 95 % CI 1.83–138.97). In the absence of clear data, it would be inappropriate to assume that these adverse effects associated with pregnant women with substance misuse would necessarily be seen in pregnant women who are being treated with amphetamines for ADHD; most of the latter will be relatively young and should be taking regular, more modest doses, orally, not intravenously. The number of women who are being treated with amphetamines for ADHD and who will, in addition, be abusing other drugs or alcohol would be expected to be much smaller than the number of those who are abusing amphetamines and are also abusing other substances. However, there is clearly a need to monitor women who are being treated for ADHD carefully to determine whether any such potential adverse effects occur in this group. With regard to fetal effects, Oei et al. concluded that amphetamine exposure had not been proven to be definitely teratogenic even for pregnancies in mothers who were abusing these drugs. They did, however, point out that Eriksson et al. [33] had found that infants of mothers who were abusing amphetamine had a smaller mean head circumference than expected. Head circumference at birth and at 1 year of age correlated with measures of school achievement.

Over 30 years ago, Naeye [34] analysed data from a large prospective study in which 237 of 42,101 women took dexamfetamine to control their weight gain. They found that birth weight was not significantly affected if the dexamfetamine was discontinued before 28 weeks of gestation. If the dexamfetamine was continued after 28 weeks, birth weight was 4 % lower (144 g) in high-weight-gain gestations ($p < 0.01$). Perinatal mortality, body length and head circumference were not affected. It is interesting to contrast this with the results of Eriksson et al. [33], who found that head circumference was smaller for infants whose mothers abused amphetamines, perhaps emphasizing the point that, for a number of reasons, findings in the population who abuse medication are not necessarily comparable to findings in subjects who use medication therapeutically.

In an even older publication, Milkovich and van der Berg [35] reported the results of a very large prospective observational study of pregnant women who took weight-reduction drugs (amphetamines and phenmetrazine). The severe congenital anomaly rate per 100 live-born children at 5 years of age did not differ from the rate in children whose mothers had not used these drugs. However, there was an excess of oral clefts in the children whose mothers had been prescribed amphetamines within the first 56 days from the last menstrual period.

No relevant references for lisdexamfetamine were found, but since this drug is metabolized to dexamfetamine, any results relating to dexamfetamine would also have been relevant to lisdexamfetamine.

6.3 Atomoxetine

The US FDA has rated atomoxetine as "pregnancy category C" (see Sect. 1). The package insert for atomoxetine (Strattera) states that drugs should be given only if the potential benefit justifies the potential risk to the fetus. However, since so little information about the risks to the fetus is available, it could be argued that it would be difficult to make an informed judgement.

The pharmaceutical company has stated that no adequate and well-controlled studies have been conducted with atomoxetine in pregnant women (Lilly, data on file). Because the trials excluded females who were not using contraception, were already pregnant or were breastfeeding, there is little information from the trial data. The pharmaceutical company attempted to follow instances of pregnancies and breastfeeding that did, nevertheless, occur, and they also collected spontaneous reports from the Lilly Worldwide Safety Database. If the report of atomoxetine exposure during pregnancy occurred before the known outcome, it was classified as prospective. If the report occurred after an abnormal diagnosis had been established or after there was a known outcome for the pregnancy, it was classified as retrospective. In the period to 31 January 2010, 49 pregnancies were identified prospectively, with a reported outcome. Seven of these underwent elective termination, without any known fetal defect. They were not included in further analysis. Of the remaining 42 pregnancies that were identified prospectively, the rates of spontaneous abortion ($n = 4$, 9.5 %), ectopic pregnancy ($n = 0$), premature birth ($n = 3$, 7.1 %), post-term birth ($n = 0$) and congenital abnormality ($n = 1$, 2.4 %) were all lower than the historical control rate in the general population. In addition, there were three babies with unspecified conditions, for whom no further information is available. It was concluded that the data were insufficient to indicate whether there was either an association or a lack of association between atomoxetine and adverse pregnancy outcomes (Lilly, data on file). Not only are the numbers small but, despite the efforts made by the pharmaceutical company, the completeness of the data cannot be guaranteed, implying that the data were, as indicated by the pharmaceutical company, insufficient to allow any firm conclusions to be drawn.

Some animal data on rabbits and rats have also been made available from the pharmaceutical company. It should be noted that these data are of very limited relevance—not only because teratogenicity in animals does not

necessarily imply teratogenicity in humans, and lack of teratogenicity in animals does not prove lack of teratogenicity in humans—but also because the doses used are not comparable.

Throughout the period of organogenesis, pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine (about 23 times the maximum human dose in mg/m^2). However, it should be noted that it was stated that the area under the curve of atomoxetine at this dose in rabbits was estimated to be only 3.3 times higher than the levels in humans receiving the maximum dose who are extensive metabolizers, or 0.4 times those in humans who are poor metabolizers. It was stated that these doses caused slight maternal toxicity in the rabbits. One of three studies reported a decrease in live fetuses and an increase in early resorptions. There were "slight increases" in the incidence of atypical origin of the carotid artery and absent subclavian artery. The "no-effect dose" for these outcomes was 30 mg/kg/day (Lilly, Strattera package insert, 2013).

The atomoxetine treatment of rats was up to approximately 50 mg/kg/day (about six times the maximum human dose in mg/m^2). The atomoxetine was administered from 2 weeks before mating (females) or 10 weeks before mating (males) and was continued throughout organogenesis and lactation. In one of two studies, pup weight and survival were decreased (Strattera package insert, 2013). Decreased pup survival was also seen at 25 mg/kg/day but not at 13 mg/kg/day. In a study in which rats were treated over periods similar to those just stated, there was a decrease in fetal weight of females only and an increase in the incidence of incomplete ossification of the vertebral arch at doses of 40 mg/kg/day but not at 20 mg/kg/day (Strattera package insert, 2013). The pharmaceutical company data also state that "no adverse fetal effects" (which presumably included malformations) were seen when pregnant rats were treated with up to 150 mg/kg/day throughout the period of organogenesis.

In contrast to the situation for methylphenidate and dexamfetamine, atomoxetine has been used only recently for the treatment of ADHD, implying that the experience with this drug, particularly in pregnancy, is limited.

7 Other Possible Adverse Effects on the Fetus

The main drugs used for treating ADHD are all sympathomimetic. The mean effects on the heart rate and blood pressure in children are relatively small, but there are larger effects, notably on blood pressure, with atomoxetine in some individuals [36]. Whether similar effects occur in the fetus, and what the long-term outcome of such effects might be, are not known at present.

No information could be found on spontaneous abortion rates or on therapeutic/requested abortion rates for apparently healthy fetuses.

8 Health Considerations for the Newborn Baby, Including Breastfeeding

Most drugs cross the placenta and can potentially affect not only the fetus but also the newborn baby. There is evidence for this with regard to amphetamines, at least for women abusing these drugs [37, 38]. In theory, ADHD medication could affect the heart rate and blood pressure of the newborn baby but, again, no relevant data could be found.

It is also possible that the newborn baby might have adverse effects from no longer receiving the drug, having received it as a fetus in utero, via placental transfer, in some cases from conception. There have been reports of withdrawal syndromes in babies of mothers abusing amphetamines [39] in pregnancy but, again, the relevance of this situation to mothers taking therapeutic medication for ADHD is questionable, because people who abuse medication may be taking much larger doses, often via the intravenous route, and may also be misusing other substances.

The health consequences of the mother suspending ADHD treatment could, as already indicated, affect the care and consequently the wellbeing of the baby. From this point of view, if the decision had been made to stop ADHD treatment during pregnancy, there might be an argument for recommencing it as soon as possible after delivery. However, continuing the treatment might have implications for breastfeeding. The American Academy of Pediatrics has considered that amphetamines are contraindicated during breastfeeding [40]. Data on transfer of medication used to treat ADHD into breast milk is presented in the next section.

8.1 Breastfeeding Data

Breastfeeding has a number of well-publicized psychological and physical benefits [41]. In addition, a retrospective study of 56 children with ADHD compared with 52 sibling controls and 51 non-sibling controls indicated that children with ADHD were less likely to have been breastfed at 3 and 6 months of age than children in the two control groups, suggesting that breastfeeding might have a protective effect against ADHD in later childhood [42]. On the other hand, there is a reluctance to breastfeed if the mother is taking medications that are transferred into the breast milk, because of concerns that these might have adverse effects on the newborn child. Exposure of maternal medication to the fetus/baby could be minimized

by discontinuing medication during the pregnancy (see earlier for discussion) and recommencing it, if clinically indicated, after delivery. If the mother wanted to breast-feed the baby, she could then make a decision on whether to recommence the medication at that stage, to delay it until after the baby had been weaned or, if the clinical risk/benefit assessment allowed, not to recommence it at all.

8.1.1 Dexamfetamine

Ilett et al. [43] studied four breastfeeding women taking dexamfetamine, and their infants. Blood samples were taken from all four women. In two cases, a single blood sample was taken 3 to 4 h after the first dexamfetamine dose of the day. In the other two cases, samples were taken just before the first morning dose and at 2, 4 and 6, 7 or 8 h after this dose. In one of these two cases, a blood sample was also taken 24 h after the dose. Breast milk was collected either by hand expression or by a manual breast pump just before the morning dose and again every time the infant was fed over the next 24 h, usually 6 to 8 feeds. The maternal dexamfetamine dose ranged from 15 to 45 mg daily (median 18 mg/day), and the median ratio of the milk to plasma concentration was 3.3 (interquartile range [IQR] 2.2–4.8). The median absolute infant dose was 21 μg/kg/day (IQR 11–39) and the relative infant dose was 5.7 % (IQR 4–10.6 %). In the three infants who were tested for plasma dexamfetamine, none was detected in one (limit of detection 1 μg/L). In the other two infants, the concentrations were 18 and 2 μg/L. No adverse effects were seen in the infants. From the limited data available, no specific concerns were identified. In particular, it should be noted that the absolute infant dose was very small. However, it should also be noted that the numbers studied were very small.

8.1.2 Methylphenidate

Spigset et al. [44] presented a single case report of a mother taking immediate-release methylphenidate 15 mg daily who breastfed her baby with no apparent adverse effects on the infant.

Hackett et al. [45] reported three cases in which breastfeeding mothers took methylphenidate in doses from 35 to 80 mg daily. Again, no adverse effects were apparent in the infants. These authors also pointed out that the amount of drug ingested by the baby compared with the maternal dose is likely to be very small.

The case report by Bolea-Alamanac et al. [28] has been detailed above: no methylphenidate was found in the mother's breast milk or in the baby's blood (see earlier).

8.1.3 Atomoxetine

Although there are no data indicating that atomoxetine is excreted in human breast milk, up to 31 January 2010 there were reports of two infants who slept longer than usual after being breastfed by mothers who were taking atomoxetine (Lilly, data on file). It was stated that neither the mothers nor the breastfed infants had any serious adverse events. The pharmaceutical company commented that information from all data sources to date is insufficient to indicate either an association or a lack of association between atomoxetine and lactation outcomes.

Atomoxetine and/or its metabolites are said to be excreted in the milk of rats (Lilly, data on file). No further information was available.

9 Health Considerations in Later Childhood

As discussed earlier, the offspring of mothers with ADHD may be more liable to develop ADHD themselves, not only because of genetic considerations but also because of environmental factors [46], including the risk of maternal comorbid substance abuse [12]. There are several publications indicating that taking illicit heroin, cocaine and other drugs of misuse during pregnancy can increase the risk of ADHD in the child [15]. From this point of view, as already indicated, good management and continued treatment of the ADHD in the mother might help to protect the child against also developing this disorder.

Is there any evidence that treatment might have adverse effects in later childhood? The metabolites of methamphetamine include amphetamine. In a recent study of the effects of prenatal methamphetamine exposure on attention, as assessed by continuous performance tests, Kiblawi et al. [47] tested 153 exposed and 148 comparison children at 5.5 years of age, using the Conners Kiddie Continuous Performance Test. Although they found no differences between the groups in omission errors, commission errors or reaction time for correct trials, there were some subtle differences in the test results: an increased slope of reaction time across blocks ($p < 0.001$), increased variability in reaction time with longer interstimulus intervals ($p < 0.01$) and an increased likelihood of greater than 50 % on the ADHD confidence index (odds ratio 3.1, 95 % CI 1.2–7.8, $p = 0.02$). In another study [48], the same group showed that methamphetamine exposure in pregnancy was associated with increased emotional reactivity and anxious/depressed problems in the children at both 3 and 5 years of age, and externalizing and ADHD problems by age 5 years. Heavy exposure was related to attention problems and withdrawn behaviour at both ages. However, because of confounding factors, including the

possibility that the mothers misused other substances, and because the drug taken by the mothers was not methylphenidate, dexamfetamine or atomoxetine, it is difficult to draw any firm conclusions from the results of these studies.

Reference has already been made to the possible general beneficial effects of breastfeeding [41], including the possibility that breastfeeding itself might be protective against ADHD in the offspring in later childhood [42], although it should be noted that the latter study was not performed in children of mothers who were taking ADHD medication during lactation.

10 Controversies

10.1 Should ADHD Medication Be Stopped Before, During or After Pregnancy?

In the absence of firm data, no clear recommendations can be made. The best policy is usually for the professional to be open and honest about the lack of data with regard to the risks of continuing the medication, while being equally open and honest about the risks of discontinuing the medication. Both treatment and non-treatment bear potential risks. While discontinuation of medication might reduce the risk of chemically harming the child, it might also lead to an increase in potentially harmful behaviours in the mother, related to an increase in the core features of ADHD; this implies a risk of general deterioration in the mother's mental health, including the possible emergence or exacerbation of erratic and disorganised behaviour, impulsivity, emotional instability and poor risk management (such as dangerous driving or the use of drugs, alcohol, or tobacco during pregnancy). Risk to the developing baby may also arise from increased stress levels [49]. Considerations will need to be guided by the levels of risk in individual patients. Because of the high rate of unplanned pregnancies [50], there is an argument for ensuring that these discussions take place soon after girls with ADHD become of childbearing potential, but the timing and nature of the discussion will depend on the needs and abilities of the individual patient.

10.2 Should ADHD Medication Doses Be Adjusted During the Course of the Pregnancy or After Delivery?

In the absence of reliable pharmacokinetic and pharmacodynamic data, until the necessary research has been performed, it might be reasonable to manage the situation clinically, although any dose increases would need to be balanced against the general principle of trying to keep maternal medication doses low. Because of the absence of any clear information indicating an increased risk to the fetus, at least for methylphenidate, it might appear reasonable to allow some flexibility in the dose, should dose adjustments prove to be necessary on clinical grounds.

10.3 Should Breastfeeding Be Encouraged or Discouraged?

The data do not allow an overall conclusion to be drawn. The information is particularly lacking with regard to atomoxetine, which has been available for only a relatively short period. From the data available on methylphenidate and dexamfetamine, it appears that, although it can be transferred to breast milk, the dose received by the baby is likely to be very small. Again, with no clear risk having been established, it would seem reasonable to discuss the possible advantages and disadvantages with the pregnant mother and allow her to make a decision.

11 Conclusions

Thousands of pregnant women are being treated for ADHD in the USA alone. With the growing recognition of the importance of ADHD in teenagers and adults, the numbers are likely to increase greatly, both in that country and worldwide. Against this background, it is remarkable that there is so little information on the risks of treatment and, indeed, the benefits of well-managed treatment in this group of individuals. Although there is not enough evidence to recommend either continuation or discontinuation of treatment during pregnancy and breastfeeding, from the very limited data available, it appears that the risks of continued treatment with methylphenidate are probably not high, while the risks of discontinuing treatment could be considerable. The harmful effects of amphetamines on the fetus in mothers who abuse drugs are well documented, but confounding factors do not allow these findings simply to be applied to mothers who are taking dexamfetamine therapeutically for ADHD. The information on atomoxetine is very limited, implying that there can be little confidence in providing guidance on continuing this drug in pregnancy. When discussing the potential risks and benefits, clinicians should, as always, be open about the limited information available and should provide a balanced view.

Recommendations for research include well-conducted prospective comparative studies on the effects of ADHD treatment during pregnancy and breastfeeding on the wellbeing of both the mother and the offspring. Such studies should include careful monitoring of the control of ADHD symptoms during pregnancy, together with adequate blood-level data to determine whether there are any major pharmacodynamic or pharmacokinetic implications

for treatment during the various stages of pregnancy and in the postpartum period. Studies on the outcome of the pregnancy should include information not only on spontaneous abortion and the malformation rate but also on the developmental progress of the children. Such information should enable women of childbearing age to make much more adequately informed decisions about how to manage ADHD treatment during pregnancy and breastfeeding in the future.

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