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Review article

Parental ADHD in pregnancy and the postpartum period – A systematic review

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders worldwide, and in the majority of patients persists into adulthood. However, it remains unclear how maternal ADHD could affect pregnancy and birth as well as early mother-(father)-child interaction. There are several studies investigating the effect of depressed or anxious parents on parent-child-interactions in early infancy, but data about the influence of parental ADHD is lacking although it is a common mental disorder in parents. Additionally, the prescription of stimulant and other ADHD medication for adult ADHD patients is rising due to improved diagnostic procedures and a greater awareness of this disorder in adulthood among psychiatrists and psychologists. However, this leads to increased numbers of treated ADHD women that wish to have children or experience unplanned pregnancies while taking stimulant medication. In our systematic review we aimed at analysing the current evidence for the association of maternal ADHD with pregnancy and birth outcomes, pregnancy risks and health behaviour in pregnancy, as well as the association of parental ADHD with early parent-child interaction and early child development in the first 3 years. Furthermore, we reviewed recent evidence on the risks of stimulant and non-stimulant treatment for ADHD in pregnancy and lactation.

1. Introduction

Attention-deficit/hyperactivity disorder is the most common neurodevelopmental disorder and persists into adulthood with a prevalence of ~3 % adult patients worldwide (Zhu et al., 2017). There are currently several published studies and reviews investigating the contribution of pre-, peri-, and postnatal risk factors and gene-environment-development interactions on the development of ADHD in children (Palladino et al., 2019; Tole et al., 2019). There are also several studies investigating parent-child interaction in ADHD parents and their ADHD or non-ADHD children, with most of the studies conducted on children aged 3 years or older. However, research on how ADHD in the mother could increase the risk of pregnancy and birth complications, negative birth outcomes as well as postnatal difficulties is sparse. Furthermore, because of a generally less healthy life style in ADHD patients, it seems obvious that ADHD women might also show this during pregnancy, of which obstetricians should be aware if that assumption would hold true. It has previously been shown that mothers suffering from other mental health issues such as depression, bipolar disorder, and anxiety disorders are known to have an increased risk of pregnancy and birth complications (Rusner et al., 2016). Furthermore, mothers with mood disorders are at an increased risk of early dysfunctional mother-child-interactions that might negatively influence the development of the children (Doucette et al., 2014; Hirshfeld-Becker et al., 2012; Marcus, 2009). Given the high comorbidity of ADHD with other mental disorders such as major depression, anxiety and bipolar disorder, it is therefore likely that similar might be true for mothers or parents with ADHD, but there are only few data to date regarding the

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early infancy period. It is not known so far, if mental disorders in general might lead to increased risk of pregnancy and birth complication in addition to impaired parent-child interaction in early infancy or if some of these issues are stronger associated with a specific mental disorder.

Interestingly, there is a wealth of studies investigating the risk of ADHD developing in children due to pre-, peri-, and postnatal risk factors such as smoking, alcohol, illegal drug intake, maternal depression and anxiety, and parenting style. However, the majority of these studies do not include ADHD screening in the parents (Mulraney et al., 2019), yet ADHD is a highly heritable disorder (Faraone and Larsson, 2019). There are several studies reporting that maternal depression in pregnancy and postpartum leads to an increased risk of childhood ADHD, but only very few of these studies screened for ADHD in the respective mothers. There are also several studies reporting that maternal obesity increases the risk of ADHD in the offspring, and obesity is also more common in patients with ADHD (Andersen et al., 2018; Landau and Pinhas-Hamiel, 2019). However, again the mothers were mostly not assessed for ADHD in these studies, and thus it is unclear what the causal factor may be that mediates this association (Andersen et al., 2018).

There is currently also a lack of data regarding the risks of stimulant and non-stimulant medication in pregnancy and lactation. Due to the rising number of ADHD medication prescribed to women at childbearing age (Anderson et al., 2018a,b), it is important to determine which medications can be considered relatively safe in pregnancy and lactation, especially as ADHD women have an increased risk of unplanned pregnancies (Owens and Hinshaw, 2020).

Previous reviews as for example conducted from Li and colleagues (Li et al., 2020) focused on outcomes of ADHD medication exposure during pregnancy but did not include the more sparse data on ADHD medication in lactation. And there is also a recent review on environmental risk and protective factors which are associated with the risk of ADHD in the offspring (Kim et al., 2020), however, to our knowledge there is no systematic review available focusing on ADHD of the parents in the perinatal period.

In our systematic review, we therefore aimed to investigate existing evidence for the association of maternal ADHD and pregnancy and birth outcomes, pregnancy risks and health behaviour in pregnancy, as well as the association of parental ADHD with parent-child-interaction in the early infancy period and early development of the children (with children until 3 years of age). Because especially the topic on birth and pregnancy complications would be incomplete without including the association of ADHD medication during pregnancy and pregnancy and birth outcomes as well as early development of the children, we additionally reviewed recent evidence on the risks of stimulant and non-stimulant treatment in pregnancy and lactation. Hereby, we aimed at drawing a broad picture of issues that are potentially associated with parental ADHD in the perinatal period and early infancy.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). We searched PubMed and Web of Science databases (all years) using the following search strategies: “ADHD OR ADD AND Mother AND Pregnancy”, “ADHD OR ADD AND Mother AND Lactation OR breastfeeding”, “ADHD OR ADD AND Mother AND postpart*”, “ADHD OR ADD AND pregnancy AND stimulants”, “ADHD OR ADD AND pregnancy AND Methylphenidate OR Amphetamine OR lisdexamfetamine OR atomoxetine OR modafinil”, “ADHD OR ADD AND lactation or breastfeeding AND stimulants”, “ADHD OR ADD AND pregnancy AND Methylphenidate OR Amphetamine OR lisdexamfetamine OR Atomoxetine OR modafinil”, “postpartum AND mother-child-interaction OR father-child-interaction AND maternal ADHD OR paternal ADHD”, “postpartum OR postpartum period AND mother-child-interaction OR mother-child-relations OR father-child-interaction OR father-child-relations OR parent-child relations AND maternal ADHD OR paternal ADHD”, as well as using "Attention-deficit", "Attention deficit", and “Hyperkinetic syndrome” instead of ADHD/ADD, and “[methylphenidate ("breast feeding" OR breastfeeding OR lactation OR "breast milk") NOT (rat OR mice OR pups OR rodent) NOT (review)]”. We additionally searched using “[amphetamine ("breast feeding" OR breastfeeding OR lactation OR "breast milk") NOT (rat OR mice OR pups OR rodent) NOT (review)]”, “[atomoxetine ("breast feeding" OR breastfeeding OR lactation OR "breast milk") NOT (rat OR mice OR pups OR rodent) NOT (review)]”, “[guanfacine ("breast feeding" OR breastfeeding OR lactation OR "breast milk") NOT (rat OR mice OR pups OR rodent) NOT (review)]”, and “[modafinil ("breast feeding" OR breastfeeding OR lactation OR "breast milk") NOT (rat OR mice OR pups OR rodent) NOT (review)]”.

The final search and decision regarding which studies to include was conducted initially on 31/07/2020 and finally on the 21/11/2020. Articles were individually searched for adherence to our inclusion criteria. Specifically, regarding our three research questions, we included articles that investigated pregnancy and birth outcomes as well as pregnancy risks and health behaviours in pregnancy of women with a diagnosed ADHD. Here, we also included studies on unplanned and teenage pregnancies in association with ADHD. Second, we included articles that reported findings on parent-child interaction of parents diagnosed with ADHD with their children aged 3 years and younger, because the early infancy seemed much more understudied than the influence of parental ADHD in older children. Parent-child interaction is defined as an appropriate, responsive and reflective (in terms of mentalizing) interaction of a parent with its child. This is important for a healthy early development of the child. The parent-child interaction includes language acquisition, socializing and learning processes, but also the development of a secure attachment style, which is a protective factor for mental and physical health (Brumariu, 2015; Papousek, 2007, 2012). We also searched for studies on the association of parental ADHD and early development of the children. And the third topic, treatment with ADHD medication in pregnancy and breast feeding was chosen because it closely relates to pregnancy and birth outcomes/pregnancy risk/-pregnancy health behaviours of ADHD women. Here we included articles on the use and outcome of ADHD medication (stimulants and the non-stimulants atomoxetine and guanfacine as well as modafinil given its common off label use in ADHD). We included only original research papers. In the meta-analysis and review articles that were found, the reference lists were searched for additional original research articles that could be of interest and met our inclusion criteria. Inclusion criteria were retrospective and prospective clinical studies, registry studies, naturalistic studies, observational studies, open label studies and case series as well as case reports with regard to breastfeeding and lactation due to the paucity of data on this topic. We only included reports written in English so that the authors were able to read and recognize the whole content of the manuscript. Exclusion criteria were reviews, meta-analysis, animal studies, in vitro studies, and studies including children aged >3 years. We also excluded studies on illegal stimulant use (methamphetamine, cocaine, amphetamine, and methylphenidate) and caffeine use and studies in which parental ADHD was not evaluated. Inclusion and exclusion criteria were based on consensus among all authors; unanimity was required for both and was achieved through Delphi rounds. Excluded studies from the last step can be found in supplementary Table 1. Two rounds were sufficient to reach complete agreement among authors. We did not pre-register our review in the planning phase, which needs to be mentioned as a limitation. Furthermore, even if the included studies differed in the study designs, we rated the quality of the included studies using the GRADE system (Guyatt et al., 2008). The GRADE system (Grading of Recommendations Assessment, Development and Evaluation) can not only be used for guideline development but also to rate study quality and quality of evidence in systematic reviews. The following criteria are included in the rating study design: limitations, indirectness of evidence, inconsistency of results, imprecise data, publication/reporting bias. After evaluation of

those criteria, the studies are rated to high (the true effect might be similar to the estimated effect), moderate (true effect might be close to the estimated effect), low (true effect might be markedly different from the estimated effect) and very low quality (true effect is probably markedly different from the estimated effect). The quality rating of evidence is mentioned in Tables 1–3 and more detailed displayed in supplementary Table 2.

3. Results

A total of 817 records were retrieved using our search criteria (see Fig. 1). After initial screening of titles and removal of duplicates, 416 papers were excluded. 81 more paper were excluded either because there were no abstract or full text available or they were poster/conference abstracts. Additionally, 270 papers were further excluded as they were unrelated articles, not written in English, repeated publications, no abstract available, reviews, meta-analysis, meeting abstracts, animal models, or study protocols of planned studies without actual results as well as inclusion of illegal stimulant users (methamphetamine, cocaine, amphetamine and methylphenidate), focused on caffeine use, or presented as case reports or case series (with the exception of case series and case reports on lactation). In a last step, after reading the full manuscripts, 18 studies were excluded because of the inclusion of children aged > 3 years at baseline visit, inclusion of illegal stimulant users (methamphetamine, cocaine, amphetamine and methylphenidate), focused on caffeine use, or presented as case reports or case series (with the exception of case series and case reports on lactation).

The final number of papers included in our review was 32, which again was split based on the four research questions: association of maternal ADHD and health behaviour in pregnancy, pregnancy and birth risks and outcomes (n = 7), association of parental ADHD on parent-child interaction in early infancy including parenting styles and parenting stress and early development of the children (n = 9), ADHD medication in pregnancy (n = 12) and ADHD medication in lactation (n = 4). Two articles are discussed in as well the paragraph about maternal ADHD and birth and pregnancy outcomes as in the paragraph about stimulant medication in pregnancy. Synthesized results from each of the topic/search terms are described below (see Fig. 1 and Tables 1–3, excluded articles are shown in supplementary Table 1). Because of the paucity of data, we included a relatively broad variety of studies, including studies that were rather focused on ADHD or the risk of ADHD in children but reported about the paternal ADHD as well. As expected, there were no studies of high quality of evidence, only moderate and moderate to low with regards to maternal ADHD and health behaviour in pregnancy, pregnancy and birth risks and outcomes (n = 3 moderate, n = 3 low to moderate, n = 1 low quality of evidence), association of parental ADHD with parent-child interaction in early infancy including parenting styles and parenting stress and early development of the children (n = 5 moderate, n = 3 low to moderate, n = 1 low quality of evidence), ADHD medication in pregnancy (n = 6 moderate, n = 1 moderate to low; n = 5 low). Because there were only case reports or case series available regarding ADHD medication in lactation, the quality of evidence here was only low or very low (see Tables 1–3 and supplementary Table 2).

3.1. Association of maternal ADHD with health behaviour in pregnancy, pregnancy and birth risks and outcomes

Two studies were identified not only investigating the association of ADHD medication with perinatal outcomes but including the discussion of the association with maternal ADHD itself. The authors came to the conclusion that the maternal ADHD diagnosis rather than ADHD medication was associated more significantly with perinatal outcomes. In 2017 Nörby et al. studied singletons born between 2006−2014 in Sweden (n = 964 734), comparing infants whose mothers' received medication during pregnancy, only before or after pregnancy, or received no medication at all (Norby et al., 2017). Information regarding ADHD diagnosis was not available; however, as only psychiatrists can prescribe stimulant drugs in Sweden, the authors' assumed reasonable ADHD diagnosis. The results showed that exposure to ADHD medication during pregnancy was associated with a higher admission rate to new-born intensive care units (adjusted OR 1.5, 95 % CI, 1.3–1.7), compared to no use of these drugs. Use of ADHD medication during pregnancy was also associated with a higher frequency of central nervous system-related disorders (adjusted OR 1.8, 95 % CI, 1.3–1.7) and moderately preterm birth (adjusted OR 1.3, 95 % CI, 1.1–1.6) compared to no drug use. However, substantial differences in background characteristics were found between women who received ADHD medication and controls, particularly for those who received medication throughout their pregnancy. This led the authors to suggest that the birth outcomes

Table 1
Maternal ADHD and healthy behaviours in pregnancy and pregnancy and birth risks and outcomes.

Study	Study population, n	Age of the children	Primary Outcome	References	Quality of evidence
Perinatal Outcomes after Treatment with ADHD Medication during Pregnancy	Singletons born between 2006−2014 in Sweden (n = 964,734)	Newborns	Birth outcomes may not be directly due to ADHD medication, but rather due to underlying lifestyle factors and/or disease	Nörby et al. (2017)	Moderate
Perinatal Outcomes of Women Diagnosed with Attention-Deficit/ Hyperactivity Disorder: An Australian Population-Based Cohort Study	n = 5056 cases maternal ADHD, n = 25 245 healthy controls	Newborns	Adverse birtch outcomes were likely due to some aspect of ADHD and not ADHD medication	Poulton et al. (2018)	Moderate
Childhood predictors of becoming a teenage mother among Finnish girls	n = 2867 females	N/A	Childhood ADHD problems were independently associated with becoming a teenage mother	Lehti et al. (2012)	Low to Moderate
Adolescent Mediators of Unplanned Pregnancy among Women with and without Childhood ADHD	Women with (n = 140) and without (n = 88) childhood ADHD	N/A	Young women with a history of childhood ADHD had a 4-times higher rate of unplanned pregnancies in comparison to non-ADHD controls	Owens and Hinshaw (2020)	Moderate
Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures	n = 7921 mothers	N/A	Maternal genetic liability for ADHD is associated with certain pregnancy-related exposures, and could mediate the association between these exposures and increased risk of offspring ADHD	Leppert et al. (2019)	Low to Moderate
Attention-deficit/hyperactivity disorder symptom clusters differentially predict prenatal health behaviours in pregnant women	n = 198 pregnant women	N/A	Inattention, hyperactivity and impulsivity/ emotional lability all showed significant associations with prenatal health behaviours	Jones et al. (2018)	Low to Moderate
Associations Between ADHD Symptoms and Occupational, Interpersonal, and Daily Life Impairments Among Pregnant Women	n = 250 pregnant women	N/A	Different ADHD symptoms differentially impacted occupational, interpersonal and daily life, which may negatively affect pregnancy health behaviours	Eddy et al. (2019)	low

ADHD = attention-deficit/hyperactivity disorder; N/A = not applicable.

Table 2
Maternal and paternal ADHD and parent-child interaction.

Study	Study population, n	Age of the children	Primary Outcome	Reference	Quality of evidence
The reciprocal relationship of ASD, ADHD, depressive symptoms and stress in parents of children with ASD and/or ADHD	n = 174 families with children with ASD (n = 48), ASD + ADHD (n = 59) or ADHD (n = 67) diagnosis (two genetic study cohorts: Biological Origins of Autism (BOA) and International Multicenter ADHD Genetics (IMAGE) studies)	2–20 years or 5–19 years	Maternal (but not paternal) ADHD symptoms have a direct effect on parenting stress (regarding the affected and unaffected offspring). Parental ADHD symptoms had an effect on depressive symptoms and thereby on parenting stress	Van Steijn et al. (2014)	Moderate
Mediators and Moderators of the Relation between Parental ADHD Symptomatology and the Early Development of Child ADHD and ODD Symptoms	n = 258 children and their parents	3–6 years (longitudinal study)	Maternal ADHD predicted greater laxness and over-reactivity in parenting styles, while mothers' over-reactivity again predicted greater ADHD and oppositional defiant disorder prevalence in the offspring after 3 years	Breaux et al. (2017)	Moderate
Longitudinal Study of the Relation Between Family Functioning and Preschool ADHD Symptoms	n = 197 children and their parents	3–6 years (longitudinal study)	Parental ADHD symptoms were weakly correlated with warm parenting, with lax parenting and weakly to moderately correlated with over-reactive parenting.	Breaux and Harvey (2019)	Moderate
Are parental autism spectrum disorder and/or attention-deficit/ Hyperactivity disorder symptoms related to parenting styles in families with ASD (+ADHD) affected children?	n = 96 families with at least one child with a clinical diagnosis of ASD and one unaffected sibling	2–20 years	Paternal (but not maternal) ADHD symptoms had a significant effect on child symptoms (affected vs non-affected offspring) for all parenting styles (authoritative, authoritarian and permissive).	van Steijn et al. (2013a,van Steijn et al., 2013b	Moderate
Match or Mismatch? Influence of Parental and Offspring ASD and ADHD Symptoms on the Parent–Child Relationship	n = 132 families with at least one child with ASD and/or ADHD diagnosis	2–20 years	Higher paternal (but not maternal) ADHD symptoms were related to poorer scores on a conflict resolution scale.	van Steijn et al. (2013a,van Steijn et al., 2013b	Moderate
Do maternal attention-deficit/ hyperactivity disorder symptoms exacerbate or ameliorate the negative effect of child attention-deficit/hyperactivity disorder symptoms on parenting?	n = 192 mother–child dyads	3 years	Maternal ADHD symptoms correlated with more negative expressed emotions/more negative comments in a direct observation of mother-child interaction, but a simple slope analysis showed that high maternal ADHD symptms resulted in a more positive and affectionate parenting of a child with high ADHD symptoms.	Psychogiou et al. (2008)	Low to moderate
Prediction of preschool aggression from DRD4 risk, parental ADHD symptoms, and home chaos	n = 84 boys and their parents	2–6 months (longitudinal study until 4.5 years)	The child's aggression was significantly correlated to mother's and father's total ADHD score and "home chaos" mediated the relationship between parental ADHD symptoms and child's aggression.	Farbiash et al. (2014)	Low to moderate
Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD?	n = 83 child-mother pairs	3 years	High maternal ADHD symptoms were realted to lower self-rated parenting competence and to a limited improvement of ADHD symptoms in the offspring after an 8-week parent training.	Sonuga-Barke et al. (2002)	Low to moderate
Effects of Maternal Psychopathology and Education Level on Neurocognitive Development in Infants of Adolescent Mothers Living in Poverty in Brazil	n = 50 mothers and their newborns	6 months	Higher maternal ADHD was associated with an increased absolute and relative theta power, which might reflect a vulnerability to emotion and attention regulations problems.	Shephard et al. (2019)	Low

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorders; ODD = oppositional defiant disorder.

may not be directly due to ADHD medication, but rather due to underlying lifestyle factors and/or disease (Norby et al., 2017).

The second study used health records of the New South Wales population to compare perinatal outcomes of women diagnosed with ADHD and receiving medication, versus women without ADHD and therefore no medication (Poulton et al., 2018). The birth period assessed was 1994–2012, and five comparison women were matched with every treated woman (n = 5056 and n = 25 245 respectively), based on maternal age and infant year of birth. The authors found that treatment for ADHD at any time (before, during or after pregnancy) was associated with increased risk of caesarean delivery, active neonatal resuscitation, and neonatal admission, and reduced likelihood of spontaneous labour. Moreover, women whose treatment preceded pregnancy had a higher risk for pre-eclampsia, pre-term birth and 1-min Apgar score <7. These outcomes were also observed in mothers who only took medication after pregnancy, leading the authors to suggest that the outcomes were likely due to some aspect of ADHD itself. Supporting this, a history of prior treatment was associated with additional adverse outcomes, which could be potentially be correlated with more severe ADHD.

Two studies were found that support an association between maternal ADHD and decreased maternal age at first birth (MAFB). Lehti et al. (2012) focused on psychosocial factors of the mothers at age 8, and how they might mediate the risk of becoming a mother under the age of 20 (n = 2867) (Lehti et al., 2012). Single predictor analyses revealed that conduct problems (OR 1.4, 95 % CI, 1.3–1.6) and hyperactivity (OR 1.4, 95 % CI, 1.3–1.6) were independently significantly associated with

Table 3
ADHD medication in pregnancy.

	N exposed vs. unexposed	Congenital malformations	Cardiovascular malformations	CNS disorders	Induced abortion	Miscarriage/ spontaneous abortion	Preeclampsia	Placental abruption	Preterm birth	Neonatal death	SGA	LGA	Birth weight	low Apgar score	Perinatal complications or NICU	Quality of evidence
Methylphenidate																Low
Källén et al., 2013	208 vs. ~1.5 million	0	(+)	0	NA	NA	0	0	0	NA	NA	NA	0	0	NA	moderate
Pottegård et al. 2014	222 vs. 2220	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	moderate
Diav-Citrin et al., 2016	382 vs. 382	0	0	NA	+	+	NA	NA	0	NA	0	0	0	NA	+	moderate
Cohen et al., 2017	1515 vs. ~1.5 million	NA	NA	NA	NA	NA	+	0	+	NA	0	NA	NA	NA	NA	moderate
Huybrechts et al. 2018	2072 vs. ~1 million and 1402 vs. ~2.6 million	0	+ (+++*)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	moderate
Damkier and Bro, 2020	963 vs. ~828 thousand	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Low
Medical amphetamines																
Källén et al., 2013	132 vs. ~1.5 million	0	0	0	NA	NA	0	0	0	NA	NA	NA	0	0	NA	Low
Cohen et al., 2017	3331 vs. ~1.5 million	NA	NA	NA	NA	NA	+	0	+	NA	0	NA	NA	NA	NA	moderate
Huybrechts et al. 2018	2072 vs. ~1 million and 1402 vs. ~2.6 million	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	moderate
Rose et al., 2020	54 vs. 104	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0	0	NA	0	Low
Atomoxetine																
Cohen et al., 2017	453 vs. ~1.5 million	NA	NA	NA	NA	NA	0	0	0	NA	0	NA	NA	NA	NA	moderate
Guanfacine																
Philipp, 1980	30 exposed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	(+)	NA	NA	Low
Modafinil																
Damkier and Bro, 2020	49 vs. ~828 thousand	++	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Low
Mixed ADHD medication																
Källén et al., 2013	122 vs. ~1.5 million	0	0	0	NA	NA	0	0	+	NA	NA	NA	0	0	NA	Low
Haervig et al., 2014	480 vs. ~1.1 million	0	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	Moderate to Low
Bro et al., 2015	186 vs. ~1 million	0	NA	NA	0	0	NA	NA	0	0	0	0	0	+	NA	moderate
Nörby et al., 2017	1591 vs. ~1 million	0	0	+	NA	NA	NA	NA	+	0	0	+	+	0	+	moderate
Anderson et al., 2018a	98 vs. ~43 thousand	+	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Low

NA = not assessed or analysed; 0 = non-significant risk; (+) = suspected but non-significant risk; + = low risk; ++ = moderate risk; +++ = high risk.

becoming a teenage mother, particularly at age 15−17. The authors concluded that childhood ADHD problems were independently associated with becoming a teenage mother. The final study investigated mediators of unintended pregnancy in females with and without childhood ADHD (Owens and Hinshaw, 2020). Young women with a history of childhood ADHD had a 4-times higher rate of unplanned pregnancies in comparison to non-ADHD controls that were recruited in the same summer camp. Mediators for sexual risky behaviour and the subsequent risk of unintended pregnancy in this study were academic achievement and substance use frequency.

Leppert et al. (2019) attempted to further delineate the relationship between environmental factors and increased risk of offspring ADHD (Leppert et al., 2019). They investigated whether polygenic risk scores (PRS) for neurodevelopmental disorders such as ADHD were associated with early-life exposures, which had previously been identified as environmental risk factors. ADHD PRS (n = 7921) was associated with multiple prenatal factors, including infections (OR 1.11, 95 % CI, 1.04–1.18) and the use of acetaminophen use during late pregnancy (OR 1.11, 95 % CI, 1.04–1.18). These findings suggest that maternal genetic liability for ADHD is associated with certain pregnancy-related exposures, and could mediate the association between these exposures and increased risk of offspring ADHD. This study emphasizes that potential genetic confounding needs to be carefully controlled for, and further suggests that maternal ADHD itself may be associated with birth outcomes.

Only two studies were found that directly assessed current ADHD symptoms in pregnant women, and how these symptoms may influence health behaviours. In the first study, measures of ADHD symptoms, prenatal health behaviours, and depression were completed by pregnant women (n = 198) (Jones et al., 2018). Results revealed that inattention, hyperactivity and impulsivity/emotional lability all showed significant associations with prenatal health behaviours. Moreover, each symptom cluster differentially predicted behaviour. For example, inattention was significantly linked with poor eating, physical strain, and depression, whereas hyperactivity was significantly linked with smoking, caffeine, decreased prenatal vitamin use, physical strain and depression. The authors concluded that as many of these prenatal factors can affect the health of pregnancy, potentially resulting in negative maternal and infant outcomes, obstetricians may wish to query pregnant patients about ADHD symptoms.

Finally, Eddy et al. (2019) collected self-reported measures of ADHD symptoms, impairment and demographic information from pregnant women (n = 250) (Eddy et al., 2019). They also focused on how different symptom clusters (inattention, hyperactivity and impulsivity) could differentially influence major life domains. Controlling for the mother's education, it was found that inattentive symptoms were significant predictors of impairment in professional life, daily life and relationships, whereas impulsivity was a significant predictor of impairment only in professional life and relationships. Moreover, hyperactivity was not a significant predictor, suggesting that future research should also consider measuring hyperactivity independently. The findings implied that inattention is the most important predictor of impairment in daily home life, which could potentially negatively affect pregnancy health behaviours, by causing forgetfulness of important medical appointments and lack of preparation for the baby's arrival. The impulsivity associated with impaired daily life may also negatively affect health behaviours, for example by contributing to decisions regarding health and impulsive spending leading to poor finance management (for an overview of the included studies see Table 1).

3.2. Association of maternal and paternal ADHD with early parent-child interaction and early development of the children

Parent-child interaction is defined as an appropriate, responsive and reflective interaction of a parent with its child (Papousek and Papousek, 1983). Parenting is also part of the parent-child interaction and therefore studies reporting parenting styles and parenting stress were included in our review. Additionally, we included studies that investigated the risk of ADHD in the children associated with parental ADHD. One study was found that reported a positive correlation between maternal ADHD symptoms and general parenting stress. Van Steijn et al. (2014) investigated the role of parental ADHD, autism spectrum disorder and depressive symptoms on parenting stress in 174 families, who participated in two ASD (autism spectrum disorder) and ADHD family-genetic studies. Families were included if they had one child aged 2−20 years with either an ASD diagnosis (n = 48), an ASD and ADHD (n = 59) diagnosis, or one child (aged 5−19 years) with an ADHD diagnosis (n = 67). Parenting stress was assessed with the short version of the Parental Stress Index (PSI-SF; (de Brock et al., 1992). Van Steijn and colleagues reported that parents generally experienced more stress when parenting a child with an ASD and/or ADHD diagnosis. Specifically, maternal (but not paternal) ADHD symptoms were found to have a direct effect on parenting stress (regarding the affected and unaffected offspring). Additionally, parental ADHD symptoms had an effect on depressive symptoms and thereby on parenting stress. Diagnoses of the child (ASD, ADHD or ADHD/ASD) did not moderate the relationship between parental ADHD and parenting stress in general. One exception was paternal ADHD, which resulted in higher depressive symptoms and thus increased parenting stress, but only in the affected offspring compared to an unaffected biological sibling (van Steijn et al., 2014).

Three studies were identified that investigated the influence of parental ADHD symptoms on parenting styles. Breaux et al. (2017) included 258 3-year-old children (120 girls) and their parents in their study. Parental laxness and over-reactivity were analysed with the self-report Parenting Scale (Arnold et al., 1993) annually over a period of 3 years. In addition, mother-child interaction during a 5-min play task and a clean-up task was videotaped annually and rated for parenting warmth. Mothers' but not fathers' ADHD symptoms were found to predict later child ADHD symptoms (after 3 years). However, fathers' ADHD symptoms significantly co-varied with ADHD symptoms of the child at baseline. Family history of ADHD and father's psychopathology (e.g. anxiety or depression) predicted later child ADHD, but did not fully explain the relation between maternal and child ADHD symptoms. Interestingly, for families with less family adversity the relationship between maternal and child ADHD symptoms was stronger. Concerning parenting styles, maternal ADHD predicted greater laxness ($\beta = 0.19$, SE = 0.08, $p < 0.05$) and over-reactivity ($\beta = 0.31$, SE = 0.08, $p < 0.001$), while mothers' over-reactivity again predicted greater ADHD (indirect effect: $\beta = 0.07$, SE = 0.03, $p = 0.01$, 95 % CI [0.02–0.18]) and oppositional defiant disorder (ODD) (indirect effect: $\beta = 0.08$, SE = 0.03, $p = 0.01$, 95 % CI [0.01–0.10]) prevalence in the offspring after 3 years. There was no significant relationship between maternal ADHD symptoms and maternal warmth ($\beta = -0.01$, SE = 0.13, $p = 0.92$). Fathers' ADHD symptoms were not significantly related to parenting styles. The authors conclude that maternal ADHD symptomatology is related to disruptions in parenting and ADHD symptoms in the offspring can be influenced by parenting styles. However, the authors discuss the limitations that in this study only 6 % of the fathers and 12 % of the mothers reported clinically significant ADHD symptoms, which may affect the generalizability of the findings (Breaux et al., 2017).

In a similar study, Breaux and colleagues (2019) studied 3-year old children (n = 197, 110 boys) and parenting styles of their mother and father over a period of 3 years. Parenting was again assessed with the Parenting Scale (Arnold et al., 1993), and parental warmth was observed in a video-taped 5 min clean-up and a play task. Parental ADHD symptoms were weakly correlated with warm parenting (r = −.09 to 0.00 for mothers), lax parenting (r = .07–.21 for mothers and .00–.15 for fathers) and weakly to moderately correlated with over-reactive parenting (r = .29–.34 for mothers and .03–.21 for fathers) (Breaux et al. 2019). The aim of the study was to investigate the relationship between family functioning and ADHD in children across the preschool years. After controlling for parental ADHD, effects from maternal

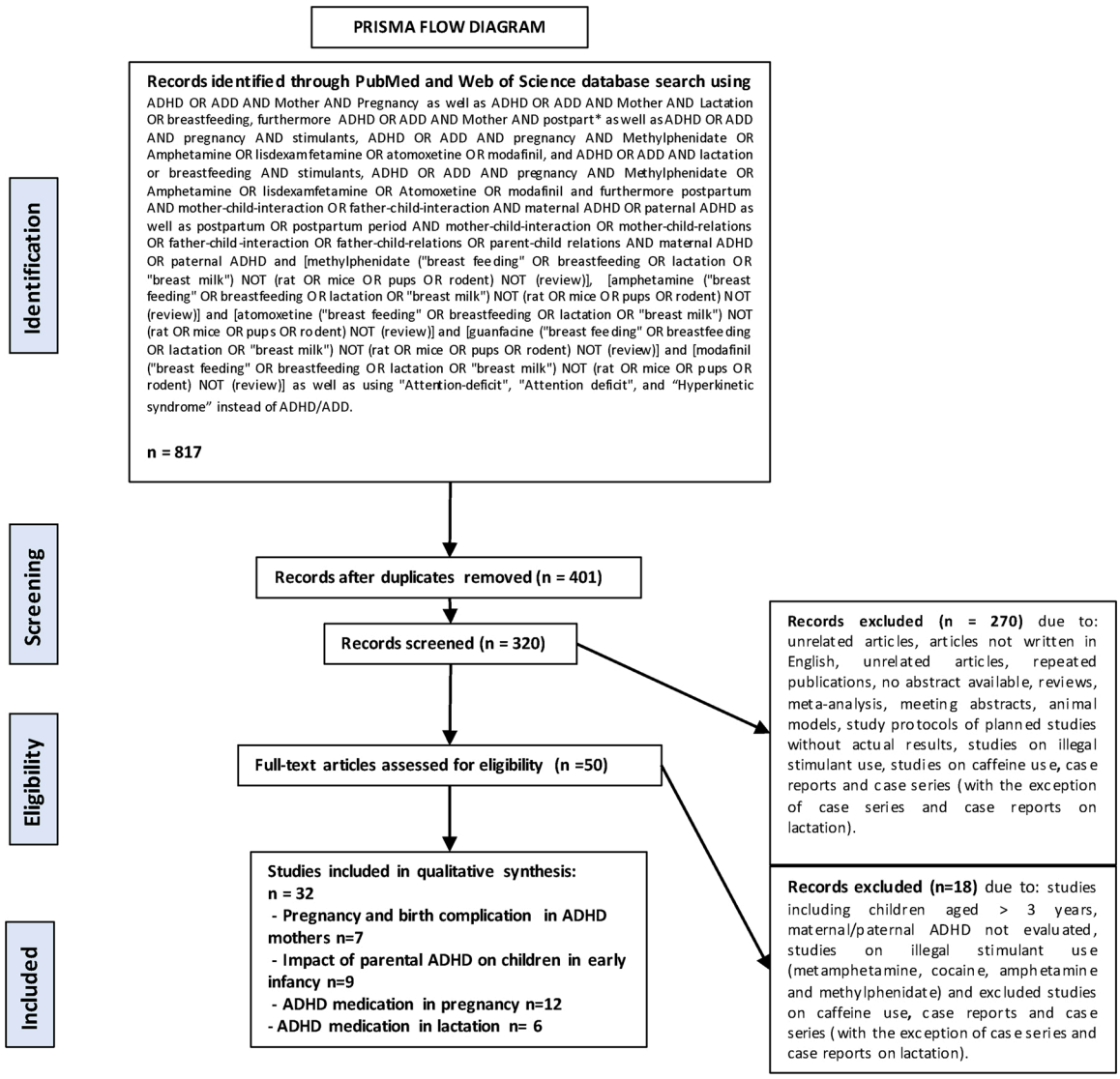

Fig. 1. PRISMA Flow Chart.

over-reactivity to child ADHD symptoms (b = .46, SE = .21, p = .03) as well as effects from child ADHD to maternal warmth (b = −.02, SE = .01, p = .002) remained significant, but effects of child ADHD symptoms on depressive symptoms in the parents became nonsignificant. Accordingly, the authors suggest that the relations between family functioning and child ADHD are largely explained by parent ADHD and genetic factors (Breaux and Harvey, 2019).

van Steijn et al. (2013a,2013b) investigated authoritative, authoritarian and permissive parenting styles in 96 families with at least one child between 2 and 20 years with a clinical diagnosis of ASD, and one unaffected sibling. Parenting styles were assessed with the Parenting Styles and Dimensions Questionnaire (PSDQ, (Robinson et al., 2001). In a repeated measures ANOVA, van Steijn and colleagues only found significant main effects for paternal (but not maternal) ADHD symptoms on child symptoms (affected vs non-affected offspring) for all parenting styles (authoritative (F (190) = 6.05, p = .02; authoritarian F (190) = 8.52, p = .003 and permissive F (190) = 6.03, p = .02) (van Steijn et al., 2013a,b).

In two studies, correlations between conflict resolution and constructive parenting were examined.

van Steijn et al. (2013a,2013b) studied 132 families with at least one child between 2 and 20 years with ASD and/or ADHD diagnosis, and found that higher paternal (but not maternal) ADHD symptoms were related to poorer scores on a conflict resolution scale (F (1, 127) = 5.05, p = .03), assessed with the Parent-Child Interaction Questionnaire-revised (PACHIQ-R; (Lange, 2001) (van Steijn et al. (2013a,2013b))). However Psychogiou and colleagues (2008) found a more positive effect of maternal ADHD symptoms on parenting, whereby mothers with high ADHD symptoms had a more positive and affectionate response to their children with high ADHD symptoms. Indeed there was a correlation between maternal ADHD symptoms and more negative expressed emotions/more negative comments in a direct observation of mother-child interaction (n = 192 mother–child dyads, 112 males, 3-year old children), but a simple slope analysis showed that high maternal ADHD symptoms resulted in a more positive and affectionate parenting of a child with high ADHD symptoms (Psychogiou et al., 2008).

One study investigated "home chaos" as a mediator between parental ADHD and child symptoms. Farbiash and colleagues (2014) assessed parental ADHD symptoms at the child's age of 2−6 months and studied "home chaos" and preschool aggression at the child's age of 4.5 years (n = 84 boys and their parents). The child's aggression was significantly correlated to mother's and father's total ADHD score (r = .32, p < .01 and r = .24, p = .05) and "home chaos" mediated the relationship between parental ADHD symptoms and child's aggression (Farbiash et al., 2014). "Home chaos" (e.g. "We are usually able to stay on top of things")

was assessed with six items of the short version of the Confusion, Hubbub, and Order Scale, CHAOS (Matheny et al., 1995; Petrill et al., 2004).

One intervention study explored the effectiveness of parent training (n = 83 3-year-aged child-mother pairs) (Sonuga-Barke et al., 2002). The parent training intervention was an 8-week structured program of home visits focusing on educating parents about ADHD and improving the quality of parent-child relationship. Participants were divided into high, medium and low maternal ADHD groups. Mothers in the high-ADHD group scored lower on the satisfaction and efficacy scale of the Parenting Sense of Competence Scale (Johnston and Mash, 1989) ($F(2,79) > 5.45$, $p < .007$). More importantly, children in the high-ADHD group only showed little changes in ADHD symptoms after parental training, while children in the low-ADHD group showed a reduction of symptoms (interaction effect of group x time: $F(4,160) = 3.13$, $p < .05$) (Sonuga-Barke et al., 2002).

In a study investigating adolescent motherhood, Shephard and colleagues (2019) investigated 50 young mothers (between 14 and 19 years of age) for maternal psychopathology and electroencephalography (EEG) and cognitive behavioural assessments of their 6 month old newborns. Higher maternal ADHD was associated with an increased absolute and relative theta power, which might reflect a vulnerability to emotion and attention regulation problems as discussed by the authors, although there were no quantifiable changes in infants' overt cognitive behavioural abilities (Shephard et al., 2019).

It needs to be considered that five of the above studies included children from the age of 2 or 3 years and older, had a wide range of age (van Steijn et al., 2013a,b; van Steijn et al., 2014) or conducted a longitudinal study from the age of 3 years over a period of 3 years (Breaux et al., 2017; Breaux and Harvey, 2019). Accordingly, these studies did not explicitly investigate parent-child interaction during early infancy, but as these studies also included 2 or 3 year old children and revealed important influences of parental ADHD on parenting, we included these studies in the review (for an overview of includes studies see Table 2).

3.3. Dopaminergic and noradrenergic ADHD treatment in pregnancy

A Canadian study recently showed that that the absolute numbers of continuous use of psychotropic drugs during pregnancy, including ADHD medication, rose by the factor 6.4 between 2000 and 2011 (Leong et al., 2017). A Danish register-based study even suggested that the incidence of pregnancies exposed to ADHD medication increased from 5 to 533 per 100 000 person-years between 2003 und 2010, which is a more than 100-fold increase within 7 years (Haervig et al., 2014). Moreover, Leong et al. (Leong et al., 2017) showed that 44.6 % of the women taking prescribed stimulants discontinued their intake before the 1st trimester and 36.4 % before the 2nd trimester, while 19 % showed intermittent or continuous medical stimulant use throughout pregnancy. These data indicate the strong and growing clinical relevance of prescribed use of ADHD medication during pregnancy.

3.3.1. Methylphenidate (n = 6)

Methylphenidate is a catecholamine reuptake inhibitor with preferential binding to the human dopamine transporter ($k_i = 34$) but also some affinity for the human norepinephrine transporter ($k_i = 339$) (Bymaster, 2002). However, it does not show measurable binding to the serotonin transporter ($k_i > 10'000$). The drug is thus able to largely increase dopamine and noradrenaline concentrations in the PFC and also of dopamine in the nucleus accumbens, without affecting serotonin concentration in these regions (Bymaster, 2002). Methylphenidate is first line treatment for childhood as well as adult ADHD in several guidelines (Faltinsen et al., 2019; Hage et al., 2020).

In an analysis from Källén et al. (Källén et al., 2013) 1,575,847 born infants from the Swedish Medical Birth Register (1996–2011) were included. In this sample, 208 infants were exposed to methylphenidate during pregnancy. Five of the exposed infants displayed relatively severe congenital malformations (2.4 %) – all affected the cardiovascular system. In the total cohort, 49,499 relatively severe congenital malformations occurred (3.1 %), of which 16,145 were cardiovascular defects (1%). The authors stated "There are weak indications that use of methylphenidate causes an increased risk for cardiovascular defects" (Källén et al., 2013;).

In a population-based cohort study using several Danish health registers (2005–2012), Pottegård and colleagues (Pottegård et al., 2014) investigated the risk of major congenital malformations following first-trimester exposure to methylphenidate. The analysis included 222 exposed and 2220 unexposed pregnancies, which were propensity score-matched at the individual level (1:10). The risk for major malformations (point prevalence ratio [PPR] = 0.8 [95 %CI 0.3–1.8]) or cardiac malformations (PPR = 0.9 [95 %CI 0.2–3.0]) was not increased by in utero exposure to methylphenidate. Sensitivity analyses provided similar results. The authors concluded that methylphenidate use during the first-trimester does not substantially (i.e., >2-fold) increase the risk of major congenital malformations in exposed infants (Pottegård et al., 2014).

Diav-Citrin et al. (Diav-Citrin et al., 2016) compared 382 methylphenidate-exposed pregnancies with 382 non-exposed pregnancies matched for maternal age, gestational age, and year at initial contact. No group differences were observed regarding major congenital malformations (3.2 % vs. 3.6 %, respectively) or cardiovascular anomalies (2.4 % vs. 3.4 %), but a significantly higher rate of miscarriages (14.1 % vs. 7.1 %) and elective terminations of pregnancy (8.1 % vs. 2.6 %) were found in the methylphenidate group. Methylphenidate exposure was also a significant predictor for miscarriage in a Cox proportional hazards model considering several relevant predictors (adjusted hazard ratio = 1.98 [95 %CI 1.23–3.20]). Their data suggest low teratogenic potential of methylphenidate but a potential risk for miscarriages.

In a U.S. population-based cohort study using Medicaid data, the association between methylphenidate treatment (as well as amphetamine-dextroamphetamine and atomoxetine treatment, see below) during the first 140 days of pregnancy and placental-associated pregnancy outcomes were analysed (Cohen et al., 2017). In this analysis 1515 methylphenidate exposed vs. 1,461,493 unexposed infants were included. In unadjusted analyses, monotherapy with methylphenidate was related to an increased risk for preeclampsia, small size for gestational age and preterm birth, but these effects disappeared after adjustment for a number of confounders. However, continuation of stimulant monotherapy (amphetamines and methylphenidate combined) in the second half of pregnancy was associated with increased risk for preterm birth when compared to discontinuation (aRR = 1.30 [95 %CI 1.10–1.95]). When the time window of exposure was restricted to the period of placentation (8–18 weeks), methylphenidate exposure was significantly associated with preeclampsia (aRR = 1.30 [95 %CI 1.02–1.67]) but no other placental dysfunction. Consequently, methylphenidate treatment during pregnancy might be associated with a small increase in the risk for preeclampsia and, specifically in the second half of pregnancy, also with preterm birth (Cohen et al., 2017).

Huybrechts et al. (Huybrechts et al., 2018) recently analysed two very large data sets with respect to the risk of congenital malformations in association with amphetamine and methylphenidate treatment; 1, 813,894 publicly insured pregnancies (Medicaid data) between 2000–2013 in the U.S. and as a validation data set 2,560,069 pregnancies from five Scandinavian countries (Denmark: 2005–2012; Finland: 1996–2010; Iceland: 2003–2012; Norway: 2005–2012; Sweden: 2006–2013). In the U.S. cohort, 2072 women were dispensed with methylphenidate during the first trimester. Using a non-adjusted model, the prevalence of any congenital malformations was initially higher in methylphenidate-exposed infants in comparison to unexposed infants (45.9 vs. 35.0 per 1000 infants, respectively RR = 1.31 [95 %CI 1.08–1.59]). However, after adjustment for confounders the association was strongly reduced and no longer significant (aRR = 1.11; [95 %CI 0.91–1.35]). The same result was found for cardiovascular defects (18.8

vs. 12.7 per 1000 infants; RR = 1.48 [95 %CI 1.08–2.02], aRR = 1.28; [95 %CI 0.94–1.74]). In an analysis of specific cardiac defects, the risk for conotrunctal defects was strongly increased in methylphenidate-exposed infants (aRR = 3.44 [95 %CI 1.54–7.65]). When two cardiovascular malformations of limited clinical relevance were excluded, the risk for cardiovascular defects related to methylphenidate became significant (aRR = 1.50 [95 %CI 1.05–2.14]). In the large Scandinavian validation sample, 1402 infants were exposed to methylphenidate. In the adjusted models neither the risk for all congenital malformations (aRR = 0.99 [95 %CI 0.74–1.32]) or for cardiovascular defects (aRR = 1.28 [95 %CI 0.83–1.97]) was significant in the Scandinavian sample alone. However, after pooling the adjusted estimates of both data sets, the risk for cardiovascular malformations became significant (aRR = 1.28 [95 %CI 1.00–1.64]). The authors concluded that methylphenidate treatment during the first trimester of pregnancy increases the risk for cardiovascular defects in exposed infants and estimated three additional infants born with congenital cardiac malformations in every 1000 women (Huybrechts et al., 2018).

A very recent study investigated the risk of congenital malformations after first-trimester exposure to methylphenidate (963 pregnancies) in comparison to unexposed infants (828,644 pregnancies) (Damkier and Broe, 2020). The adjusted odds ratio (aOR) for the comparison methylphenidate vs. unexposed was 0.7 (95 %CI: 0.69–1.3) suggesting no increased risk for major congenital malformations upon methylphenidate treatment during pregnancy.

3.3.2. Amphetamines (n = 4)

All amphetamines are monoamine releasers but with different affinities for each of the monoamine transporters, e.g. dextroamphetamine has the strongest effect on noradrenaline (IC_{50} = 7.1 nM) and dopamine release (IC_{50} = 24.8 nM) with little effect on serotonin (IC_{50} = 1′765 nM), while methamphetamine shows a similar pattern but with less effect on the noradrenaline and more effect at the serotonin transporter (noradrenaline: IC_{50} = 12.3 nM; dopamine: IC_{50} = 24.5 nM; serotonin: IC_{50} = 736 nM)(Rothman et al., 2001). Additionally, most amphetamines show significant affinity at the recently discovered trace amine-associated receptor-1 (TAAR1), which is additionally involved in the modulation of dopaminergic and serotonergic activity (Simmler et al., 2013). For example, in Germany amphetamines are only approved for the treatment of childhood ADHD, with the exception of the long-acting prodrug lisdexamfetamine. However, international guidelines differ regarding the treatment of adult ADHD with amphetamines (Faltinsen et al., 2019; Hall et al., 2016; Kooij et al., 2010).

In the analysis of the Swedish Medical Birth Register (1996–2011) including 1,575,847 born infants, 132 infants with medical amphetamine exposure during pregnancy were identified (Källén et al., 2013). Within exposed infants four congenital malformations (3%; one severe, three isolated) occurred, while in the total cohort 70,339 malformations were detected (4.5 %). ORs or RRs were not reported for amphetamine exposure. The authors concluded that psychostimulants such as amphetamine do not have a “strong teratogenicity” (Källén et al., 2013;).

Placental-associated pregnancy outcomes related to amphetamine and/or dextroamphetamine exposure were analysed in a U.S. population-based cohort study including 3331 exposed vs. 1,461,493 unexposed infants during the first 140 days of pregnancy (Cohen et al., 2017). In unadjusted analyses, monotherapy with the respective amphetamines in the first half of pregnancy posed an increased risk for all placental-associated outcomes (preeclampsia, placental abruption, being small for gestational age, and preterm birth); however, after adjustment for confounders only an elevated risk for preeclampsia remained (aRR = 1.33 [95 %CI 1.12–1.58]). Continuation of stimulant monotherapy (amphetamines and methylphenidate combined) in the second half of pregnancy was associated with increased risk for preterm birth when compare to discontinuation (aRR = 1.30 [95 %CI 1.10–1.95]). Additional sensitivity analyses suggest that amphetamines were significantly associated with preeclampsia (aRR = 1.44 [95 %CI 1.19–1.74]), placental abruption (aRR = 1.54 [95 %CI 1.16–2.04]), and preterm birth (aRR = 1.16 [95 %CI 1.04–1.30]), when the time window of exposure was restricted to the period of placentation (8–18 weeks, n = 2589). Moreover, the risk for preeclampsia clearly increased with the number of days of amphetamine exposure during the first 140 days of pregnancy, an effect that was not identified for placental abruption and preterm birth. However, the risk of preterm birth was elevated when amphetamine use was for longer than 90 days in the first half of pregnancy (Cohen et al., 2017). Thus, amphetamine exposure in utero is likely associated with an elevated risk for preeclampsia, placental abruption, and preterm birth.

In the U.S. cohort studied by Huybrechts et al. (Huybrechts et al., 2018), 5571 women were included who were dispensed with medical amphetamines during the first trimester (see 3.3.1). In a non-adjusted model, the prevalence of any congenital malformations was higher in amphetamine-exposed in comparison to unexposed infants (45.4 vs. 35.0 per 1000 infants, respectively; RR = 1.30 [95 %CI 1.15–1.46]) but after adjustment for confounders the association was strongly reduced and not significant anymore (aRR = 1.05; [95 %CI 0.93–1.19]). Cardiac malformations showed a similar pattern (15.4 vs. 12.7 per 1000 infants; RR = 1.21 [95 %CI 0.98–1.49], aRR = 0.96; [95 %CI 0.78–1.19]). Due to the null findings in the U.S. cohort, analyses of the amphetamine-exposures in the Scandinavian validation data set were not reported. The authors concluded that amphetamine treatment in the first trimester is not associated with an increased risk for congenital malformations (Huybrechts et al., 2018).

In relatively small study, Rose et al. (Rose et al., 2020) investigated the association between birthweight and amphetamine–dextroamphetamine treatment during pregnancy in 54 exposed mother–infant pairs and 104 matched unexposed controls. The difference in mean birthweight between exposed and unexposed was 26.9 g, which was neither significant (95 %CI −141−195 g) nor clinically relevant. Other pregnancy or birth outcome variables also did not show any group differences. The authors concluded that amphetamine treatment during pregnancy does not impact birthweight of the infant.

3.3.3. Atomoxetine (n = 1)

Atomoxetine is a selective noradrenaline reuptake inhibitor (SNRI) (Bymaster, 2002), which elevates both noradrenaline and dopamine levels in the PFC. In contrast, dopamine levels in the striatum or nucleus accumbens seem to be unaffected by the drug (Sauer et al., 2005). Atomoxetine has been approved for the treatment of ADHD in 2002 and is used also in ADHD patients with comorbid substance abuse disorders, as stimulant treatment is not recommended as a first line treatment for these disorders except in specialised settings.

Only one population-based cohort study from the U.S. investigated the specific effects of a monotherapy with atomoxetine on placental-associated pregnancy outcomes in 453 women in comparison to 1,461,493 unexposed pregnancies (Cohen et al., 2017). Atomoxetine treatment during early pregnancy was not associated with any of the investigated adverse pregnancy outcomes including preeclampsia, placental abruption, growth restriction, and preterm birth. These data suggest that atomoxetine might be a safe medication during pregnancy. However, data on potential teratogenicity in humans are lacking so far.

3.3.4. Guanfacine (n = 1)

Guanfacine is a selective α2A adrenergic receptor agonist initially developed for the treatment of hypertension, which is also approved as a medication for ADHD in children (Scahill, 2009). The only available study investigated pregnancy outcomes of 30 women with preeclampsia treated with guanfacine for time periods between 16 and 68 days (Philipp, 1980). Foetal or maternal heart rate was not changed during treatment and malformations of infants were not detected after birth. Six of the infants (20 %) had low birth weight but all later developed normally (Philipp, 1980). However, low birth weight is also commonly

associated with maternal preeclampsia (Spracklen et al., 2014). Given the lack of data on the effects of the drug in pregnancy, discontinuation of guanfacine treatment has been recommended (Ornoy, 2018).

3.3.5. Modafinil (n = 1)

The exact mechanism of modafinil is still a matter of debate. Recently, it was suggested that it is an atypical and selective dopamine reuptake inhibitor (Hashimoto et al., 2011) which indirectly activates the histaminergic and orexinergic systems (Ishizuka et al., 2012). In animal models using microdialysis the application of modafinil increased dopamine and noradrenaline in the PFC, and dopamine in the striatum (Rowley et al., 2013), while an earlier study also showed additional increases of serotonin in the PFC and selective increases of noradrenaline in the hypothalamus (Hilaire, Orosco et al., 2001). Modafinil is not recommended for use as ADHD medication in recent guidelines but it was used previously more often as an off-label medication, therefore we included it in our review.

A recent study used the Danish national health registries in order to investigate the risk of congenital malformations after first-trimester exposure to modafinil (49 pregnancies) in comparison to methylphenidate (963 pregnancies) and unexposed infants (828,644 pregnancies) (Damkier and Broe, 2020). The absolute risk for major congenital malformations was 12 % for modafinil, 4.5 % for methylphenidate and 3.9 % for unexposed children, suggesting a significantly increased risk for modafinil. The aORs were 3.4 (95 %CI: 1.2–9.7) in the comparison modafinil vs. methylphenidate and 2.7 (95 %CI: 1.2–9.7) for the comparison modafinil vs. unexposed. This data strongly suggests that modafinil treatment during pregnancy bears a pronounced risk for major congenital malformations in the infant. However, more evidence is needed to provide clear treatment guidelines.

3.3.6. Population analyses with pooled ADHD-medications (n = 5)

Källén and colleagues (Källén et al., 2013) used the Swedish Medical Birth Register (1996–2011) and provided a pooled analysis of three medications prescribed for ADHD treatment (methylphenidate, modafinil, and atomoxetine, in sum 122 exposed infants among 1,575,847 born infants) beyond their single substance analyses of amphetamine and methylphenidate exposure (see 3.3.1, 3.3.2, 3.3.3, 3.3.6). Only the risk for preterm birth was significant for the three pooled substances (OR = 1.83 [95 %CI 1.00–3.36]), and given the normal risk for congenital malformations the authors concluded that psychostimulants in general do not seem to have strong teratogenicity (Källén et al., 2013).

Three further Scandinavian studies analysing birth registers investigated the impact of ADHD treatment on adverse pregnancy outcomes without separation of specific drug effects (Bro et al., 2015; Haervig et al., 2014; Nörby et al., 2017):

(1) In a large cohort study using the Danish National Health register, 1,054,494 registered pregnancies between 1999 and 2010 were assessed (Haervig et al., 2014). Of these, 480 were exposed to ADHD medication (methylphenidate: 81.9 %, atomoxetine: 9.4 %, modafinil: 8.8 %). Exposed pregnancies had an increased risk of induced abortions on maternal request (OR = 4.70 [95 %CI 3.77–5.85]), induced abortions on special indication (OR = 2.99 [95 %CI 1.34–6.67]), and miscarriage (OR = 2.07 [95 %CI 1.51–2.84]) in comparison to unexposed pregnancies. However, a low powered cross-over analysis comparing exposed pregnancies to unexposed pregnancies of the same woman suggested that the risk for induced abortion upon maternal request and miscarriage might be more attributable to the ADHD diagnosis rather than to its medication. Despite the latter finding the authors highlight that induced abortions and miscarriage occur more frequently in pregnancies exposed to ADHD medication (Haervig et al., 2014).

(2) Also using the Danish National Health register, Bro et al (Bro et al., 2015) examined the effects of ADHD medication (only methylphenidate and atomoxetine were included) in 989,932 pregnancies between 1997 and 2008. Women with an ADHD diagnosis and taking ADHD medication (n = 186; 89 % used methylphenidate, 9.7 % atomoxetine, and 1.1 % both drugs) were compared with women with ADHD but without medication (n = 275), and women without ADHD or related medications (n = 989,471). Both exposure to ADHD medication and an ADHD diagnosis without medication were associated with an increased risk of spontaneous abortion/miscarriage (adjusted relative risk [aRR] 1.55 [95 %CI 1.03–2.36] and 1.56 [95 %CI 1.11–2.20], respectively). In contrast, ADHD medication exposure were associated with lower Apgar scores (<10) (aRR 2.06 [95 %CI 1.11–3.82], while an ADHD diagnosis alone was not (aRR 0.99 [95 %CI 0.48–2.05]). The risk for congenital abnormalities or neonatal death and other adverse pregnancies outcomes was not elevated by ADHD medication or diagnosis. The authors concluded that ADHD medication during pregnancy carries a higher risk for low Apgar scores and miscarriage; however, the latter finding was confounded by the ADHD diagnosis itself.

(3) Using Swedish Medical Birth Register data (2006−2014), Nörby et al (Nörby et al., 2017) analysed data of 964,734 infants, of which 1′591 (0.2 %) were exposed to ADHD medication during pregnancy as already described above. Of these, 1464 were exposed to stimulants (90 % methylphenidate) and 165 to atomoxetine. Additionally, 9475 women with ADHD were included in the analysis, who only used ADHD medication before or after pregnancy. Compared to non-exposure, ADHD medication during pregnancy but also before and after increased the risk for admission to a neonatal intensive care unit for children of ADHD mothers (NICU; aOR = 1.5 [95 %CI 1.3–1.7] and aOR = 1.2 [95 %CI 1.1–1.4]), indicating that this phenomenon might not be independent from an ADHD diagnosis. Exposed infants also had a higher risk for moderately preterm birth (aOR, 1.3; 95 % CI, 1.1–1.6), and were larger for gestational age (aOR = 1.3 [95 % CI, 1.0–1.7]) in comparison to non-exposed infants. Finally, infants exposed during pregnancy displayed a higher risk for CNS-related disorders (16 infants) compared to non-exposed infants (aOR = 1.9 [95 %CI 1.1–3.]), including infants of mothers with ADHD who stopped ADHD medication during pregnancy (aOR = 1.8 [95 %CI 1.0–3.3]). The risk for congenital malformations, low Apgar scores or perinatal death was not increased in exposed infants. The authors finally stated that ADHD medication during pregnancy was associated with a higher risk for neonatal morbidity, especially in the central nervous system, however it remains unclear what contribution the ADHD diagnosis of the mother and potentially unhealthy life style contributed to these findings (Nörby et al., 2017).

Anderson et al. (Anderson et al., 2018a,b) investigated data from National Birth Defects Prevention Study (NBDPS) between 1998 and 2011 in order to evaluate the effect of ADHD medication use during pregnancy of 12 selected birth defects. The NBDPS is a multisite, population-based, case-control study of risk factors for more than 30 major structural birth defects comparing mothers with infants having birth defects (cases) and mothers with infants not having these defects (controls). For the present study, only 98 from 42,667 mothers (0.2 %; 31,213 cases, 11,454 controls) reported use of ADHD medication at any time during pregnancy, while the prevalence of ADHD medication use was highest in the three months before conception but fell sharply during the first trimester of pregnancy. The combination of amphetamine/dextroamphetamine (Adderall®, 40 %) and methylphenidate (38 %) was the most prevalent ADHD medication among exposed mothers. ADHD medication use in the first trimester (cases: N = 64, controls: n = 20) was more commonly reported by mothers of infants with gastroschisis (n = 7, cOR = 2.9 [95 %CI 1.2−6.9]), omphalocele (n = 3, cOR = 4.0 (95 %CI 1.2–13.6]), and transverse limb deficiency (n = 4, cOR =

3.3 [95 %CI 1.1–9.6]) compared to unexposed mothers. The effect for gastroschisis remained significant after adjustment for maternal age (aOR = 3.0 [95 %CI 1.2–7.4]). The authors concluded that ADHD medication use during early pregnancy was associated with an increased risk for three of 12 birth defects examined; gastroschisis, omphalocele, and transverse limb deficiency, although it should be noted that the risk remained low (Anderson et al., 2018a,b) (for an overview see Table 3).

3.4. Dopaminergic and noradrenergic ADHD treatment in lactation

In general, there is a lack of controlled studies on the transfer of ADHD medication into breast milk and its effects on child health, which is not surprising given the ethical restrictions of such studies. However, large cohort studies in this field are also scarce. Therefore, as an exception for this specific section, we are mostly reporting the main results of the available case studies. A key measure for the transfer of a medication into breast milk is the relative infant dose (RID; the ratio of the quantity of the drug incorporated by the child compared with the maternal dose). RIDs below 10 % are usually considered as safe for breastfeeding (Taddio and Ito, 2001).

3.4.1. Methylphenidate (n = 3)

Although methylphenidate hydrochloride is highly soluble in water and has a low molecular weight, several case reports suggest that the drug was found only in small concentrations in milk of medicated mothers and remained generally undetected in the blood of exposed infants (Collin-Lévesque et al., 2018; Hackett et al., 2016; Spigset et al., 2007). The RID was below 1% in all cases. Adverse effects of maternal methylphenidate medication on breastfed children have not been reported (Collin-Lévesque et al., 2018; Hackett et al., 2016; Spigset et al., 2007). It was therefore concluded that there is no contraindication of methylphenidate during breastfeeding (Bolea-Alamanac et al., 2014; Ornoy, 2018). However, long-term consequences have not yet been studied.

3.4.2. Amphetamines (n = 2)

A number of case reports with breastfeeding mothers showing a medical (ADHD, narcolepsy) or non-medical use of amphetamines (amphetamine, dextroamphetamine, methamphetamine) suggest that all these drugs are generally highly transferred into breast milk (Ariagno et al., 1995; Bartu et al., 2009; Blandthorn et al., 2017; Chomchai et al., 2015; Ilett et al., 2007; Öhman et al., 2015; Steiner et al., 1984). However, medical treatment with racemic amphetamine (for narcolepsy) or dextroamphetamine (for ADHD) showed low RID of 2% and 5.7 %, respectively (Ilett et al., 2007; Öhman et al., 2015). A daily dose of 20 mg/day amphetamine sulphate has led to 3 to 7-times higher concentrations in breast milk compared to maternal plasma. This dose was also sufficient to transfer measurable amounts of amphetamine to the urine of an exposed infant (Steiner et al., 1984). Three case reports of mothers with prescribed amphetamine use did not report any short-term adverse effects in their breastfed infants (Ilett et al., 2007; Öhman et al., 2015; Steiner et al., 1984), and two reports did not find any notable developmental alterations of the infants after up to two years of monitoring (Öhman et al., 2015; Steiner et al., 1984). A study including breastfed children of mothers treated with various doses of amphetamine did not show signs of insomnia or stimulant intoxication in the infants during a 2 year observation period (Ayd, 1973). Finally, no data on the long-term consequences of amphetamine exposure through breastfeeding are available so far. Based on the high drug concentrations transferred to breast milk, in a previous review it was concluded that ADHD treatment with amphetamines during breast feeding is contraindicated (Ornoy, 2018).

3.4.3. Atomoxetine and guanfacine

As no data exist on the effects of atomoxetine and exposure on breast fed infants, no recommendation can be given yet.

3.4.4. Modafinil (n = 1)

A single case report published recently reported pharmacokinetic parameters of armodafinil, the main metabolite of modafinil, in a breastfeeding woman taking a daily dose of 250 mg of modafinil as a treatment against her idiopathic hypersomnolence (Aurora et al., 2018). The RID was 5.3 % and the absolute infant dose was 180 μg/kg/day, but no health outcomes of the child were reported. Although the authors concluded that there is likely a minimal risk for infant toxicity due to a low RID and an assumed high first-pass effect of the drug (which is mainly metabolized in the liver), modafinil treatment during breastfeeding cannot be recommended at this time given the scarce evidence base regarding infant safety, and the availability of low risk and on-label treatment alternatives for ADHD with much better evidence such as methylphenidate.

4. Discussion and clinical implications

About 3% of adults worldwide suffer from ADHD and adult ADHD patients have a substantial risk of comorbid mental and somatic disorders, such as major depression and obesity (Altfas, 2002; Chen et al., 2018). Other mental disorders as well as somatic disorders like obesity have already been shown to be associated with increased pregnancy and birth risks as well as impaired development of children of the affected parents (Mei-Dan et al., 2015). But there is surprisingly little data on parents with ADHD regarding the perinatal period and early infancy of their offspring. Most studies focus on risk factors regarding the development of ADHD in children, but do not consider the effect of parental psychopathology. We conducted a systematic review on the data available, and though more studies are necessary, we found several aspects of parental mental health that affect the peripartum and early infancy period and are therefore important for clinicians to consider.

4.1. ADHD is associated with the risk of teenage and unintended pregnancies

Child and adolescent psychiatrists and psychologists should be aware that adolescent girls with ADHD might have an increased risk of becoming teenage mothers. Furthermore, adolescents and young adult women with ADHD seem to experience a significantly higher number of unintended pregnancies. Lower academic achievement and more frequent substance abuse is associated with enhanced sexual risky behaviour in girls with ADHD (Chang et al., 2014; Lehti et al., 2012). Therefore, psychoeducation in adolescents with ADHD needs to include contraceptive methods and education on sexual behaviour. From the available data we could not conclude that ADHD teenage boys might also be at risk for early fatherhood, although it is likely, and further studies are needed.

4.2. Maternal ADHD is associated with pregnancy and birth complications

Though there are only few studies, the data consistently suggests that women with ADHD might have a higher risk of pregnancy and birth complications, such as pre-eclampsia, infection and caesarean section. Furthermore, pregnant women with ADHD appear more likely to demonstrate negative health behaviours compared to pregnant women from the general population (Poulton et al., 2018). Children born from women with ADHD also seem to be at a higher risk of being treated in intensive care units as new-born babies, and of being born pre-term. In conclusion, even if pregnant women with ADHD do not take medication, they should be advised to give birth in a specialised hospital with a paediatric unit due to a potential higher risk of birth complications. Positive health behaviours in pregnancy should also be discussed specifically with women with ADHD (see Fig. 2).

4.3. Maternal and paternal ADHD during the early infancy period

There is a lack of studies focusing on the relationship between parental ADHD and the development of children in the postnatal period and early infancy, therefore we included studies investigating children up to age 3. From those data, it appears that paternal and maternal ADHD may exhibit differential effects on children, and that maternal ADHD might lead to more warmth when parenting a child with ADHD. However, several negative outcomes were shown regarding parents with ADHD and their affected and non-affected children such as increased parenting stress, increased risk of ADHD development in the children, reduced effects of parent-training in affected children, lax- and over-reactive parenting, and increased aggression in children which was associated with high levels of chaos at home (Breaux et al., 2017; Breaux and Harvey, 2019; Petrill et al., 2004). Therefore, in the psycho-education and psychotherapy of adult ADHD patients that become parents, information and support regarding parenting skills should be implemented to attenuate negative impacts on the development of the children (see Fig. 2).

4.4. ADHD medications seem not to be major teratogens

Most ADHD medications rapidly cross the placental and foetal blood–brain barriers via simple diffusion, and potentially interfere with placenta function but also with physiological development of the infant specifically linked with the monoamine systems such as neuronal or cardiovascular development. However, after reviewing 12 studies investigating the association between in utero exposure to different ADHD medications and pregnancy and infant health outcomes, the overall risk for adverse outcomes seem to be relatively low. Most of the studies did not find an elevated risk for congenital malformations by treatment with methylphenidate or medical amphetamines during pregnancy. However, a recent report suggested a moderate risk for congenital birth defects in infants exposed to modafinil in utero. As the drug is also not recommended in ADHD treatment it should therefore be avoided (Damkier and Broe, 2020). Even if some studies suggested a low risk for cardiovascular malformations due to methylphenidate and amphetamine treatment (Huybrechts et al., 2018; see also follwing meta-analysis: Jiang et al., 2019; Källén et al., 2013) and a low risk for CNS-related disorders of the infant (Nörby et al., 2017) as well as an increased but still low risk for specific birth defects (such as gastroschisis, omphalocele, and transverse limb deficiency) (Anderson et al., 2018a,b), these risks are so low that medication should not be stopped if the ADHD is so severe that the treatment is necessary for daily functioning of the affected women (see also: Baker and Freeman, 2018; Bolea-Alamanac et al., 2014). The teratogenic effects of atomoxetine and guanfacine have not been systematically investigated, so no conclusions can be drawn yet. Certainly, prescription of ADHD medication to pregnant women should always be considered after an individual risk-benefit estimation with the patient and the partner.

4.5. ADHD medications seem to be associated with a low risk for pregnancy and birth complications

Specific stimulant treatment during pregnancy seem to be associated with a low risk for placental dysfunctions, miscarriage, and preterm birth. This could be due to an inhibition of serotonin and norepinephrine transporters in the placenta that might lead to elevation of these neurotransmitters in the intervillous space potentially causing uterine contraction and vasoconstriction, resulting in decreased placental blood flow and premature delivery (Ganapathy, 2011). However, some data also suggest that these placental risks might also be elevated in ADHD in general and therefore potentially not a specific effect of the medication (Bro et al., 2015; Haervig et al., 2014; Nörby et al., 2017; Poulton et al., 2018). There is also controversial evidence that ADHD medication may have a small impact on birth weight, neonatal health and perinatal complications (Table 3). However, this evidence is mostly from small studies and studies analysing different ADHD medications together. Nevertheless, a recent meta-analysis suggested a low but significant increased risk for NICU admission of the infant when the mother was taking ADHD medication during pregnancy (RR = 1.88 [95 %CI 1.7–2.1]) (Jiang et al., 2019).

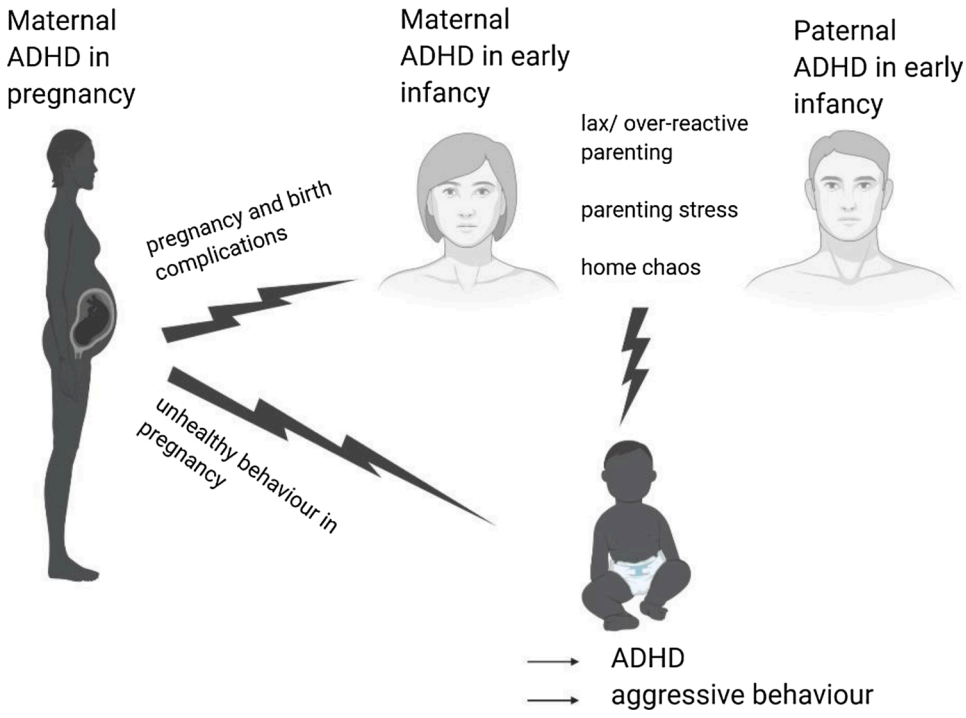

Fig. 2. Associations of parental ADHD with pregnancy, birth and early infancy risks in the offspring.
This figure was created with BioRender.

Atomoxetine appears to be safe regarding placenta function and associated outcomes, however data for guanfacine is not available.

4.6. Methylphenidate seems to be justifiable after risk-benefit consideration in breastfeeding

As controlled studies are lacking we only reviewed case reports and case series reporting safety data regarding the treatment with ADHD medication during lactation and breastfeeding. Methylphenidate use during lactation seems to be safe as there is only little transfer into breast milk and because no adverse effects for the infant have been reported. In contrast, amphetamines are well-transferred into breast milk, where they reach relatively high concentrations, and although the overall risk for an intoxication of the infant seems to be low it cannot be fully excluded. Amphetamines are thus considered to be contraindicated during breastfeeding (Ornoy, 2018). There are little related safety data for atomoxetine, guanfacine, and modafinil, therefore they cannot be recommended for prescription during lactation and breastfeeding. Guanfacine in particular should be discontinued during breastfeeding because of its known effect on prolactin secretion (Anderson, 2018).

5. Conclusions

Clinicians should be aware of a potential higher risk of unplanned and teenage pregnancies in ADHD girls and women. Furthermore, parental ADHD could have a negative impact on early parent-child-interaction, therefore further studies are needed to gain more insight and develop preventive interventions for young parents with ADHD. Regarding ADHD medication, amphetamines seems to have no risk for congenital malformations and likely little risk for placental dysfunction (specifically in the second half of pregnancy) making them relatively safe medications during pregnancy. Methylphenidate might have some risk for cardiovascular malformations, placental dysfunctions, and perinatal complications; however it is still unclear if those associations are caused by methylphenidate or the maternal ADHD itself. Also, more studies with a higher quality are needed in all the investigated areas. However, due to ethical reasons, double-blinded randomised and controlled study designs to investigate negative influence on the development of children are not feasible. But future longitudinal large studies using for example sibling designs and including as many as possible confounders and variables could strengthen the evidence about the influence of parental ADHD and ADHD treatment in pregnancy and early infancy.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.01.002.

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