Medications for Attention Deficit Hyperactivity Disorder in Pregnancy

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Objective

- Perform a risk/benefit analysis about continuation or not of psychostimulant medication during pregnancy and breastfeeding

No conflict of interest to declare

ADHD: Epidemiology and Diagnosis

- About 3% of adults meet criteria for ADHD – inattentive type more common in adults
- Highly comorbid – Increased risk for depression, anxiety, and substance use disorder
- Associated to functional impairment, increased smoking, car accidents, etc. Treatment reduces these complications.

CADDRA (2018)

Table 1

DSM-5 criteria for diagnosis of ADHD in adults

≥5 symptoms per category in adults, persisting at least 6 months; present prior to age 12; several symptoms are present in ≥2 settings; symptoms interfere with, or reduce the quality of social, academic, or occupational functioning
Inattention
a. Lack of attention to details/careless mistakes
b. Difficulty sustaining attention in tasks
c. Does not seem to listen when spoken to directly
d. Does not follow through on instructions
e. Difficulty organizing tasks and activities
f. Avoids tasks that require sustained mental effort
g. Loses or misplaces objects
h. Easily distracted
i. Forgetful in daily activities
Hyperactivity and impulsivity
a. Fidgetiness (hands or feet)/squirms in seat
b. Leaves seat frequently
c. Feeling restless
d. Unable to engage in leisure activities quietly
e. Always "on the go," difficulty being still for extended time
f. Talks excessively
g. Blurts out answers
h. Difficulty waiting his or her turn
i. Interrupts or intrudes on others

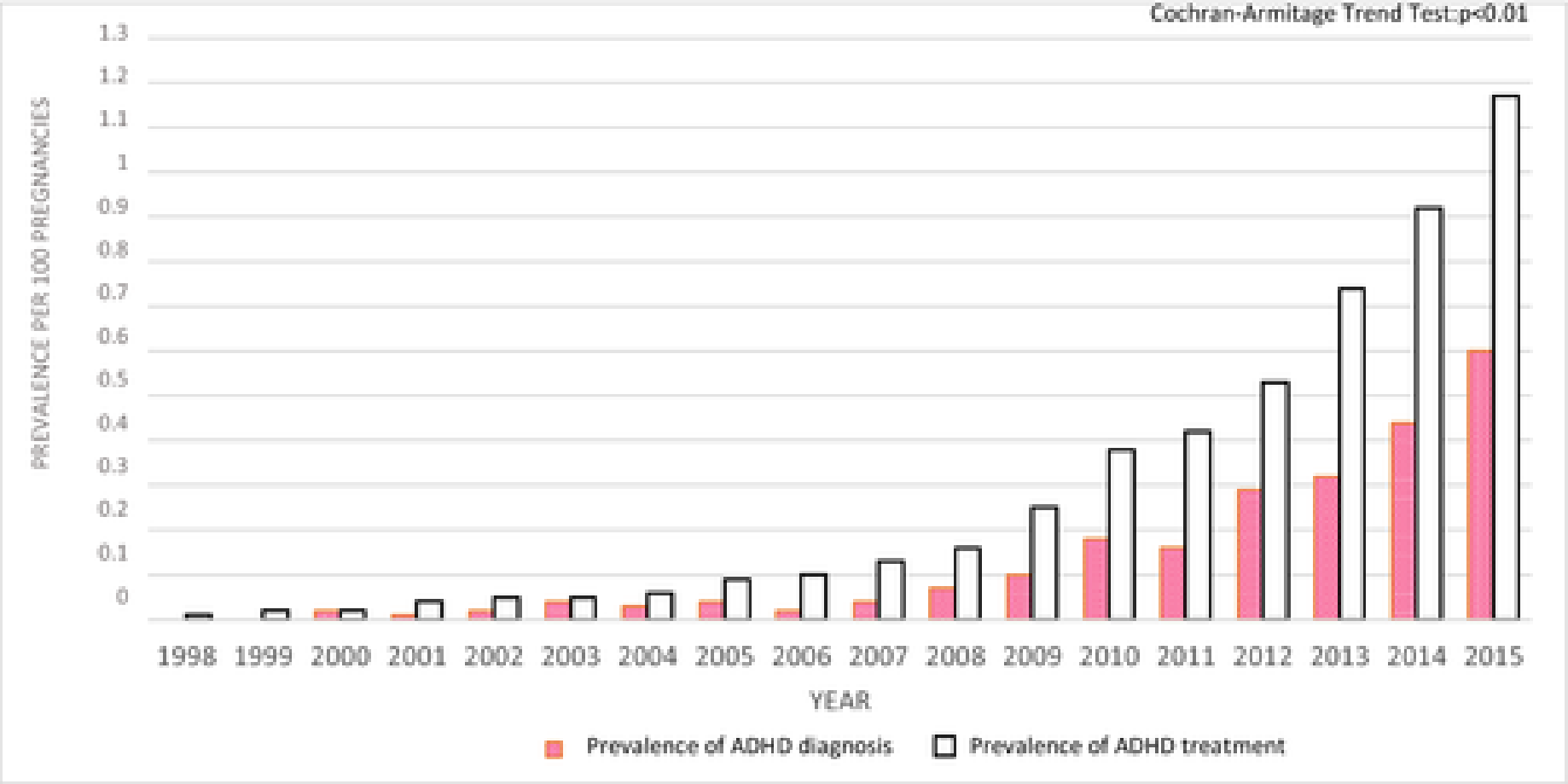
ADHD: attention-deficit/hyperactivity disorder

Source: Reference 13

Limited litterature on stimulant use in pregnancy

- No RCTs; observational studies with multiple possible biases including confounders and confounding by indication
- Data from pregnant patients abusing amphetamines extrapolated to patients under prescribed amphetamines use
- No guidelines on treatment of ADHD during pregnancy
    - **COPE (Center of Perinatal Excellence) Guidelines Australia 2023** – concerning medication for ADHD, there is currently insufficient evidence on their use in the perinatal period for conclusions to be drawn.
    - **NICE guidelines - Antenatal and postnatal mental health: clinical management and service guidance (updated 2020):** No mention of ADHD
    - **British Columbia - Best Practice Guidelines for Mental Health Disorders in the Perinatal Period – 2014** no mention of treatment of ADHD. Update to come specifically for ADHD.

Use of ADHD medication in pregnancy - Quebec



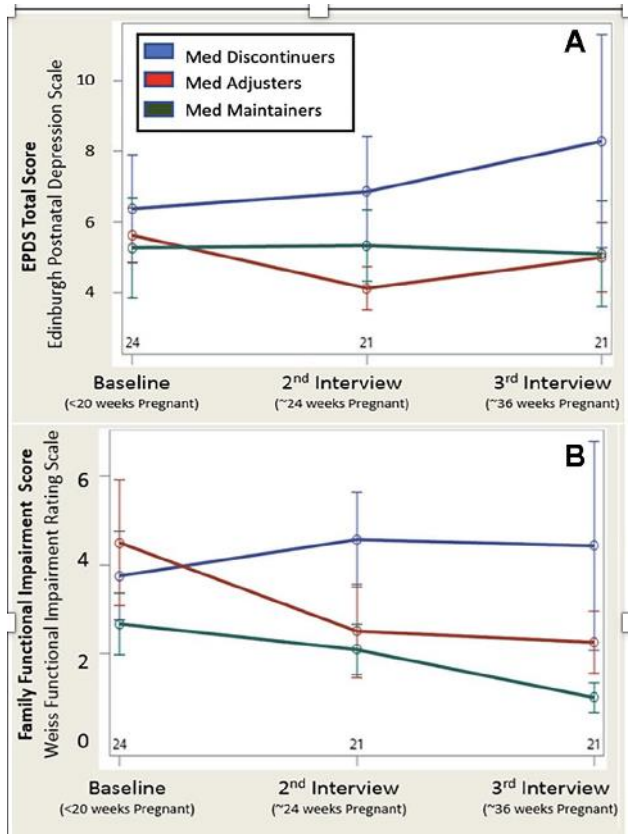
Lemelin et al. (2021)

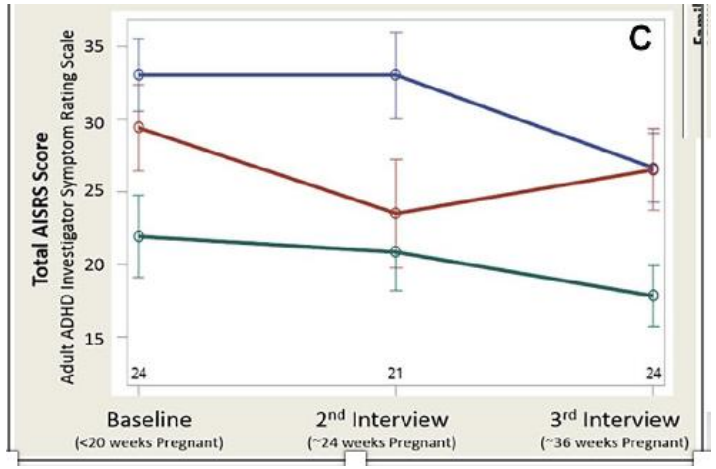
ADHD during pregnancy and postpartum

- The gestational and postpartum period require organizational skills (appointments, following recommendations during pregnancy and for baby, etc.)
- ADHD is an independent risk factor for postpartum depression and postpartum anxiety **(Andersson et al., 2023)**
- Course during pregnancy? Very small study looking at outcomes depending on maintenance of medication, decreased use or cessation **(Baker et al., 2022)**

The course of ADHD during pregnancy

- Statistically significant increase in EPDS score in discontinuers (clinically significant?)
- Statistically significant increase in Family functioning Impairment Score (clinically significant?)
- No statistically significant difference in ADHD Investigator Rating Scale
- ADHD symptoms alone may not be a reliable proxy for overall functioning when it comes to understanding the course and impact of ADHD in pregnancy.





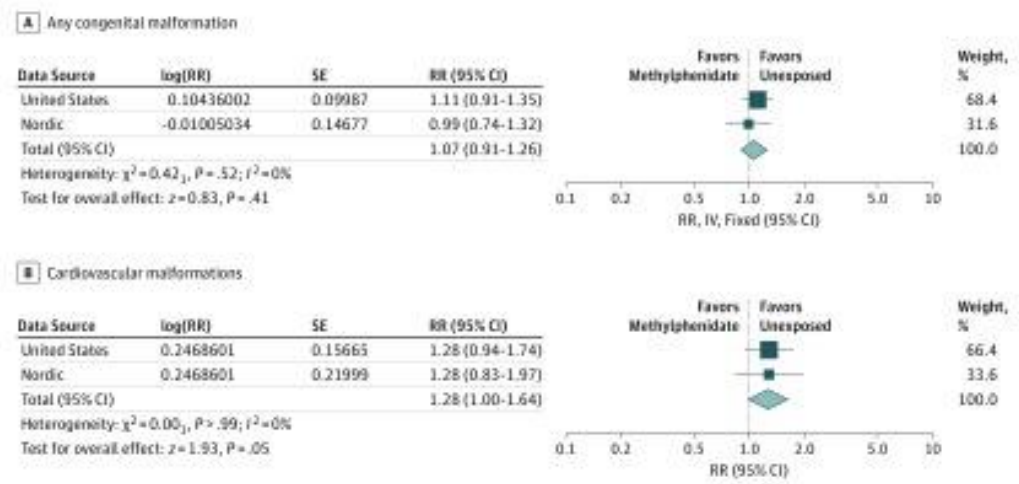
Baker et al. (2022)

First trimester exposure – Teratogenosis and abortion

No association between methylphenidate and amphetamine and major malformations (Szpunar et al., 2023)

Some studies have found an association between cardiac malformations and MPH while others have not. Pooled data from US and Nordic Countries found a 1.28 (95% CI, 1.00-1.64) for cardiac malformations

If there is an increased risk, the increased absolute risk is small - Some recommend a fetal echocardiography/others no



Huybrechts et al. (2018)

Some studies have found an increased risk of abortion (induced or spontaneous) in women taking ADHD meds – not a causal association

Haervig et al. (2014)

Obstetrical outcomes

- Women with ADHD are at higher risk of being younger at childbirth, smoking during pregnancy and having babies with LBW or PT birth regardless of medication **(Bang Madsen et al., 2023)**

- Association of stimulant use in pregnancy with preeclampsia aOR 1.29 (1.11-1.49) – absolute risk ins crease is small **(Cohen et al., 2017)**

Perinatal outcomes

- Swedish registry study: exposure to ADHD medication during pregnancy vs before/after vs general population
  - 90% Methylphenidate
  - 16% only using medication in last trimester

- Women who use medication (before/during/after) differ from general population

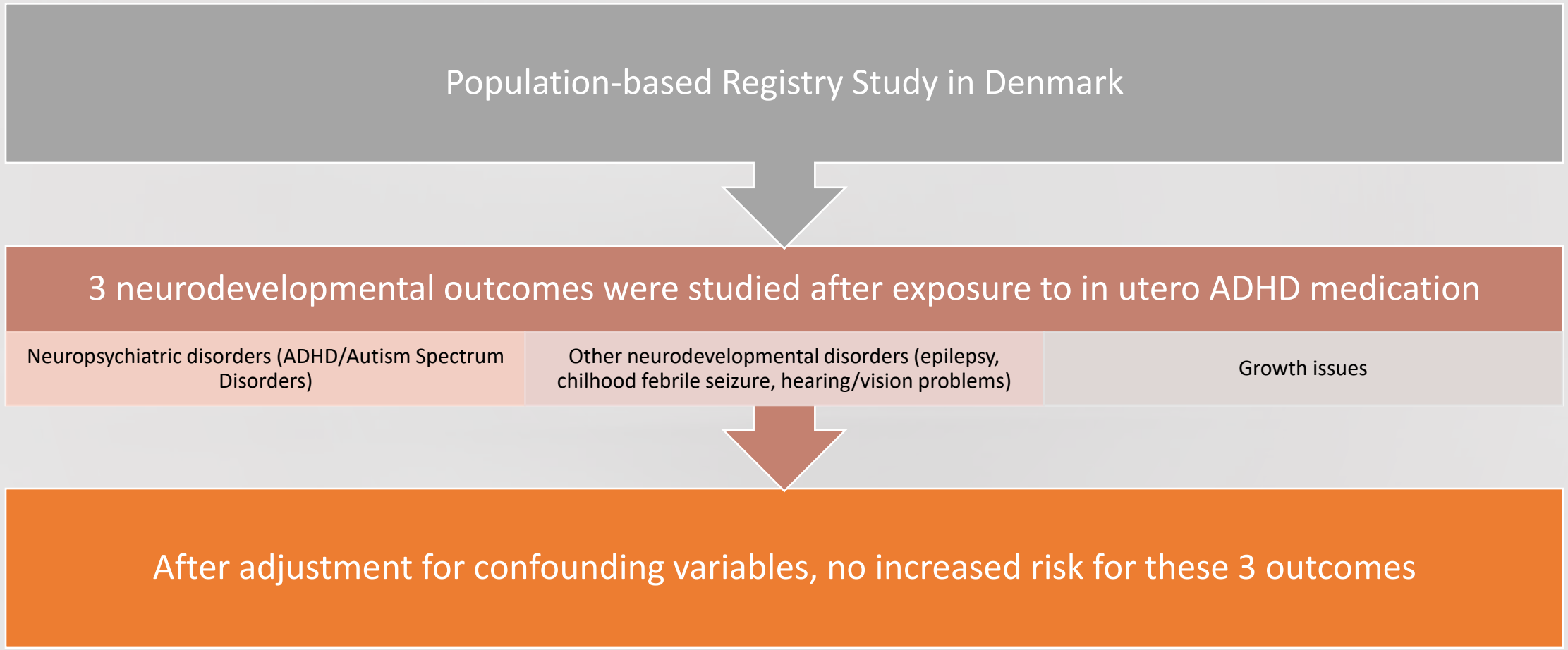
Nörby et al. (2017)

Perinatal outcomes

- Higher risk of NICU admission aOR 1.5 (1.3-1.7) 1.2 (1.1-1.4)
- No association with specific diseases except CNS disorders aOR 1.9 (1.1-3.1)
- Increased risk of moderate preterm birth aOR 1.3 (1.1-1.6) 1.2 (1.0-1.4)
- No association with congenital malformations or perinatal mortality
- Trends – low Apgar scores/feeding difficulties/hypoglycemia/withdrawal sx

Nörby et al. (2017)

Long term neurodevelopmental consequences



Bang Madsen et al. (2023)

Psychostimulants and breastfeeding

- Very limited data (case reports) – even less in premature/very young babies
- MPH and amphetamines have low passage in breast milk (relative infant dose 10%)
- Amphetamines may reduce prolactin – impact on milk production?
- Immediate release options may help reduce exposure

Nunacs (2021)

Other medications – Non psychostimulants

- **Modafinil:** Some studies suggest an increase in major malformations. Health Canada 2019 advises against use in pregnancy
- **Atomoxetine:** No increase in major malformations in pregnancy-register US/Nordic Countries (Bröms et al., 2023) Limited reassuring data for other outcomes. Not first choice).
- **Bupropion**: relatively reassuring data (less studied than other antidepressants in pregnancy but more than many ADHD treatments)
- **Guanfacine**: very limited data

Baker et al. (2020)

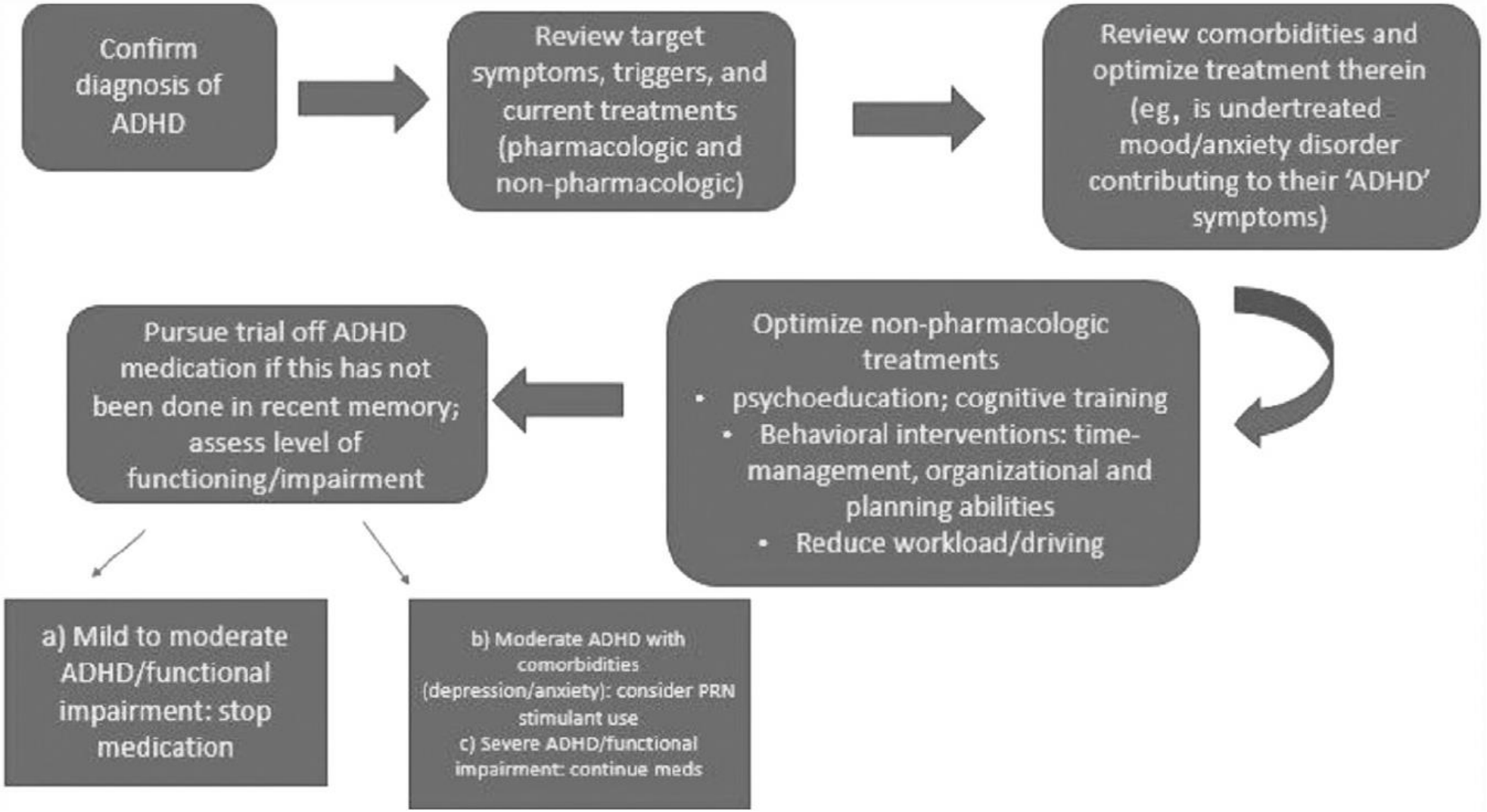


Fig. 2. Explanatory algorithm for clinicians working with pregnant patients with ADHD.

Baker & Freeman (2018)

Individualized decision

What is the severity of my patient's disease?
Personal history of symptoms
Periods of time without ADHD medication in the past? **Functioning?** Distress? Accidents?
Psychiatric and medical comorbidities? Is the treatment of these comorbidities optimized?
Are non-pharmacological treatments optimized?
Psychotherapy +/- Occupational therapy
Reduction of workload
Can exposure to the medication be safely reduced while still being effective?
Drug holidays
What is my patient's personal preference?

Summary

- ADHD is a common disorder which can have significant impacts on functioning and well-being.
- The litterature is highly biased – incomplete, confounders, effects of ADHD and comorbidites hard to separate.
- There may be a small absolute risk in cardiac malformations 2nd to MPH
- Other possible associations include PT birth, NICU admissions, CNS disorders. Developmental outcomes appear to be reassuring.
- Risk/Benefit analysis needs to be tailorized to patient according to patient preference, personal psychiatric history (for ADHD and other comorbidities)
- Optimize non-pharmacological interventions

References

- Andersson, A., Garcia-Argibay, M., Viktorin, A., Ghirardi, L., Butwicka, A., Skoglund, C., ... & Larsson, H. (2023). Depression and anxiety disorders during the postpartum period in women diagnosed with attention deficit hyperactivity disorder. *Journal of Affective Disorders*, *325*, 817-823.
- Baker, A. (2020). Course and Treatment of ADHD and Comorbid Disorders During Pregnancy and the Postpartum Period. Presentation Harvard University for the MGH continuing medical education. Found online: https://mghcme.org/app/uploads/2020/10/Baker-WMH-Talk-Updated-Baker-8.9.20.pdf
- Baker, A. S., & Freeman, M. P. (2018). Management of attention deficit hyperactivity disorder during pregnancy. *Obstetrics and Gynecology Clinics*, *45*(3), 495-509.
- Baker, A. S., Wales, R., Noe, O., Gaccione, P., Freeman, M. P., & Cohen, L. S. (2022). The Course of ADHD during Pregnancy. Journal of Attention Disorders, 26(2), 143–148. https://doi.org/10.1177/1087054720975864
- Bang Madsen, K., Robakis, T.K., Liu, X. *et al.* In utero exposure to ADHD medication and long-term offspring outcomes. *Mol Psychiatry* 28, 1739–1746 (2023). https://doi.org/10.1038/s41380-023-01992-6
- Bröms, G., Hernandez-Diaz, S., Huybrechts, K. F., Bateman, B. T., Kristiansen, E. B., Einarsdóttir, K., ... & Kieler, H. (2023). Atomoxetine in Early Pregnancy and the Prevalence of Major Congenital Malformations: A Multinational Study. The Journal of Clinical Psychiatry, 84(1), 45077.
- Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines, 4e édition [En ligne]. Toronto : CADDRA; 2018 [cité le 13 mai 2020]. Disponible: https://www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf
- Cohen, J. M., Hernández-Díaz, S., Bateman, B. T., Park, Y., Desai, R. J., Gray, K. J., ... & Huybrechts, K. F. (2017). Placental complications associated with psychostimulant use in pregnancy. Obstetrics and gynecology, 130(6), 1192.
- Hærvig, K. B., Mortensen, L. H., Hansen, A. V., & Strandberg-Larsen, K. (2014). Use of ADHD medication during pregnancy from 1999 to 2010: a Danish register-based study. Pharmacoepidemiology and drug safety, 23(5), 526-533.
- Huybrechts, K. F., Bröms, G., Christensen, L. B., Einarsdóttir, K., Engeland, A., Furu, K., Gissler, M., Hernandez-Diaz, S., Karlsson, P., Karlstad, Ø., Kieler, H., Lahesmaa-Korpinen, A. M., Mogun, H., Nørgaard, M., Reutfors, J., Sørensen, H. T., Zoega, H., & Bateman, B. T. (2018). Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study From the International Pregnancy Safety Study Consortium. JAMA psychiatry, 75(2), 167–175. https://doi.org/10.1001/jamapsychiatry.2017.3644

References

- Lemelin, M., Boukhris, T., Zhao, J. P., Sheehy, O., & Bérard, A. (2021). Prevalence and determinants of attention deficit/hyperactivity disorder (ADHD) medication use during pregnancy: Results from the Quebec Pregnancy/Children Cohort. *Pharmacology Research & Perspectives*, *9*(3), e00781.
- Nonacs, R. (2021). Essential Reads: Breastfeeding and ADHD Medications. MGH Center for Women's Mental Health. https://womensmentalhealth.org/posts/essential-reads-breastfeeding-and-stimulants/
- Nörby, U., Winbladh, B., & Källén, K. (2017). Perinatal outcomes after treatment with ADHD medication during pregnancy. Pediatrics, 140(6).
- Szpunar, M. J., Freeman, M. P., Kobylski, L. A., Rossa, E. T., Gaccione, P., Chitayat, D., ... & Cohen, L. S. (2023). Risk of Major Malformations in Infants After First-Trimester Exposure to Stimulants: Results From the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications. *Journal of Clinical Psychopharmacology*, *43*(4), 326-332.