

Research Round up March- Prescribing in Pregnancy

Introduction

Last month the research round-up provided you with an overview of articles looking at adverse drug reactions (ADRs). This month we will review three articles looking at the complex issues encountered when prescribing in pregnancy. The first article looks at polypharmacy and associated risks in pregnancy, the second examines antidepressant use in pregnancy and the risk of gestational diabetes, and finally we review a study looking at the impact of regulatory safety notices on the prescribing of valproate in women of childbearing potential.

Polypharmacy during pregnancy and associated risk factors: a retrospective analysis of 577 medication exposures among 1.5 million pregnancies in the UK, 2000-2019

Subramanian et al. (2023) *Polypharmacy during pregnancy and associated risk factors: a retrospective analysis of 577 medication exposures among 1.5 million pregnancies in the UK, 2000-2019* BMC Medicine 21:21

This article, published in BMC Medicine, used a retrospective cohort study approach to examine data between the years 2000 and 2019. The main driver for the researchers was to shed light on the prevalence of multiple medication use in pregnancy and to identify risk factors for polypharmacy. They accessed the Pregnancy Register within the Clinical Practice Research Datalink which contains the anonymised medical records of over 20 million patients within 973 GP practices. Within the pregnancy section data could be gathered on estimated start and end dates of pregnancy as well as estimated dates for each trimester. Also accessible are GP issued prescriptions during that time.

The database contained 3,202,461 pregnancies and of those 812,354 over the selected time period. Of these 1,521,317 met the inclusion and exclusion criteria, of these 812,354 and 774,247 pregnancies had complete follow-up through the first trimester and the entire pregnancy respectively. The prescription records for 577 medication categories (as defined by the BNF) were also obtained.

The researchers found that of the 812,354 records competing the first trimester, there was a prevalence of polypharmacy that increased from 8.7% to 18.7 between the period 2000-2019. Looking at numbers of medicines from 2+ to 11+, the prevalence ranged from 24.6% at the low end to 0.1% at the upper. When comparing this to the whole pregnancy (774,247), prevalence ranged from 58/7 at 2+ to 1.4% at 11+ medications.

A review of the medication prescribed revealed that the commonest prescribed medications were broad spectrum penicillins at 6.6% of total, non- opioid compound analgesics at 4.5% and antifungal treatments at 4.3% of total. If the researchers filtered this to only account for patients with multimorbidity the commonest were SSRI's, selective beta 2 agonists and broad-spectrum penicillins.

In an analysis of the risk factors for polypharmacy in the first trimester (the authors looked from 2+ medications upwards) they identified obesity, ethnic minorities, smoking and previous smoking to all have an impact on likelihood of increased prescribing. Additionally, being of a higher maternal age (45-49 years) or lower (15-19 years) increased the incidence of prescribing compared to women in the ages in between. Another factor seen was the increased number of co- morbidities and increased level of social deprivation. Also, a higher gravidity increased risk of prescribing compared to women in their first pregnancy. The authors conclude that the prevalence of polypharmacy in pregnancy has increased over the past 20 years and is highest in women of younger or older age

during pregnancy as well as in the obese, smokers, multimorbidity and deprivation. They suggest further research is necessary to understand how this increased drug use in pregnancy may affect the development in utero.

<https://link.springer.com/article/10.1186/s12916-022-02722-5>

Antidepressant use during pregnancy and the risk for gestational diabetes: a systematic review and meta-analysis

Xiao-yan Wang, Xian-hua Ying and Hai-yin Jian (2023) *Antidepressant use during pregnancy and the risk for gestational diabetes: a systematic review and meta-analysis* THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE 2023, VOL. 36, NO. 1, 2162817 <https://doi.org/10.1080/14767058.2022.2162817>

This article published in the Journal of Maternal- Fetal and Neonatal Medicine looked to review published research on the relationship between antidepressant use in pregnancy and the risk of developing gestational diabetes. The drivers for the authors were their noted increase in the use of antidepressant use in pregnancy for the conditions of depression and anxiety but also their use in OCD, fibromyalgia and headache. They acknowledge that gestational diabetes is a relatively common condition of pregnancy and sought to review observational studies to assess the association, if any, between antidepressant use and the onset of gestational diabetes. This well conducted systematic review of the literature and meta-analysis used PubMed and EMBASE databases with publications up to 2019 being included and using the Meta-Analysis for Observational Studies in Epidemiology (MOOSE) checklist was used as a reporting guideline (Stroup et al 2000). The search strategy is well outlined and there is good adherence to inclusion and exclusion criteria.

The authors initially identified 488 potential articles in the two databases but with exclusions of duplicates (36), removal at further critical scrutiny (432), removal after full text evaluation (15), five articles were eligible for inclusion. Based on these articles the authors meta-analysis suggests that mothers who take antidepressant medications during pregnancy are at a significantly higher risk of developing gestational diabetes with a relative risk of 1.20, with a 95% confidence interval stated. They do acknowledge confounding by indication and when this is considered there is no clear evidence of antidepressant use in pregnancy and increased risk of gestational diabetes. They also suggest the risk may be different for each class of antidepressant with SSRIs being the lowest risk compared to venlafaxine or amitriptyline. They conclude, based on their small sized review, that any significant association between antidepressant use during pregnancy and gestational diabetes may be overestimated and that evidence remains insufficient to form a firm link. They suggest larger prospective cohort studies are needed to clarify any effects.

<https://www.tandfonline.com/doi/full/10.1080/14767058.2022.2162817>

Impact of regulatory safety notices on valproate prescribing and pregnancy outcome among women of child-bearing potential in Scotland: a population-based cohort study

Stuart McTaggart ,¹ Gavin MacColl ,² Karen Gronkowski,² Rachael Wood ,^{1,3} John Paul Leach ,⁴ Marion Bennie

This article published in the BMJ Open, looked at the impact of regulatory safety notices on valproate prescribing and pregnancy using a population-based cohort study. The Medicines and Healthcare products Regulatory Agency issued strong guidance on the prescribing of valproate to women and girls of childbearing potential following a Europe wide review of the impact on foetal development and valproate prescribing in 2014.

The researchers identified all valproate prescriptions issued to women aged between 14 and 45 years between the dates of January 2011 and December 2019. This study was carried out in Scotland and accessed linked records using MHS numbers and the unique Community Health Index (CHI) number. Data was linked by Public Health Scotland and approved by appropriate Caldicott Guardians. Data from the National Prescribing Information Service was used to ascertain valproate prescriptions reimbursed during the time of review. Pregnancy outcome was also reviewed looking at live birth, still birth, miscarriage, and termination. In total 21,983 women meeting the inclusion criteria were prescribed valproate between January 2011 and December 2019. They report that the annual prevalent rate of valproate prescribing declined from 40.5% in 2011 to 18.3% in 2019 per 10,000 population in women between the ages of 14-45 years. Statistically significant changes occurred around the times of the MHRA safety alerts. The authors conclude that the impact of the safety alerts has been positive and has resulted in a major reduction in the use of valproate in women of childbearing potential and the use of a pregnancy prevention plan has been successful in reducing pregnancies occurring in women prescribed the drug. They suggest a national surveillance capacity could continue to minimise the in-utero exposure to valproate with better long-term outcome.

<https://bmjopen.bmj.com/content/12/4/e058312.abstract>

Conclusion

Prescribing in pregnancy can be a worry to many prescribers medical and non-medical and the premise is often to only give medications if the benefit to the mother outweighs the risk to the foetus. For many expectant mothers there are pre-existing health conditions that necessitate medication, and these should be well monitored. Avoidance of unnecessary polypharmacy is something prescribers should strive for in all populations but especially here. It is important to be mindful of side effects that may not occur in a non-pregnant mother and monitor accordingly.

Additional Reference

Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–2012