PSYCHOTROPIC MEDICATION EXPOSURE DURING PREGNANCY:

NEURODEVELOPMENTAL EFFECTS IN OFFSPRING

B. Jorge¹, J. Carvalho¹, C. Campos¹, D. Vilaverde¹, S.J. Carneiro¹, C.P. Fernandes¹.

¹Hospital de Braga, Departamento de Psiquiatria e Saúde Mental, Braga, Portugal.

METHODS

INTRODUCTION

In utero exposure to psychotropic medication has been mostly assessed for the risk of teratogenic malformations, preterm birth and neonatal complications. The association between prenatal exposure and neurodevelopmental effects is less known (Gentile, 2010). Thus, understanding the neurodevelopmental consequences of prenatal psychotropic exposure is an imperative demand in the search for safer and more effective psychotropic medication administered during pregnancy.

OBJECTIVE: to **review** whether prenatal psychotropic medication exposure increases the risk of impaired child neurodevelopment.

Pubmed/MEDLINE, Web of Science and Google Scholar were searched for the period between April 1992 and April 2019, using the following keywords: pregnancy, child development, antidepressant, antipsychotic, mood stabilizer/antiepileptic drug, benzodiazepine/anxiolytic. Resultant articles were cross-referenced for other relevant articles not identified in the initial search. Studies collecting primary data on neurodevelopment of infants exposed in utero to psychotropic drugs were selected. **Thirty-five** studies met the inclusion criteria.

RESULTS – WHAT DO WE KNOW SO FAR?

ANTIDEPRESSANTS represent the class of psychotropics with the highest number of studies investing neurodevelopment effects. The **majority of studies showed normal progress of several aspects of neurodevelopment** (Bellantuono, Marini, & Lucarelli, 2013), with no effect on cognition and behaviour (Galbally, Lewis, & Buist, 2011; Galbally, Lewis, & Buist, 2015). These conclusions had been previously described (Irena et al., 2002), revealing that early utero exposure to either tricyclic antidepressant drugs or fluoxetine did not affect global IQ, language development or behavioral development in preschool children. The same results were reproduced throughout the duration of gestation (Nulman et al., 2002). In a prospective, longitudinal study (Austin et al., 2013), pregnancy antidepressant exposure (mostly serotonin reuptake inhibitors) was not associated with poorer cognitive, motor or language development outcomes in infants at 18 months. There was, however, a small increased risk of poorer motor development in children exposed to antidepressant medication during pregnancy (Grove, Lewis, & Galbally, 2018). These results were consistent with the previous findings compatible with poorer fine motor development at 6 months of age (Galbally et al., 2011; Galbally et al., 2017). Antidepressant exposure was also evaluated in preterm infants (Brown et al., 2013) and focusing in SSRI. This retrospective case control study did not show an association with adverse neurodevelopment above the baseline risk for this degree of prematurity. Among the classes of antidepressants, SSRI is, evidently, the most deeply studied. Despite the conclusions mentioned above, **contradictory findings were found in literature**. Skurtveit et al. (Skurtveit, Selmer, Roth, Hernandez-Diaz, & Handal, 2014) described that prolonged use of SSRI during pregnancy was associated **with lower language competence** in children by age three (independently of depression) and altered speech perception (Weikum, Oberlander, Hensch, & Werker, 2012). Similar results were published a few years later (Brown et al., 2016). Some studies even point a **linkage between Autism Spectrum Disease and SSRI exposure** (Kobayashi, Matsuyama, Takeuchi, & Ito, 2016; Healy, Le Noury, & Mangin, 2016). It was also found that children exposed to SSRI in late pregnancy had an increased risk of anxious/depressed behaviour by age 5 years compared with unexposed children, although there was no evidence for a substantial prenatal SSRI effect on externalizing, social, and emotional problems (Lupattelli et al., 2018).

MOOD STABILIZERS

The **dose-response relationship between valproate and cognitive impairment is well established in literature**, with higher doses associated with poorer global cognitive abilities compared to other mood stabilizers/antiepileptic drugs (AED) (Cummings, Stewart, Stevenson, Morrow, & Nelson, 2011; Bromley et al., 2013; Meador et al., 2013; Haskey & Galbally, 2017; Veroniki et al., 2017). **IQ values were lower for children exposed to high-dose** (>800 mg daily) of valproate, with a similar significant effect observed for the verbal, nonverbal, and spatial subscales (Baker et al., 2015). **Data concerning other mood stabilizers remains, nonetheless, limited and inconsistent**. One study revealed no significant associations between neurodevelopment and exposure to other AED such as carbamazepine, lamotrigine or phenytoin (Veroniki et al., 2017), while a Denmark nationwide population-based cohort study found an increased risk of requiring special needs education, attending special needs school and having neurological or mental disorders following AED exposure (Wibroe, Mathiasen, Pagsberg, & Uldall, 2017). There was an earlier observational study linking neurodevelopmental impairment to in utero exposure to carbamazepine, as well as valproate (Cummings et al., 2011). Lamotrigine exposed children also showed reduced motor and sensory scores, with no differences found between valproate and lamotrigine exposed children (Rihtman, Parush, & Ornoy, 2013). In contrast, no significant differences in autistic characteristics, learning disabilities or developmental delays were observed with lamotrigine (Cohen-Israel et al., 2018). Regarding **lithium** exposure, few clinical cohort studies have been performed, all of which reporting **normal development** (Poels et al., 2018).

ANXIOLYTICS & HYPNOTICS

Scarce and conflicting data results are observed in this category. No strong association was determined between prenatal use of anxiolytics and hypnotics and lower language competence in the offspring at age 3 years (Odsbu et al., 2015). There was a moderate association between benzodiazepine/z-hypnotic exposure in late pregnancy and greater gross motor and communication deficits, but the extent of this impairment had no clinical relevance (Lupattelli et al., 2019). In the past, it has been suggested that prenatal exposure to benzodiazepines could cause a general delay in mental development up to 18 months of age (Viggedal, Hagberg, Laegreid, & Aronsson, 1993). Thus, **the global impact of prenatal exposure to benzodiazepines on infant development remains uncertain**.

ANTIPSYCHOTICS

The data available is still considerably limited also. Recent studies have shown a **trend for short-term developmental delay in cognition, motor skill, social-emotional, and adaptive behavioral** (Peng et al., 2013; Poels et al., 2018). In a prospective, case-controlled study, more clozapine-exposed infants had delayed development for adaptive behavior at 2 and 6 months of age than other atypical antipsychotics, despite **all these differences disappeared after 6 months of age** (Shao et al., 2015).

DISCUSSION – REFLECTING THE DIFFERENCES

- **Sample sizing proved to be the most impactful limitation.** Most of the studies had relatively small samples, affecting results statistical significance. In order of improvement, larger population-based studies are emerging (El Marroun, White, Verhulst, & Tiemeier, 2014).
- There are **several confounding factors** significantly associated with child developmental outcome independently of maternal psychotropic exposure (Rotem-Kohavi & Oberlander, 2017). Although some studies have taken them into account, many did not **undertake adequate statistical control** (Haskey & Galbally, 2017).
- It must also be considered that the majority of studies **were limited by the age at which the children are assessed** (Gentile & Galbally, 2011) and **inconsistency in methodology scales** used to evaluate child neurodevelopment (Shao et al., 2015), which often falls short of where neurodevelopmental testing carries greater accuracy and predictive validity.
- In addition, the paucity of evidence regarding long-term effects of intrauterine exposure may lead to a **blunted motivation to invest** in studies of the potential adverse neurodevelopmental consequences and consequent underreporting of associations (Poels et al., 2018).

CONCLUSION

The uncertain impact of most psychotropics on infant neurocognitive development should clearly be discussed with the mother and her partner in order to obtain a valid, informed consent prior to taking such medications during pregnancy. **Further investigation should be performed.**