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Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: A systematic review and meta-analysis

Berihun Assefa Dachew[a,b,c,*], Abdullah Mamun[a,b], Joemer Calderon Maravilla[a,b], Rosa Alati[a,b]

[a] The University of Queensland, Institute for Social Science Research, Indooroopilly, Qld 4068, Australia
[b] The University of Queensland, School of Public Health, Herston, Qld 4006, Australia
[c] Department of Epidemiology and Biostatistics, Institute of Public Health, University of Gondar, Ethiopia

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ABSTRACT

Hypertensive disorders of pregnancy are a major cause of maternal and offspring morbidity and mortality worldwide. However, its effect on offspring mental and behavioural disorders is unclear. The aim of this study is to provide the best scientific evidence on the association between hypertensive disorders of pregnancy and offspring mental and behavioural problems. We systematically searched Scopus, PubMed, Cochrane, EMBASE, CINAH and PsycINFO databases. A total of 23 studies (11 included in meta-analysis) were identified. Of the 23 studies included in this review, 15 studies found that hypertensive disorders of pregnancy had a negative impact for at least one mental or behavioural disorder. The pooled effect of 11 studies included in the meta-analysis showed that preeclampsia was associated with increased risk of offspring schizophrenia. However, we found inconclusive finding on the effect of hypertensive disorders of pregnancy and other mental and behavioural disorders. Further high quality, large sample, birth cohort studies are needed to further progress this area of research.

1. Introduction

Hypertensive disorders of pregnancy (HDP), also known as maternal hypertensive disorder, are a group of conditions which includes gestational hypertension, preeclampsia/ eclampsia, chronic hypertension and preeclampsia superimposed on chronic hypertension (National High Blood Pressure Education Program, 2000). Gestational hypertension is usually defined as having a blood pressure higher than 140/90 mmHg measured on two separate occasions, at least 4 h apart in a women who are normotensive before 20th week of gestation. Preeclampsia is defined as gestational hypertension with proteinuria (> 300 mg of protein in a 24-h urine sample) and chronic hypertension as high blood pressure before the 20th week of gestation or not resolved after delivery (ACOG, 2013; National High Blood Pressure Education Program, 2000).

HDP are a major cause of maternal morbidity and mortality worldwide (Duley, 2009; Global Burden of Disease Study, 2015; Say et al., 2014). Globally, about 10% of pregnancies are complicated by HDP (WHO, 2011). Preeclampsia, together with other hypertensive disorders, is the second most common direct cause of 14% of maternal death worldwide (Say et al., 2014). HDP are also responsible for stillbirth (Flenady et al., 2011) and infant death (Basso et al., 2006) and major risk factors for adverse perinatal outcomes such as preterm birth (Ferrazzani et al., 2011), low birth weight (Villar et al., 2006), and intrauterine growth restriction (Bakker et al., 2011; Ferrazzani et al., 2011; Villar et al., 2006). Since these adverse perinatal outcomes are associated with numerous mental health morbidities in offspring (Betts et al., 2011, 2013; Johnson and Marlow, 2011; Yanney and Marlow, 2004) it is possible that HDP may affect brain development via uteroplacental vascular insufficiency and fetal malnutrition and lead to subsequent neurobehavioral difficulties (Walker et al., 2015).

Although existing evidence on the effect of HDP on offspring mental and behavioural disorders is not well-established, studies have been conducted to identify the risk of HDP on the mental and behavioural health of offspring. Therefore, the aim of our study was to systematically review the existing literature on this topic in order to provide the best scientific evidence regarding the association between HDP and offspring mental health and behavioural disorders. We also performed a comprehensive meta-analysis to further evaluate the relationship between HDP and schizophrenia.

* Corresponding author at: The University of Queensland, Institute for Social Science Research, Indooroopilly, Qld 4068, Australia.
E-mail addresses: b.dachew@uq.edu.au (B.A. Dachew), mamun@sph.uq.edu.au (A. Mamun), j.maravilla@uq.edu.au (J.C. Maravilla), r.alati@sph.uq.edu.au (R. Alati).

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2. Methods

This systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) (Moher et al., 2015) (See Supplementary Table S1).

2.1. Data sources and search strategies

We systematically searched PubMed, Scopus, Cochrane, EMBASE, CINAHL and PsycINFO databases with no publication year restriction until September/2016. The PubMed database was searched using a combination of key words as follows: Search#1: ((((((((((Preeclampsia OR Pre-eclampsia OR Gestational hypertension) OR Maternal hypertension) OR Pregnancy induced hypertension) OR Hypertension diseases of pregnancy) OR Hypertensive pregnancy disorders) OR Hypertension in pregnancy) OR Hypertension during pregnancy) OR Hypertensive disorders of pregnancy) OR Obstetric complications. Search # 2: (((Offspring OR Child*) OR Adolescent*) OR Adult*. Search #3: ((((((((((((Mental illness) OR Mental disorders) OR Behavioural disorders) OR Behavioural problems) OR Hyperactivity) OR Violent behaviour) OR Aggressive behaviour) OR Delinquency) OR Temperament) OR Attention deficit disorder) OR Depression) OR Anxiety) OR Mood disorders) OR Psychosis) OR Schizophrenia and search 4: Search #1 AND Search #2 AND search #3. Likewise, Scopus, Cochrane, EMBASE, CINAHL and PsycINFO databases were searched using similar search terms tailored to each database. The reference lists of included studies were further searched for additional eligible studies. No authors were contacted for additional studies or data.

2.2. Study selection

All retrieved records were screened for five eligibility criteria: Cohort or case control studies, human subjects, published in English, HDP (gestational hypertension and/or preeclampsia) treated as exposure and/-or confounding variable, and offspring mental and behavioural disorders (namely internalizing symptoms, externalizing behaviours, delinquency, temperament, and aggressive behaviour, attention deficit hyperactivity disorder, anxiety, depression, psychosis, schizophrenia and mood disorders) as outcome variable. Developmental disorders such as autism, intellectual disability and specific learning and motor disorders were excluded. The eligibility of each study was assessed independently by two investigators (BAD and JCM) and disagreements were solved through discussion. We excluded studies that did not fit the eligibility criteria and those which were not published in their entirety such as conference abstracts and letters to editors. After duplicates removal, a total of 2203 articles were identified and 1926 were excluded during initial assessment as their title was found to be irrelevant. We further screened the abstracts of the remaining 277 studies and excluded 225 of these since they did not fulfil the eligibility criteria. The reaming full text papers were screened for relevance and a total of 23 papers (11 for meta- analysis) were found to be eligible for analysis. One study (Kendell et al., 2000) supplied information on 2 independent birth cohorts, therefore we treated the estimates as two separate studies in the meta-analysis (Fig. 1).

2.3. Quality assessment

The quality of all studies were assessed using Newcastle-Ottawa quality assessment tool for cohort and case control studies (Wells et al., 2016). This tool consists of three domains: selection, exposure and comparability domains. A study can be given a maximum of one star for each numbered item within the selection and exposure categories and a maximum of two stars can be given for comparability. Finally, the results are summarised in three categories as good quality (3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain), fair quality (2 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain) and poor quality (0 or 1 star in selection domain or 0 stars in comparability domain or 0 or 1 stars in outcome/exposure domain). Quality scores were assigned by dividing each score by the score of the highest scoring study in the group. Quality assessment of each study was carried out by two of the authors independently (BAD and JCM) and any disagreements were resolved through discussion.

2.4. Data extraction

Information about year of publication, country, study design, sample size, exposure type, ascertainment of exposure, outcome diagnostic criteria, offspring age at diagnosis, confounding variables adjusted and effect estimate were extracted.

2.5. Data synthesis

As art of our qualitative analysis, we summarised, compared, and contrasted the extracted data for all included studies. As to our quantitative analysis, we calculated the pooled RR with 95% CI using random-effects (Berkey et al., 1995) and quality-effects model (Doi and Thalib, 2008). Reported odds ratio were converted to relative risk using the Ersatz package (EpiGear International, 2016). Heterogeneity was assessed by measuring Cochran's Q and I^2 test statics (Higgins and Thompson, 2002). Subgroup analysis were performed by study design, sample size, year of publication, study subject selection, study quality and age at the diagnosis of schizophrenia as possible sources of heterogeneity between studies. Subgroup analysis by exposure status were not performed as all studies included in meta-analysis were used preeclampsia as an exposure (except the two studies which were used HDP as one diagnostic criteria). Doi plot and Egger's test were used to detect publication bias (Egger et al., 1997). Sensitivity analyses were performed by excluding each study one by one and calculating a pooled estimate for the reminder of the studies. All statistical analyses were performed using MetaXL version 5.3 and STATA13 *metan* package.

3. Results

3.1. Study characteristics

A total of 23 studies were included in the present review. Of these, 15 were good, 5 were poor and 3 were fair in quality (Table S2). The studies were predominantly conducted in Europe (n = 15). The remaining studies were conducted in North and South America (n = 4) and Australia (n = 4). More than half of the studies (n = 13) were cohort in study design. Seven studies defined preeclampsia and/or gestational hypertension using the currently accepted definition. Schizophrenia was the most frequently mentioned mental health outcome identified by 11 studies followed by childhood behavioural problems (n = 5). The outcomes of the remaining studies were psychosis (n = 3) attention deficient hyperactivity disorder (n = 2), depression (n = 2), anxiety (n = 2) and mood disorder (n = 1). Of the 23 studies included in this review, 15 studies found that HDP had a negative impact for at least one mental or behavioural disorder (Table 1).

3.2. Confounding variables

Among the 23 studies included in the analysis, 22 adjusted for maternal age and about three fourth of the studies controlled for child sex. However, other important confounding factors like maternal body mass index (BMI), marital status, family income, medication use during pregnancy, maternal alcohol/tobacco use, maternal mental illness, parental occupation, parity, birth weight and gestational age were not always accounted for (Table 2).