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REVIEW

UNTREATED DEPRESSION DURING PREGNANCY: SHORT- AND LONG-TERM EFFECTS IN OFFSPRING. A SYSTEMATIC REVIEW

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Abstract—Aim of this systematic review is to assess short- and long-lasting effects of antenatal exposure to untreated maternal depressive symptoms. Pertinent articles were identified through combined searches of Science.gov, Cochrane library, and PubMed databases (through August 2015). Forty-three, selected articles revealed that untreated gestational depression and even depressive symptoms during pregnancy may have untoward effects on the developing fetus (hyperactivity, irregular fetal heart rate), newborns (increased cortisol and norepinephrine levels, decreased dopamine levels, altered EEG patterns, reduced vagal tone, stress/depressive-like behaviors, and increased rates of premature deaths and neonatal intensive care unit admission), and children (increased salivary cortisol levels, internalizing and externalizing problems, and central adiposity). During adolescence, an independent association exists between maternal antenatal mood symptoms and a slight increase in criminal behaviors. In contrast, the relationship between gestational depression and increased risks of prematurity and low birth weight remains controversial. Given this background, when making clinical decisions, clinicians should weigh the growing evidences suggesting the detrimental and prolonged effects in offspring of untreated antenatal depression and depressive symptoms during pregnancy against the known and emerging concerns associated with *in utero* exposure to antidepressants.

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Key words: child outcomes, pregnancy, prenatal depression.

Contents

INTRODUCTION

Pregnancy may increase the risk of depressive episodes, with more than 10% of women experiencing mood symptoms during the gestational period (Marcus et al., 2003; Melville et al., 2010). Major depression is prevalent in 3.3% of pregnant women (Andersson et al., 2003). In adolescent mothers, this proportion rises up to 17% (Dietz et al., 2007; Figueiredo et al., 2007; Viguera et al., 2011).

Women with a history of either perinatal or non perinatal major depression are likely to relapse during pregnancy (Stewart, 2011). This is especially true in the case of concomitant psychosocial stressors, such as unintended pregnancy, unmarried status, poor social support, lower socioeconomic status, and episodes of domestic violence (Lancaster et al., 2010; Altemus et al., 2012). Specific medical conditions, such as pre-existing hypertension, may also contribute to the onset of antenatal depression (Katon et al., 2012).

Despite this background, the course of depression across pregnancy has been poorly investigated. Two studies highlight that many patients who experience

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Abbreviations: 5-HT, serotonin; ASDs, autism spectrum disorders; DA, dopamine; FHR, fetal heart rate; NE, norepinephrine; NGF, Nerve Growth Factor; NICUs, neonatal intensive care units; VAS, vibroacoustic stimulus.

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depressive symptoms during early pregnancy may show improvement during the second and third trimesters (Kumar and Robson, 1984; Figueiredo and Conde, 2011). Other studies report the highest levels of depressive symptoms between week 34 and 38 of gestation (O'Hara et al., 1990; Melville et al., 2010).

Clinically, prenatal depression is characterized by a relatively high frequency of somatic symptoms and suicidal thoughts (Newport et al., 2007; Yonkers et al., 2009a). The risk of suicidal behaviors is particularly high in adolescent mothers. In such women, the frequency of suicidal attempts may be as high as 20.0% (Freitas et al., 2008; Yonkers et al., 2009b; Farias et al., 2013). Indeed, suicide remains a leading cause of maternal death in the UK (Cantwell and Oates, 2011).

Maternal consequences of depression during pregnancy include the onset of medical complications, such as an increased risk of preeclampsia (Qiu et al., 2009), difficulties in performing usual activities, failure to seek prenatal care, inadequate diet, tobacco, alcohol, and other harmful substance abuse. Significant associations have also been found between antenatal depression, more severe forms of hyperemesis gravidarum, and prolonged sick leave. Moreover, planned cesarean delivery and epidural analgesia during labor are significantly more frequent in women diagnosed with antenatal depression (Andersson et al., 2004a). In recent reports, a decrease in the levels of Nerve Growth Factor (NGF) in placental tissue of untreated depressed women has been demonstrated, not only in comparison with healthy controls, but also with antidepressant-treated women (Kaihola et al., 2015). NGF signaling may increase the risk of miscarriage and preterm birth (Dhobale et al., 2013). Recent findings also suggest that maternal mental health problems are associated with impaired brain development in offspring and poor child cognitive functioning (Bjørnebekk et al., 2015).

Furthermore, prenatal depression is a specific risk factor for postpartum psychosis (Ebeid et al., 2010), the most severe form of postnatal affective disorders (Gentile, 2012, 2013).

On the other hand, antenatal antidepressant exposure has also been associated with poor pregnancy outcomes (Goldstein et al., 1997; Bérard et al., 2007; Gentile, 2010a; Pedersen et al., 2010), prenatal antidepressant exposure syndrome (Gentile, 2010a), and, recently, with an increased risk of autism spectrum disorder (ASD) (Gentile, 2015a). However, several studies reviewed elsewhere (Gentile, 2008, 2010b; Galbally et al., 2013) show reassuring findings.

Thus, the specific aim of this article is to assess systematically short- and long-lasting effects in offspring of *in utero* exposure to maternal depression or depressive symptoms, in order to help clinicians to balance the risk for the baby of intrauterine drug exposure with the effects of maternal mood disorders.

EXPERIMENTAL PROCEDURES

I conducted a combined search of Science.gov, Cochrane library, and PubMed databases (through August 2015) using the following MeSH terms: antenatal[All Fields] OR ((''prenatal care''[MeSH Terms] OR (''prenatal''[All Fields] AND ''care''[All Fields]) OR ''prenatal care''[All Fields] OR ''prenatal''[All Fields]) AND (''depressive disorder''[MeSH Terms] OR (''depressive''[All Fields] AND ''disorder''[All Fields]) OR ''depressive disorder''[All Fields] OR ''depression''[All Fields] OR ''depression'' [MeSH Terms])). The first search, limited to human studies published in English in peer-reviewed journals, provided 12,253 studies. After excluding duplicates, 1020 articles were identified. Review articles, meta-analyses, all articles which did not provide primary data, and those focused to postpartum depression were also excluded. This filtered search identified 80 articles which provided original data about the effects of antenatal maternal depression in the babies. Only articles clearly focused on untreated gestational depression were selected. For those articles which did not specify whether or not depressed mothers were taking antidepressant medications, the authors were contacted to obtain this information. Among the requests I sent, Dr. Barker kindly confirmed (through a personal communication) that his study (Barker et al., 2013) involved untreated depressed mothers. Dr. Pawbly kindly stated (through a personal communication) that only two of the mothers in her study had taken antidepressants in pregnancy. Thus, this study (Pawlby et al., 2009) was also included. Hence, forty-three articles were selected for being reviewed. Fig. 1 shows the study selection process.

RESULTS

Effects on pregnancy outcomes (shown in Table 1)

The direct relationship between maternal depression and low birth weight and prematurity found by Zax et al. (1997) confirmed the previous results of the study by Steer et al. (1992). The risk of spontaneous preterm labor was particularly high in depressed mothers with a prepregnancy body mass index (BMI) < 19 (Dayan et al., 2002) and in women with concomitant Posttraumatic Stress Disorder (Yonkers et al., 2014). The degree of severity of maternal depression, social and reproductive risk factors, obesity, and stressful events may further exacerbate this effect (Li et al., 2009). In other three studies (Chung et al., 2001; Orr et al., 2002; Engelstad et al., 2014), maternal depression was also associated with increased rates of premature delivery and an increase in the frequency of admission in neonatal intensive care units (NICUs).

However, the relationship between maternal depression and premature birth and/or low birth weight remains controversial (Andersson et al., 2004b; Suri et al., 2004, 2007; Oberlander et al., 2006; Ertel et al., 2010a; Chang et al., 2014).

Fetal effects (shown in Table 2)

Physiological effects. Allister et al. (2001) found a significant impact of maternal depression on both fetal heart rate (FHR) and fetal reactivity to external stimulus. Partic-

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