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Fetal sex and maternal postpartum depressive symptoms: biology or culture?

Raffaella Panza, Manuela Capozza, Nicola Laforgia

Neonatology and Neonatal Intensive Care Unit, 'Aldo Moro' University of Bari, Bari, Italy

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Summary. Postpartum depression (PPD) etiology is complex and multifactorial, with biological, social and psychological factors involved. PPD affects the maternal emotional health and well-being and may cause long-lasting consequences on the physical, psychological, social and economic outcomes for both the mother and her child. A prospective study by Cowell et al. points out that the male sex of the fetus is an independent risk factor for maternal PPD, due to decreased estradiol and progesterone levels and higher variations of these hormones after delivery. Conversely, a recent meta-analysis involving 119,736 women shows that the mothers of a female neonate have a higher risk of PPD (OR 1.15), mainly in Asia (OR 1.30), China (OR 1.80) and India (OR 2.61). According to current knowledge, the sex of the fetus may predispose to PPD due to cultural reasons, rather than biological ones.

Keywords. Gender medicine, fetus, postnatal, postpartum, pregnancy, sex, infant, depressive disorder.

The causal relationship between the infant's gender and postnatal maternal depression (PPD) has long been a matter of debate. However, the results obtained so far are conflicting. In this invited commentary we discuss the findings reported by Cowell et al.,[1] in light of other recent studies retrieved by searching the Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases. The search was performed on September 1, 2021 and was based on the following algorithm: postpartum depression AND infant gender. No language restrictions were applied during the literature search.

Studies carried out in developed Western countries found a limited or no association between the infant's sex and PPD,[2] while data from Eastern or developing countries showed that mothers giving birth to a female newborn do have a higher risk of PPD.[3,4] Such conflicting results refer to the effect of the infant's sex on the maternal well-being, based on biological bases, rather than cultural ones.

In the study by Cowell et al.,[1] male fetal sex is a significant factor for the development of PPD, together with individual predisposition.

Pregnancy and early postpartum are very challenging periods for women: indeed, both physical and hormonal modifications, the concern for the delivery itself and for any subsequent life changes contribute to the development of anxiety, depression and signs and symptoms of stress.[5] The etiology of postpartum depression is multifactorial, in fact biological, social and psychological factors are involved. PPD affects the mother's emotional health and well-being, and may cause long-lasting consequences on both the mother's and her baby's physical, psychological, social and economic outcomes.[6] A recent review found that maternal psychological disorders are linked to infantile functional gastrointestinal disorders (FGIDs), since FGIDs may either be able to trigger the onset of maternal psychological distress, or be themselves the result of an impaired attachment style caused by the maternal psychological status.[7]

Recent data highlighted the importance of maternal well-being throughout pregnancy and postpartum, because a healthy mother-baby dyadic interaction is more likely to ensure a safe development of the offspring. Within this perspective, gynecologists, general practitioners and pediatricians should be able to early identify mothers at risk for psychological distress and PPD, in order to timely start effective and targeted interventions.

The prospective study by Cowell et al.[1] assessed the onset of maternal depression both during pregnancy and over the 5-6 months after delivery in two different cohorts. The authors point out that the male sex of the fetus was as an independent risk factor for the onset of PPD after delivery in only one of the cohorts studied (*PRISM cohort (N = 528): odds ratio [OR] 5.24, 95% confidence interval [CI] = 1.93, 14.21); ACCESS cohort (N = 346): OR 2.05, 95% CI = 0.86, 4.93*). They concluded that PPD is more frequent in women who give birth to a male child, while there are no differences based on gender regarding the incidence of depression during pregnancy. Their findings are in keeping with the previous data on PPD.[8-10]

The excessive number of uncompleted questionnaires – as well as the socio-economic status of the group studied, where a significant prevalence of disadvantaged populations is evident – bias both the reproducibility and the soundness of their data.

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The pathogenetic role of the hormonal changes induced by gender needs to be interpreted with caution, also because there are no data on the hormonal levels in these women before pregnancy. The authors have explained their findings as due to hormone levels and fluctuations following delivery: the levels of both estradiol (a modulator of the serotonergic system) and progesterone rapidly decrease after delivery, with a greater decline in male-bearing pregnancies, suggesting that the lower estrogen levels of women carrying a male fetus could affect the neurobiological response to the estrogen decrease after delivery, with a causative role in the onset of PPD.

However, a recent meta-analysis of 29 studies involving 119,736 women led to different conclusions.[11] Mothers who give birth to a female neonate experience a significantly higher risk of developing PPD compared with the control group (OR 1.15, 95% CI: 1.01-1.31; p 0.03), particularly in the Eastern part of the world, such as Asia (OR 1.30), China (OR 1.80), or India (OR 2.61). The higher risk of developing PPD in mothers of female newborns may be related not to hormonal differences, but instead to the gender discrimination and low social status of women in some developing countries. In some countries, in fact, the gender of the infant is a matter of concern, due to several reasons, such as personal or parental preferences, socio-cultural differences and economic issues. In countries where boys are preferred to girls, pregnant women expecting a baby girl may receive less familiar and social support, with negative effects on their well-being and the consequent increase in the rate of PPD. The different finding by Cowell et al.[1] might be explained by the characteristics of the population studied, since in Black and Hispanic communities boys are often subjected to aggression and violence, which expose them to a higher risk for school dropout or imprisonment. It is therefore possible that, in these settings, the birth of a male child may cause greater psychological stress and maternal depressive symptoms.

Male and female fetuses react differently to the same intrauterine environment, suggesting biological variation at cellular and molecular level. This may be due to the fact that the placenta acts as a sexually dimorphic organ, with one sex possibly more vulnerable than the other, as a consequence of epigenetic changes, altered inactivation of the X-chromosome, or other mechanisms. Whatever the underlying mechanism, the result is that changes in maternal diet, stress, and exposure to other extrinsic factors are likely to impact differently the placenta of male versus female fetuses. Thus, the cumulative placenta responses in each sex are important variables to consider when trying to understand gender-related differences in maternal and infantile diseases.[12] A recent study showed that maternal inflammation – as indicated by C-reactive protein levels – is significantly associated with depression only in pregnancies with male fetuses.[13] Male sex is a known risk factor for adverse pregnancy and neonatal outcomes, e.g. preterm delivery, incidence of congenital malformations, altered response to drugs, neurological and respiratory diseases. The functional and structural development of the lungs occurs significantly earlier in females, especially in preterm newborns.[14] Accordingly, the greater incidence of PPD in mothers of male neonates could be also related to the "hypothesis of the male disadvantage". However, in the study by Cowell et al.[1] no association between fetal sex and neonatal adverse outcomes was found, although it is not mentioned whether the occurrence of adverse neonatal outcomes increased the risk of PPD *per se*. It is significant that the time of evaluation was around 5-6 months after delivery, thus reducing the possible impact of adverse outcomes during the neonatal period.

In conclusion, according to current knowledge, the etiological link between infant's gender and maternal PPD seems to be strongly related to cultural and socioeconomic reasons, together with biological differences. Further research on the influence of baby gender on maternal well-being is warranted, since a healthy interaction of the mother-baby dyad is crucial to ensure the safe short- and long-term mental and physical development of the offspring. It this view, infant's gender should be regarded as a further factor potentially favoring the onset of PPD in vulnerable women, and healthcare providers should take it into account when assessing mothers at risk for PPD.

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Correspondence to:
Raffaella Panza
Neonatology and Neonatal Intensive Care Unit
Department of Biomedical Science and Human Oncology
'Aldo Moro' University of Bari
Policlinico Hospital
Piazza Giulio Cesare 11
70124 Bari, Italy
email raffaella.panza@uniba.it