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Maternal obesity and impaired offspring neurodevelopment: could fetal iron deficiency be a pathogenic link?

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To the Editor:

We thank Drs. Tong and Kalish [1] for their excellent review article summarizing associations between maternal obesity and impaired offspring neurodevelopment. We respectfully propose including one additional entry to their list of potentially responsible causal mechanisms. Specifically, we propose including the association between maternal obesity and fetal biochemical iron deficiency, and between fetal iron deficiency and neurodevelopmental delay.

Pregnancy is normally characterized by increased intestinal absorption of iron to meet maternal and fetal needs. However, both maternal obesity and excessive gestational weight gain are associated with maternal and fetal iron deficiency. In 2014, Phillips et al. demonstrated that women with a prepregnancy body mass index ≥ 30 kg/m^2 or excessive gestational weight gain delivered offspring with lower serum ferritin concentrations, compared to nonobese women or those without excessive gestational weight gain [2]. Although in their study maternal diabetes was associated with diminished infant iron status, obesity in the absence of diabetes was also an independent predictor of decreased infant iron status [2]. Subsequent studies have upheld this association [3–7].

There is growing evidence that iron deficiency in the neonatal period is associated with poor neurodevelopment in infancy and childhood. A study of 278 children by Tamura

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Compliance with ethical standards

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et al. [5] demonstrated an association between umbilical cord blood ferritin levels below the 25th percentile and lower mental and psychomotor development at 5 years of age. Additional reports from preterm and term infants corroborate these findings. While these studies are primarily observational or epidemiological in nature, consistent findings of neurodevelopmental delay in iron deficient neonates born to obese women are concerning.

The mechanisms that account for the increased risk of iron deficiency in obese mothers is likely multifactorial. Aberrantly elevated levels of maternal hepcidin, a major regulator of iron absorption, appear to play a significant role in this pathophysiology [6]. In normal pregnancies, maternal hepcidin levels decrease as a means of increasing dietary iron absorption. However, pregnancies associated with obesity are characterized by increased hepcidin levels in response to a chronic inflammatory state. Recent studies in pregnant animal models suggest that maternal hepcidin levels determined embryo iron endowment. Specifically, Sangkhae et al. showed that higher levels of maternal hepcidin caused maternal iron restriction resulting in lower embryo weight, increased incidence of embryo anemia and increased embryo mortality [8]. These observations support the idea that measuring maternal hepcidin levels in obese pregnancies could identify mothers at risk of reduced iron delivery to the developing fetus.

We conclude that iron deficiency in the setting of maternal obesity or excessive gestational weight gain is an additional, potentially modifiable, mechanism for abnormal neonatal and childhood neurodevelopment. Vigilant screening and treatment of iron deficiency during pregnancies complicated by obesity, and in the offspring of obese mothers, could assist efforts to reduce neurodevelopmental delay in this group of neonates.

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