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Fetal heart rate variability mediates prenatal depression effects on neonatal neurobehavioral maturity

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ABSTRACT

This study analyzed the mediating role of fetal heart rate variability (FHR) on prenatal depression and neonatal neurobehavioral maturity. A sample of 104 pregnant women was recruited and divided into two groups according to their Edinburgh Postnatal Depression Scale (EPDS) scores (depressed/non-depressed). FHR variability in response to speech stimuli was assessed at term (between 37 and 39 weeks gestation). The neonates were then assessed on the Neonatal Behavioral Assessment Scale (NBAS) during the first 5 days after birth. The fetuses of non-depressed pregnant women showed higher HR variability than the fetuses of depressed pregnant women in response to speech stimuli, and later as neonates they performed more optimally on the NBAS (on autonomic stability and total scores). FHR variability mediated the relationship between the mother's prenatal depression and the neonateís NBAS performance. Prenatal depression effects on neonatal behavior may be partially explained by its adverse effects on fetal neurobehavioral maturity.

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Prenatal depression (assessed in any of the three different trimesters) has been associated with both delayed fetal growth and delayed neonatal growth, but in separate studies. Delayed fetal growth has included lower fetal head circumference, length and weight (e.g., Conde et al., 2010; Diego et al., 2009; Henrichs et al., 2010), and delayed neonatal growth has included preterm birth and low birth-weight (e.g., Grote et al., 2010; Neggers, Goldenberg, Cliver, & Hauth, 2006; Straub, Adams, Kim, & Silver, 2012). Prenatal depression has also been associated with both delayed fetal neurobehavioral maturity and delayed neonatal neurobehavioral maturity, but again in separate studies. Prenatal depression (during the second or the third trimester) effects on delayed fetal neurobehavioral maturity have included greater fetal activity (e.g., Dieter, Emory, Johnson, & Raynor, 2008) and higher fetal heart rate (FHR) (e.g., Allister, Lester, Carr, & Liu, 2001; Monk et al., 2011; Monk et al., 2004). A slower FHR reactivity and a delay in return to baseline after vibroacoustic stimulation (Allister et al., 2001) has also been reported in one study, while a greater FHR reactivity to a lab-induced stressor was reported in another study on depressed mothers during the third pregnancy trimester (Monk et al., 2011; Monk et al., 2004).

Delayed neonatal neurobehavioral maturity following prenatal depression during the third trimester has been evidenced by lower vagal tone and delayed HR deceleration, and by less optimal neurobehavioral and socio-emotional performance (e.g., Davis et al., 2004; Figueiredo, Pacheco, Costa, Conde, & Teixeira, 2010; Jones, 2012; Pacheco & Figueiredo, 2012; Zuckerman, Bauchner, Parker, & Cabral, 1990). For example, in a face/voice preference paradigm neonates of prenatally depressed women during the third trimester did not show a visual/auditory preference for the mother's face/voice, required more trials for habituation to the mother's face/voice, and showed a greater visual/auditory preference for the stranger's face/voice after habituation compared to neonates of prenatally non-depressed women (Figueiredo et al., 2010; Pacheco & Figueiredo, 2012). Newborns of depressed mothers during the third trimester had lower basal parasympathetic tone and responded with less vocal distress, but were delayed in physiological regulation following the cry of another infant (Jones, 2012). In another study,

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maternal anxiety and depression at the third trimester, but not at 4 months postpartum, were related to infant negative behavioral reactivity to novelty at 4 months (Davis et al., 2004).

On the Brazelton Neonatal Behavioral Assessment Scale (NBAS), neonates of prenatally depressed mothers (at the second or third pregnancy trimester) showed less optimal performance on habituation, orientation, motor, range of state, autonomic stability, and depression scales (Field et al., 2004), on habituation, regulation of state, and range of state (Pacheco & Figueiredo, 2012), and on the orienting to face/voice stimulus, alertness, cuddliness, and hand-to-mouth activity items (Hernandez-Reif, Field, Diego, & Ruddock, 2006). Male newborns of prenatally depressed mothers at the third pregnancy trimester had lower scores than controls on the NBAS motor skills and regulation of states clusters in another study (Gerardin et al., 2011).

Negative effects of prenatal depression on fetal and neonatal growth were not demonstrated in other studies (e.g., Bödecs et al., 2011; Maina et al., 2008; Suri et al., 2007; Wisner et al., 2013). In these studies, prenatal depression was assessed during all different trimesters of pregnancy – at the first trimester (e.g., Bödecs et al., 2011; Suri et al., 2007), at the second trimester (e.g., Maina et al., 2008; Suri et al., 2007; Wisner et al., 2013), or at the third trimester (e.g., Suri et al., 2007; Wisner et al., 2013). Interestingly, all these studies reporting no impact of prenatal depression on fetal or neonatal outcomes included only growth measures (for example, weight, length and head circumference), and have not assess fetal and infant neurobehavioral maturity. These inconsistent findings highlight the need for further studies covering both the fetal and the neonatal periods and focusing on fetal outcomes more vulnerable to the effect of women's prenatal depression and more related with later infant developmental dimensions. However, maternal pregnancy-psychological stress has been associated with accelerated neurobehavioral maturation in at least one study (DiPietro et al., 2010). These inconsistent findings highlight the need to discriminate between the effect of maternal normative and non-normative psychological symptoms during pregnancy on the neonate neurobehavioral maturity.

We hypothesized that prenatal depression's effect on FHR variability could be an underlying mechanism leading to the poorer developmental outcomes of infants born to prenatally depressed women. Reduced FHR variability has been associated with other detrimental conditions, including women's prenatal stress and low SES (e.g., DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996; DiPietro, Costigan, Shupe, Pressman, & Johnson, 1998). Low FHR variability has been a marker of delayed fetal neurobehavioral maturity (e.g., DiPietro, Costigan, & Voegtline, 2015), and was shown to be a predictor of delayed mental and language development in early childhood (Bornstein et al., 2002; DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). However, literature lacks on longitudinal studies that analyzed the developmental trajectories of infants born to prenatally depressed women measuring FHR variability. Additionally, differences on FHR responses to various stimuli, including speech stimuli, have been providing support for the prenatal capacity to differentiate among stimulus proprieties (e.g., DiPietro et al., 2015). However, as much as we know the effect of prenatal depression on FHR variability in response to speech stimuli was not investigated.

The present study analyzed the mediating role of FHR variability on the relationship between prenatal depression and neonatal neurobehavioral maturity. FHR variability may reflect emerging individual differences in the development of the autonomic and central nervous systems related to later neurobehavioral maturity (e.g., Appelhans & Luecken, 2006; DiPietro et al., 2007, 2015). The effect of prenatal depression on FHR variability in response to speech stimuli was also analyzed.

2. Methods

2.1. Participants

All *primigravid* pregnant women attending routine prenatal care for low-risk pregnancy were contacted in two primary health care centers in the North of Portugal. Only those who were able to read, write, and speak Portuguese were approached during the second trimester of pregnancy, and 88.6% agreed to participate. Given that less favorable socio-demographic conditions are associated with prenatal depression and less optimal neonatal development (Orr & Miller, 1995), group (depressed vs. non-depressed) equivalence on socio-demographics was ensured. A sample of 104 pregnant women was selected according to their depression scores: 52 were depressed (EPDS ≥ 9) and 52 were non-depressed (EPDS < 9). Random stratified sampling was used to ensure (depressed and non-depressed) group equivalence on maternal age ($\leq$29 vs. > 30 years), years of schooling (<9 vs. $\geq$ 9 years of schooling), professional status (employed vs. unemployed), and matrimonial status (married or cohabiting vs. single). All mothers were Caucasian, primiparous and Portuguese. Most of them were less than 30 years old, had nine or less years of schooling, were employed, and married or cohabiting. The fetuses were singleton and considered at low-risk. Most of them were born at term, were of normal weight and length, and had an Apgar score equal or higher than 7 (see Table 1).

No associations were noted between the depressed and non-depressed groups on pregnancy and delivery medical data, including gestational age, $\chi^2(1) = 0.44$, $p = 0.741$, type of delivery, $\chi^2(2) = 3.89$, $p = 0.143$, epidural anesthesia, $\chi^2(1) = 0.94$, $p = 0.332$, resuscitation at birth, $\chi^2(1) = 0.08$, $p = 1.000$. Further, the groups did not differ on neonatal measures, including one minute Apgar score, $\chi^2(1) = 0.39$, $p = 0.534$, weight, $\chi^2(1) = 0.17$, $p = 0.680$, length, $\chi^2(1) = 0.27$, $p = 0.601$), head circumference, $\chi^2(1) = 1.44$, $p = 0.231$, and gender, $\chi^2(1) = 0.04$, $p = 0.843$; see Table 1).

Some women failed to attend the scheduled fetal EKG monitoring session ($n = 19$, 18.3%; $n = 6$ depressed, $n = 13$ non-depressed, $\chi^2(1) = 2.32$, $p = 0.128$), because of premature birth ($n = 9$; $n = 3$ depressed, $n = 6$ non-depressed), failure to follow the guidelines for daily reading of the nursery rhymes between 33 and 37 weeks ($n = 3$ depressed), transfer to another medical institution ($n = 3$ depressed), or other reasons ($n = 4$; $n = 1$ depressed, $n = 3$ non-depressed). No associations were found between women who failed to attend the fetal EKG monitoring session and those who attended the fetal EKG monitoring session on maternal age, $\chi^2(1) = 0.54$, $p = 0.331$, years of schooling, $\chi^2(1) = 0.89$, $p = 0.261$, professional status, $\chi^2(1) = 0.14$, $p = 0.469$, matrimonial status, $\chi^2(1) = 1.06$, $p = 0.381$, and depression, $\chi^2(1) = 0.10$, $p = 0.487$, on pregnancy and delivery medical data, including gestational age, $\chi^2(1) = 0.40$, $p = 0.529$, type of delivery, $\chi^2(1) = 2.75$, $p = 0.098$, epidural anesthesia, $\chi^2(1) = 0.69$, $p = 0.792$, resuscitation at birth, $\chi^2(1) = 0.32$, $p = 0.573$, and on neonatal measures, including one minute Apgar score, $\chi^2(1) = 0.46$, $p = 0.497$, weight, $\chi^2(1) = 3.65$, $p = 0.060$, length, $\chi^2(1) = 3.14$, $p = 0.080$, head circumference, $\chi^2(1) = 2.29$, $p = 0.130$, and gender, $\chi^2(1) = 0.83$, $p = 0.362$.

2.2. Procedures

2.2.1. Prenatal period (3rd trimester)

This study was approved by the institution's Ethics Committee and had the voluntary participation of the pregnant women who signed an informed consent. Pregnant women were interviewed to collect socio-demographic data the EPDS (between 28 and 33 weeks gestation, $M = 32.06$, $SD = 3.34$). They were instructed to recite a short nursery rhyme out loud to their fetuses every day three times successively, between the 33rd and the 37th week ges-

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