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Relation between maternal antenatal anxiety and infants' weight depends on infants' sex: A longitudinal study from late gestation to 1-month post birth

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ABSTRACT

Objective: To test for gender-differences in the relation between mothers' antenatal anxiety and infants' body weight during gestation, at birth, and at 1-month of age.
Methods: Two hundred and twelve randomly-recruited women were divided into two groups: Controls (n = 105) and Anxious Group (n = 107) based on a standard cut-off of the Beck Anxiety Inventory. Outcome measures were Fetal Weight derived from biometrics obtained from an ultrasound scan in the 3rd trimester and infants' weight at birth and at 1-month of age, both obtained from medical records.
Results: Multivariate analyses showed main effects of Gender on infants' birth weight (P = .001) and on infants' weight at 1-month of age (P = .004), but no main effects of Anxiety Group at any time-point. Gender x Anxiety Group interactions at all three time points (Fetal weight: P = .05; Birth weight: P = .03; 1-month of age: P = .10) reflected gender differences (males > females) among infants in the anxious group, but not among controls. Distinct trends regarding same sex comparisons across groups (Control vs. Anxiety) were in line with predictions (male controls < male anxious; female controls > females anxious). Controlling for Postpartum Anxiety and Antenatal and Postpartum Depression in the models did not affect primary results.
Conclusion: Gender differences in fetal and birth weight were more substantial among infants of anxious mothers than among controls due to the seemingly accelerated growth of "anxious" males and the diminution of weight among "anxious" females.

Introduction

It is well documented that pregnancies are more likely to end badly if the baby is a boy [1,2]. As examples, in the 50-70% of pregnancies that fail, the loss of male fetuses exceeds the loss of females [3,4]. Males are 20% more likely to experience a poorer outcome in pregnancies complicated by pre-eclampsia [5] and intrauterine growth restriction (IUGR) or when the mother smokes [6], drinks alcohol, or eats unhealthily during pregnancy [see review in [7]]. More males are born preterm [1] and those that survive, have poorer outcomes [8–10]. Additionally, several studies demonstrate lower than expected live birth sex ratios (i.e., the ratio of male to female live births) following natural and manmade disasters, such as the terror attacks of September 11, 2001 [11] and periods of economic decline [12].

Mechanistic causes of males' greater vulnerability than females remain poorly established [7,13–15], though accumulating evidence suggests that the increased risk of male fetuses is somehow related to "their" prioritization of growth in the face of challenge [as in [16,17][1]], as induced by pre-eclampsia, maternal asthma, and prematurity [review in [18]]. In contrast, the stress-activated mechanisms in females seem to promote the conservation of growth and, with it, reduced size, which could make them less vulnerable to gestational challenge than males. According to recent studies, these gender differences are likely mediated, in part, by the placenta and conferred by sex-specific differences in the regulation and expression of placental genes, proteins, steroids, and structure [18,19]. For males, the strategy is minimalist, with few gene protein or functional changes instituted in the placenta, which ascertains continued growth in less than optimal maternal environments. This male response is associated with bad outcomes such as IUGR, preterm delivery, or death, especially if adversity recurs or is

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[1] Study reports preliminary findings on birth weight.

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exacerbated [1]. In contrast, the female placenta responds to an adverse maternal environment with multiple placental gene and protein changes that result in a decrease in growth without growth restriction (<10th weight percentile). These female adjustments predict resilience in the face of additional or recurrent stressors that further compromise nutrient or oxygen supply to the fetus.

The idea of gender-specific stress-effects on fetal development and health also emanates from the influential Trivers and Willard evolution-based model that aims to explain changes in sex ratio in response to environmental challenges [20]. For this, the model assumes that the reproductive success (RS) is more variable and resource-sensitive for males compared to female offspring because males in good condition will reproduce frequently and with many partners, whereas compromised males may not reproduce at all. In contrast, "condition" has less influence on the RS of female offspring because almost all reproduce in their lifetimes. These presumptions predict that mothers will invest more in males when conditions are "good" and more in females when conditions are not good; and correspondingly, that intrauterine challenges will affect males more significantly than females. Assuming maternal mechanisms for the identification and abortion of the frail and weak [20], males in the surviving cohort may be, on average, bigger than usual. At the same time, these survivors may either be vulnerable to pathology because of mothers' lack of investment or they may show improved development and high indices of good health, in keeping with their size and shown capacity to survive gestational cuts [17]. Evidence to support these predictions among humans comes from studies using a wide range of stressors [e.g., [21–25]], although findings from the literature, taken as a whole, are mixed [see review in [26]].

Rationale and Hypotheses

The possibility that processes of fetal programming differ for males and females before they are born opens avenues for understanding gender differences in health and development throughout the life span. Essential to advances in this research area is further evidence of gender-distinct responses to antenatal stress during gestation, since at this time there are few prospective studies on humans on which to base conclusions and future hypotheses [review in [27]]. On this basis, we aimed to provide new evidence of sex-specific growth in relation to antenatal challenge in the form of maternal anxiety, using estimated fetal weight obtained from an ultrasound scan during the 3rd trimester, birth weights, and weights at 1-month of age as outcome measures and maternal antenatal anxiety as the gestational challenge. Anxiety is appropriate for this because it is an emotional response to stress and is accompanied by a host of physiological responses [see review in [28]], such as increased cortisol, a product of the hypothalamic pituitary axis (HPA), that is able to cross the placenta in a limited manner to affect fetal development [29]. Less directly, antenatal anxiety may affect fetal development by altering the barrier enzyme Placental 11b-hydroxysteroid dehydrogenase type 2 (HSD11B2) 11bHSD2 leading to fetuses' increased exposure to glucocorticoids [30]. Alternatives to an HPA axis-mediated mechanism, such as restricted uterine blood flow [31] and/or immunological mechanisms [32], could affect fetuses' development and health, as well.

Based on the literature reviewed, we hypothesized that males carried by anxious mothers would weigh the same or more than males in the control group both *in utero* and at birth, whereas females carried by anxious mothers would weigh less than female controls [17]. In tandem, we expected that males and females in the anxious group would show more substantial differences in weight at each time-point than counterparts in the control group. Finally, for both males and females, we posited that relations between antenatal anxiety, gender, and infant body weight would differ across the three time-points. In this regard, we hypothesized that (a) Gender effects would become more robust with time as the infants grow and develop [33,34], and (b) Gender × Anxiety Group effects would diminish after birth, assuming that a complex array of postpartum environmental variables (e.g., duration of nursing, if at all; schedule of feeding [35]) affect infants' weight after birth, thus reducing the impact of mothers' antenatal anxiety.

In sum, our aim was to compare the (body) weight of fetuses/infants born to mothers with and without significant anxiety symptoms in order to test for gender-related responses to challenge (maternal anxiety) during gestation and at and after delivery. As such, this is the first study to examine the issue longitudinally by tracking infants' weights from gestation to after birth. Results favoring our hypotheses would constitute new evidence of the effects of antenatal anxiety on fetal and infant development and could further understanding of the differential effects that some gestational challenges have on males and females before and after they are born. Finally, the study of risks related to antenatal anxiety is relevant because of the high prevalence rate of maternal anxiety symptoms, even in low risk samples (e.g., 35.8% assessed by the Hospital Anxiety and Depression Scale [36]; 18.6% assessed by BAI, with cut-off score 10 [37]).

Methods

Participants

The final sample comprised 212 infants and their mothers. As shown in Table 1, the women were on average well-educated, mature, and married. The families' median monthly salary was approximately $3000/month, which is about average by Israeli standards [38].

Procedures

Procedures were approved by institutional review boards. Pregnant women living throughout Israel were recruited from 04/09 to 12/10 by advertisements in newspapers and posters in health clinics. The data were taken from a study on stress and maternal health, motivated by the gender differences revealed in preplanned preliminary analyses of the data. Only pertinent aspects of the study are described here.

In stage 1, women received an explanation of the study by phone, and those who agreed to participate were screened at 22–30 weeks gestation (mean (M) = 28.68 weeks; standard deviation (SD) = 2.84) for chronic illnesses and pregnancy complications that served as exclusionary criteria (see below). In the following stage, 32–36 weeks into pregnancy (M = 34.17, SD = 1.29), women were examined by ultrasound (see below) to obtain biometrics, asked about health issues that may have arisen since stage 1, and filled out anxiety and depression symptomology questionnaires. At 1–3 months postpartum (M = 9.8 weeks, SD = 2.29), the women were visited in their home, where they again filled out questionnaires on symptomology. At that time, the women provided us with a copy of the infants' well-baby records, which included infants' weight at 1-month of age. The women also provided written permission to access their medical records from the hospital where they gave birth.

Exclusion and attrition

Prior to childbirth, exclusion criteria included: (a) confirmed pregnancy with multiple fetuses, (b) smoking or drinking during pregnancy, and/or (c) documented chronic illnesses or medical complications during pregnancy (e.g., maternal hypertension, diabetes mellitus, and fetal growth restriction) that were deemed dangerous to fetus and/or mother. These exclusionary criteria were applied because they refer to conditions or behaviors that increase the risk for atypical fetal growth and early deliveries [39]. Medical decisions were made on a case-by-case basis by Dr. D. Mankuta, head of delivery and labor rooms in Hadassah Medical Center, Jerusalem, Israel.

Following acceptance into the study (N = 309), 29 mothers and their infants were excluded due to pregnancy complications reported

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