COMMENTARY

Stress during pregnancy: Fetal males pay the price

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Stress—an elusive, transient, yet transformative state we struggle to define. There are stress hormones, stressors, psychological stress, physical stress, restraint stress, social stress, the stress axis, acute stress, chronic stress, stress relievers, and unpredictable stress. Stress varies. One person's motivator is another person's slayer, challenging our ability to quantify and understand stress. The concept of allostatic load provides an integrated measure of physiological stress and lifestyle (1), while measures of the developmental origins of health and disease quantify early life events that are often antecedents to adult stress (2). Then there are nebulous psychological factors such as social support or lack thereof. Walsh et al. collated all of these to generate categories of maternal stress, with the goal of finding out which factors most impact fetal health and how (3). Not surprisingly, they find that excess stress during pregnancy is bad for the unborn child; this we knew, but what is surprising is how dramatic the impact is on boys, so dramatic in fact that we are left to infer how really bad it is since highly stressed mothers were significantly less likely to birth sons than daughters. So, what could be causing such a dramatic shift in sex ratio in stressed moms?

A latent profile analysis of 187 early pregnant women using 27 variables from questionnaires and physical assessment generated 3 nonoverlapping categories: 1) healthy, 2) psychologically stressed, and 3) physically stressed. Over 65% of the women fell into the healthy category with the remaining roughly evenly split between physically and psychologically stressed. The physically stressed women had higher blood pressure and consumed significantly more calories per day than the healthy and psychologically stressed women, while the psychologically stressed scored higher on measures of anxiety, depression, and posttraumatic stress disorder. These women also had significantly higher body mass index values compared to healthy women and trended toward higher than physically stressed women. Women experiencing either form of stress also perceived it, self-reporting higher levels of stress than women deemed healthy.

In the overall sample, the ratio of newborn boys to girls was 1:1, as found in the general population, but when parsed out by group the percentage giving birth to boys was 56% for healthy women, 40% for psychologically stressed women, and a mere 31% for physically stressed moms (Fig. 1). The stressed moms represent a much smaller proportion of the sample surveyed here. However, if we think of this sample as representative of a population, of the 88 boys born, 69 came from healthy moms, while 12 were from psychologically stressed moms and only 8 from those who were physically stressed. Whether or not this matters depends on whether there is an impact on ultimate reproductive fitness of birthing sons versus daughters.

The question of how sex ratio is determined has long interested students of reproductive fitness. Most animals give birth to more than one offspring at a time, and in some mammals litter sizes can be upward of a dozen, providing ample opportunity for manipulating the sex ratio even within a single pregnancy. There are 2 mechanisms for altering the number of offspring of a particular sex. The first is fertilization, which sets the primary sex ratio, followed by delivery, which sets the secondary sex ratio. Marked shifts away from a 1:1 ratio can be achieved in only one of 2 ways. Either there is a change in the probability of fertilization of the egg by Y chromosome bearing versus X chromosome bearing sperm, i.e., the primary sex ratio, or there is exaggerated demise of embryos or fetuses of one sex, i.e., the secondary sex ratio. Both are plausible, although evidence in favor of the latter is more abundant.

In animals in which mating systems are biased such that a few winning males impregnate the majority of females, the sex ratio of offspring is shifted in favor of males when environmental conditions are good but swings the other direction when resources are limited. The thinking is that, when there are ample resources, the optimal strategy for reproductive success is to have healthy sons that will compete well against other males and thereby garner all of the females and have many progeny. However, if times

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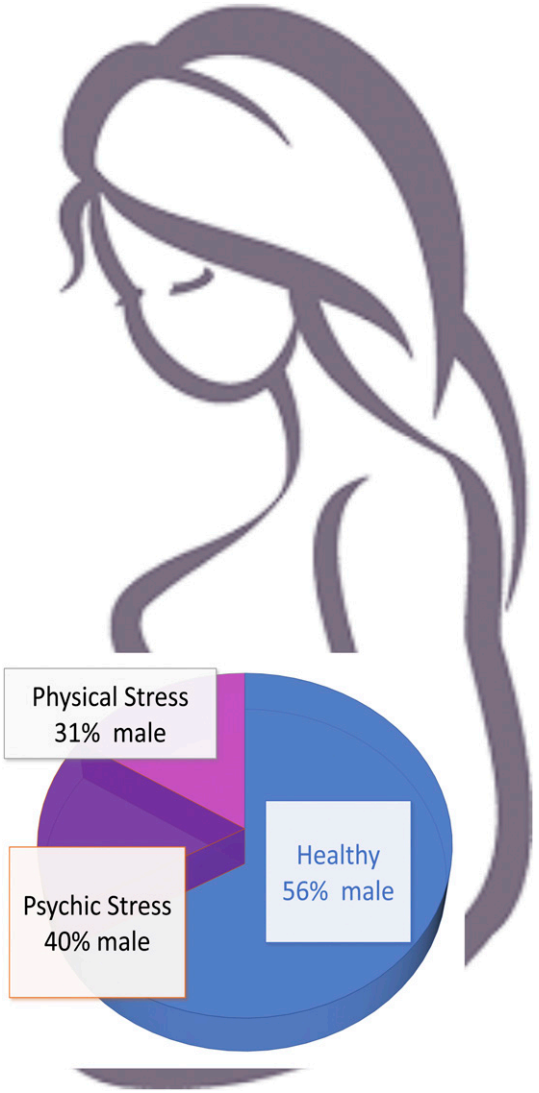

Fig. 1. Stress during pregnancy reduces male births. Sorting of pregnant women into phenotypes associated with stress found 3 categories: 1) healthy, 2) physically stressed, and 3) psychologically stressed. The majority of the women in this study were healthy, and they were significantly more likely to have sons. Fewer women were stressed, but they were much less likely to birth boys. Social support was identified as the most important variable contributing to maternal phenotype, revealing the previously unknown importance of this nebulous variable.

are tough, your sons might not be so strong and could lose out on mating all together, so it is best to count on your daughters succeeding at reproducing, albeit at a lower rate. This theory is known as the Trivers–Willard hypothesis (4). It has been tested many times and generally holds up (5).

In humans, our mating system is closer to monogamy, but this does not mean that all men have equal probability of successful reproduction. Variables such as height, education, and income all influence the probability of marriage (6), and analysis of thousands of lonely hearts advertisements reveals the value that high-status women place on financial resources and occupation in potential mates (7). If we consider the women in the study by Walsh et al. as a population, the Trivers–Willard hypothesis holds some merit in that their ultimate reproductive fitness is compromised even more severely than it first appears. Women in poor health, be it psychological or physical, exhibit evidence of compromised pregnancies, which may harm the health of their offspring. In the case of sons, this harm may manifest as loss during gestation. If they do survive, it is often with a cost that may be sufficient to impair their later reproductive success by reducing their attractiveness to high-quality mates. This could include reduced stature, intellectual disability, or lower socioeconomic status, for example. For daughters, the cost may be less as they are less compromised physically and enjoy a wider range of options from which to select mates. Young men are also at considerably higher risk of dying due to violence or accidents, at least in the United States where this study was conducted. According to the 2006 Centers for Disease Control and Prevention's Center for Health Statistics, young men are 3 times more likely to die in an accident and 4 to 5 times more likely to die due to violence than women of the same age. Given that these deaths occur during prime reproductive years, the cost in fitness is substantial. Put another way, pregnant women experiencing poor conditions, due to physical or psychological stress, risk having few or no grandchildren if they give birth to sons.

The open question, however, is, how is the sex ratio altered in response to stress? Contrary to long-standing popular belief, in humans there is not a bias toward males at conception. Instead, males and females are conceived at equal rates, but then differential waves of embryonic and fetal death result in a slightly skewed male-biased ratio at birth (8). Nonetheless, boys are generally more vulnerable to a wide range of neurodevelopmental disorders, both neurological, such as dyslexia, stuttering, Tourette's, intellectual disability, and psychiatric, including autism spectrum disorder, attention and hyperactivity disorders, and early-onset schizophrenia (9). In the case of autism spectrum disorders, one of the most highly gender-biased in prevalence, there is continuing debate regarding the relative contribution of male vulnerability versus female resilience (10, 11). Nonetheless, convergent evidence supports the view that a stressed in utero environment is ultimately more stressful for male fetuses and they more easily succumb. Inflammation during pregnancy, from the flu, autoimmune disorders, or other sources, is associated with adverse outcomes for offspring (12), and many of these outcomes are male biased, suggesting that males are more negatively impacted by in utero inflammation (13).

Given this, one would predict that the dominant latent variable that Walsh et al. would identify as differentiating the groups would be physiological indicators such as stress hormone levels, blood sugar, body weight, and even markers of inflammation. Here is where the biggest surprise comes: while these measures did vary, they were not the most important predictors. Instead, it was the amount of social support each woman felt she was the beneficiary of, and 3 aspects of social support in particular: 1) people to talk to, 2) people to spend time with, and 3) people to rely on for help. The women with the least amount of social support were those in the psychologically stressed category, but the physically stressed women also reported less social support than the healthy women. This is good news/bad news. The bad news is that a lack of social support exerts a potent biological influence on health of the mother that has lasting and impactful effects transmitted to the next generation. We do not understand at a mechanistic level how this happens. However, the good news is, as Walsh et al. state, "From the perspective of solution-oriented research. . .social support is a modifiable target for clinical engagement that could benefit women and their future children." Let's start today.

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