Journal of Psychosomatic Research 75 (2013) 327–335

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Is there a viability–vulnerability tradeoff? Sex differences in fetal programming☆

Curt A Sandman [a,*], Laura M Glynn [a,b], Elysia Poggi Davis [a,c]

[a] Women and Children's Health and Well-being Project, Department of Psychiatry & Human Behavior, University of California, Irvine, United States
[b] Crean School of Health and Life Sciences, Chapman University, United States
[c] Neurodevelopmental Research Program, Department of Psychology, Denver University, United States

ARTICLE INFO

Article history:
Received 23 March 2013
Received in revised form 30 June 2013
Accepted 14 July 2013

Keywords:
Child development
Fetal behavior
Fetal programming
HPA axis
Prenatal stress
Sex differences

ABSTRACT

Objective: In this paper we evaluate the evidence for sex differences in fetal programming within the context of the proposed viability–vulnerability tradeoff.
Methods: We briefly review the literature on the factors contributing to primary and secondary sex ratios. Sex differences in fetal programming are assessed by summarizing previously published sex difference findings from our group (6 studies) and also new analyses of previously published findings in which sex differences were not reported (6 studies).
Results: The review and reanalysis of studies from our group are consistent with the overwhelming evidence of increasing risk for viability among males exposed to environmental adversity early in life. New evidence reported here support the argument that females, despite their adaptive agility, also are influenced by exposure to early adversity. Two primary conclusions are (i) female fetal exposure to psychobiological stress selectively influences fear/anxiety, and (ii) the effects of female fetal exposure to stress persist into preadolescence. These persisting effects are reflected in increased levels of anxiety, impaired executive function and neurological markers associated with these behaviors.
Conclusions: A tacit assumption is that females, with their adaptive flexibility early in gestation, escape the consequences of early life exposure to adversity. We argue that the consequences of male exposure to early adversity threaten their viability, effectively culling the weak and the frail and creating a surviving cohort of the fittest. Females adjust to early adversity with a variety of strategies, but their escape from the risk of early mortality and morbidity has a price of increased vulnerability expressed later in development.

Introduction

Environmental pressures on population sex ratios, even prior to conception, dictate that a male or female conceptus will achieve reproductive success. These pressures are reflected in unique patterns of developmental "programming" with consequences that confer risk for morbidity and mortality early in life and vulnerability to disease later in life. It is unknown if there is a "tradeoff" between viability early in life and vulnerability later and if there is, whether it is related to sex differences in patterns of fetal programming. The purpose of this paper is to evaluate the evidence in support of a sex-dependent viability–vulnerability tradeoff established in very early experience.

Sex ratio theory

An Evolutionary Stable Strategy (ESS) is a concept derived from Game Theory applied to understand population sex ratios [1]. Among the assumptions of ESS are two that are of particular importance; first, adoption of the strategy by all members of the population ensures optimal outcomes and second, invading mutant strategies (for instance by a minority of the population) will not survive. If the mutant strategy becomes more effective over time, more members of the population will adopt it, supplanting the original strategy. The ideal ESS to maintain an optimal balance of different characteristics in the population is a 1:1 ratio of males to females. This is supported by the fact that there is no sex ratio bias in X to Y sperm [2]. Historical records and current studies [3,4], however consistently confirm that more males than females are conceived (primary sex ratio) and born (secondary sex ratio). This suggests that under certain conditions, natural selection favors a deviation from the 50/50 ESS sex ratio at conception and birth [5]. Proposed explanations for a male biased ratio are varied and include mechanisms related to population pressures [6], heritable traits [7],

☆ Research conducted at Department of Psychiatry and Human Behavior, University of California, Irvine.

* Corresponding author at: Early Human and Lifespan Development Program, One University Drive, Orange, CA 92866, United States. Tel.: +1 714 940 1922; fax: +1 714 940 1939.
E-mail address: casandma@uci.edu (C.A. Sandman).

0022-3999/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychores.2013.07.009

genetic programming [8], parental hormone levels [9] and fetal responses (programming) to adversity [9]. But most relevant for the aim of this paper is clear evidence that an objective and crucial birth outcome, secondary sex ratio, is associated with, and perhaps programmed by, preconceptional and maternal/fetal exposures to environmental events.

Fisher [10] argued that sex ratios were determined by parental expenditures or investments (e.g., nurturance) in their offspring and also that this investment should be equal for both sexes. Fisher, however was aware, even in the 1930s (and perhaps Darwin before him [9]), of the sexual disparity in favor of male births. Most explanations for the sex ratio disparity included the contribution of parental investment (PI) in the fetus and infant. Under hostile environmental conditions differential mortality and "programming" of morbidity and developmental impairments are predicted to occur early in pregnancy so that a new reproductive cycle can be initiated and that PI can be directed to another pregnancy [5]. Studies consistently show that more males than females are born preterm [3], that males have poorer neonatal and infant health outcomes [11], have higher risk for motor and cognitive outcomes, are less likely to survive in intensive care, are more likely to have a placental inflammation, decidual lymphoplasmacytic cell infiltration, velamentous umbilical cord insertion [12,13] and show delayed lung maturation compared to females equivalent to one week of gestational age despite their greater size [14]. Under adverse or hostile conditions, males are less likely to survive and more likely to suffer from profound developmental impairments reducing the number of reproductively viable males in the population.

The influential Trivers–Willard (TW) [15] sex ratio hypothesis assumes that the probability of reproductive success of male offspring is more variable and resource-sensitive than female offspring. PI in sons of "good quality" yields greater reproductive success (RS) than sons of "poor quality" because their greater size and strength allows them to out-compete their male rivals and dominate available reproductive opportunities [15,16]. The TW theory further assumes that PI has less influence on the RS of female offspring because reproductive cycles are much slower in women than in men and because almost all females do reproduce some offspring.

Consistent with the majority of findings, the TW model predicts that any environmental stress will always affect males more severely than females in very early life [5] and that these effects have both short and long-term consequences. In a recent report [17], strong evidence was presented for the immediate influence of environmental resources on sex ratios and specifically for a reduction in male births. A three-year famine (1958–1961) in China resulted in as many as 45,000,000 deaths. During this period, there was a significant reduction in male births that did not return to normal proportions (higher ratio of male births) until two years after the famine ended. Conversely, in a developed nation such as the United States, historically birth ratios have favored males, roughly 51.5 to 48.5% resulting in 5.8 million "excess" males since 1940 [4]. The TW theory argues that successful evolution and survival in the gene pool are achieved when males are conceived during favorable environmental conditions but that females are the best investment when the resources are poor.

Sexually dimorphic patterns in response to hostile conditions or more specifically stress may be programmed very early in gestation. The female placenta appears to be more responsive to changes in stress signals such as maternal glucocorticoid concentration than the male placenta resulting in different patterns of growth [18]. Male fetuses invest resources in growth, largely independent of maternal conditions, and this strategy may be a contributor to their larger size at birth. A consequence of the investment in growth is a relative poverty of resources to respond to subsequent exposures to stress and adversity. Because the male fetus has not conserved its resources and does not adapt to maternal signals, it has limited ability to adjust to adversity and is at greater risk for subsequent morbidity and mortality. In contrast, the female fetus does not invest as heavily in growth but conserves resources and adjusts to maternal conditions in multiple ways (gene and protein changes), a strategy that is relied on heavily in the context of a hostile or stressful environment. Because of this developmental/evolutionary strategy, the female fetus that has conserved its energy needs has increased probability of survival when and if exposed to stress that reduces nutrients and resources later in gestation.

The evidence supports the argument that prenatal exposure to adversity exerts unequal influences on male and female development beginning even before conception. For example, sex differences have been observed in mammalian animal models during meiosis. Meiosis (not to be confused with miosis) is a special process that creates gametes, the sperm and egg cells, by the combination of two haploid sex cells. The cells divide, without DNA replication resulting in halving of the chromosomal complement. This process is responsible for genetic diversity because of the sharing of genetic information between homologous chromosomes. It is estimated that as many of 25% of human fetuses have the "wrong" number of chromosomes. When faced with adversity (e.g. engineered mutations) male meiosis is interrupted resulting in infertility [8]. However in females, a similar adversity does not interrupt meiosis. The consequences are that only 3–4% of sperm are chromosomally abnormal but 20% of oocytes are anomalous [8]. The early mortality of the male sperm during adverse circumstances reduces male contributions to aneuploidy. The robust and persistent meiosis of oocytes is the major contributor to deviant chromosomal patterns.

The strong consensus is that consequences of exposure to adversity are exhibited in males very early in the life cycle, even as early as conception and meiosis. The tacit consensus is that females do not exhibit developmental consequences, and that they are largely and relatively immune from exposure to early adversity. However it is possible that exposure to early adversity influences both male and female conceptuses but that the developmental strategies for response are radically different. There is no question that males exposed to early adversity suffer a much higher risk than females of fetal and infant morbidity and mortality. Because they have been eliminated (high mortality) or weakened (morbidity), the surviving males constitute a relatively homogenous, less variable cohort. In contrast, females adjust to early adversity with a variety of less extreme individually determined strategies and have escaped the severe consequences of high risk for mortality and morbidity. This results in a far greater and more variable behavioral and biological repertoire among females increasing the probability that there will be associations between their developmental trajectories and early life exposures. In this paper we evaluate the evidence for sex differences in fetal programming within the context of the proposed viability–vulnerability tradeoff by review and reanalysis of data from our existing studies (see Table 1).

General methods

We have developed a longitudinal, prospective protocol to advance the understanding of prenatal influences on birth outcome and infant and child development. Our protocol includes maternal psychosocial and biological stress measures collected at five gestational intervals beginning between 14 and 16 weeks. Maternal/fetal dyads are assessed at 15, 20, 25, 31 and 36 weeks of gestation. At ~25, ~31 and ~36 gestational weeks, fetal neurodevelopment is evaluated with measures of startle and habituation. Infant assessments begin 24 h post delivery with the collection of HPA hormones and behavioral responses to the painful stress of the heel-stick procedure and measures of neonatal neuromuscular maturity. Infant cognitive, neuromotor development, stress and emotional regulation are evaluated at 3, 6, 12 and 24 months of age. Maternal psychosocial and demographic information is collected in parallel with infant assessments. Child neurodevelopment is assessed between 6–9 years of age with cognitive tests, measures of adjustment and brain imaging. Multiple assessments during gestation and during follow-up are essential because there are critical periods both for the effects of programming on the nervous system and for the expression of subsequent behaviors. All of our studies include normative samples