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Hypothesis: High levels of maternal adrenal androgens are a major cause of miscarriage and other forms of reproductive suboptimality

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HIGHLIGHTS

- Maternal stress causes the secretion of high levels of adrenal androgens.
- Epidemiological and experimental evidence relate androgens to reproductive failure.
- Most forms of reproductive suboptimality show a male bias.
- High maternal androgens at the time of conception are associated with male births.
- It is suggested that high androgens cause both the sex bias and the reproductive failure.

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ABSTRACT

A cause is proposed for several forms of reproductive suboptimality (viz foetal loss, preterm birth and low birth weight). The point is illustrated here in the case of miscarriage. I suggest that all these forms of reproductive suboptimality are partially caused by high levels of stress-related maternal adrenal androgens. The argument is supported by both experimental and epidemiological data.

1. Introduction

Consider a pregnant woman whose environmental circumstances have deteriorated sufficiently to lower the chance that her fetus will develop into an individual capable of optimal reproduction. The duration of her reproductive life is limited, so there would be potential reproductive advantage if she were to miscarry. Accordingly a process is hypothesized here, the end product of which is usually miscarriage (or occasionally stillbirth or neonatal death). However the process is *ex hypothesi* not fully efficient, and fails to avert some births that are preterm or low-birth-weight (both precursors of suboptimal reproduction). The mechanism involves stress-related maternal adrenal androgens.

Here I shall consider several forms of reproductive suboptimality viz miscarriage, stillbirth, preterm birth, low birth weight, growth retardation, and infant mortality. A recent review concluded that one cause of all these is maternal stress (Witt et al., 2014). For instance, maternal stress has been reportedly significantly associated with miscarriage (O'Hare and Creed, 1995; Wainstock et al., 2013); stillbirth (Laszlo et al., 2013); low birth weight (Newton and Hunt, 1984; Steer et al., 1992; Wainstock et al., 2014); preterm birth (Steer et al., 1992; Wainstock et al., 2014); intrauterine growth retardation (Nordentoft et al., 1996) and infant mortality (Class et al., 2013). It will be suggested here that a proximate cause of all these reproductive outcomes is high maternal adrenal androgen levels caused by the stress. This will be illustrated here in the case of miscarrige.

1.1. Catalano's findings on miscarriage

Women vary widely in their susceptibility to miscarriage. It is known that some miscarriages have genetic causes *e.g.* those with chromosomal anomalies. Other miscarriages are caused by malformations. But the causes of most miscarriages are not established (Saravelos and Li, 2012). However, in recent years, Catalano and his co-authors have used time-series analysis to reveal the effect of various sorts of stressful public events or processes on pregnant

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women. The stressors included the labour market (Catalano et al., 2012); terrorist activity (Catalano et al., 2005) and an earthquake (Catalano et al., 2013). The overall conclusion drawn by these workers is that maternal stress increases the probability that pregnant women will miscarry, and that the miscarriages will preferentially be of fetuses that are male and frail (Catalano and Bruckner, 2006). This phenomenon (here called the 'Catalano Phenomenon') has been construed as having evolutionary significance, because it is compatible with the influential hypothesis of Trivers and Willard (1973) (TW).

It is now worth briefly outlining TW because it will be invoked in support of later argument here. These authors noted that in many species, males have a greater variance of reproductive success than females. They realised that under specified conditions, this phenomenon could form the basis of reproductive advantage and so might have occasioned evolutionary adjustment to the sex ratio. Accordingly they hypothesized that women in good 'condition' would be more likely to bear sons, and that women in poor 'condition' would be more likely to bear daughters. The authors only hinted at the meaning of the word 'condition'. Since its publication, the hypothesis has been tested many times, and in most cases, it successfully withstood the testing. However, in a minority of studies, the results were significantly in the direction opposite to that predicted. The hypothesis was clearly in need of adjustment, and in James (2013), relying on my own hormonal hypothesis (later described), I offered an adjustment in the form of a more specific definition of 'condition'. Interested readers will find a fuller account in that paper. The fact that the two hypotheses cohere so readily must confer additional credibility on each.

The present note hypothesizes that a proximate cause of miscarriage (and of other forms of suboptimal reproduction) is high levels of stress-related maternal adrenal androgens. This will here be called the Target Hypothesis. If it were correct, then an additional large proportion of pregnant women subject to private stressors (bereavement and other life events, unsatisfactory domestic circumstances including marital distress, bad housing, etc.) will also be vulnerable to miscarriages.

2. Background: Reproductive endocrinology

2.1. The effects of high levels of pregnancy androgens

High pregnancy androgens in women are reportedly associated with fetal growth restriction *in utero* (Carlsen et al., 2006) and with miscarriage (Cocksedge et al., 2008). The latter authors reported that in their substantial data-set (571 women who each had had 3^+ miscarriages), the free androgen index was a more powerful predictor of a subsequent miscarriage than advanced maternal age, or than the number of prior miscarriages. Moreover, the experimental administration of testosterone to pregnant ewes reportedly had comparable deleterious effects on pregnancy (Manikkam et al., 2004; Steckler et al., 2005). The use of the sheep is now a standard model for human pregnancy (Cox et al., 2012). So this experimental work provides strong evidence that high androgen levels are, at least partially, a cause, rather than a consequence, of the reproductive suboptimality. In other words, this experimental work (of Manikkam et al., 2004; Steckler et al., 2005) adds crucial evidence on causal direction to what otherwise would be a hypothesis based merely on correlational data.

2.2. The causes of high levels of androgens in women

The major sources of androgens are the ovaries in healthy women, and the adrenals in stressed women. Bearing in mind the evidence from the risk factors considered later, it will be assumed here that the usual source of the hypothesized additional testosterone (T) in reproductive suboptimality is the adrenals. These react to stress of many sorts *e.g.* infectious disease, psychotic disorder, surgical trauma and strenuous exercise (Kemper, 1990). For instance, high androgen levels have been reported in women who are chronically stressed (Powell et al., 2002), chronically fatigued (Goldberg, 1995), chronically depressed (Baischer et al., 1995) or exposed to fearful stimuli during pregnancy (Roos et al., 2011). Lastly, in regard to the phenomenon of androgen-related sub-optimal reproduction, there is a positive feed-back in the sense that previous prenatal loss reportedly significantly predicts subsequent perinatal depression and anxiety (Blackmore et al., 2011). And both of these may be expected in turn to occasion future miscarriages. So the condition of women with recurrent adverse reproductive outcome may be expected to worsen if left untreated.

In the foregoing sections, evidence has been adduced for three propositions, viz:

1. Stress is a cause of miscarriage in pregnant women.
2. High maternal androgens are associated with miscarriage.
3. Stress in women causes the excretion of high levels of adrenal androgens.

The present challenge is to devise a causal nexus from these propositions. Accordingly, I suggest the Target Hypothesis viz that the stress causes the androgens, and that the androgens cause the miscarriages. At any rate, the proposition that maternal adrenal androgens cause miscarriage would be strengthened by the demonstration that the reduction of stress (and hence of the androgens) is associated with a diminution of miscarriage rate. Evidence will now be given for such a phenomenon.

3. Psychological factors and miscarriage

There is statistical evidence that psychological treatment by a psychiatrist (James, 1963) or humane supportive care (Clifford et al., 1997) reduce the probability of further miscarriages to women who have had previous miscarriages. The latter authors described the effects of attendance at a dedicated early pregnancy clinic on 160 women with recurrent first trimester miscarriage, contrasted with 41 untreated controls with recurrent miscarriage. Miscarriages occurred to 42 (26%) of the treated group and 21 (51%) of the controls (chi-squared = 8.3, $p < 0.005$). Thus one may infer that psychotherapeutic care alleviates maternal anxiety and depression, thus lowering maternal androgens to a level where pregnancy is less jeopardised.

4. My hormonal hypothesis

The foregoing arguments are also consistent with my hormonal hypothesis on sex ratio at birth. Notes will now be given on this because this hypothesis offers explanations for previously unexplained data (to be cited) and thus adds weight to the current reasoning.

I have given grounds for hypothesizing that the sexes of mammalian zygotes at the time they are formed (and hence the sexes of subsequent births) are partially controlled by the hormone levels of both parents around the time of conception. *Ex hypothesi*, high levels of androgens in either parent are associated with the formation of male zygotes and hence with subsequent male births (James, 1996, 2004, 2008a, 2008b, 2010). As noted above, the credibility of this hypothesis has recently been boosted by the