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Fetal sex and preterm birth☆

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ABSTRACT

Rates of preterm birth vary between different populations and ethnic groups. Epidemiologic studies have suggested that the incidence of preterm birth is also higher in pregnancies carrying a male fetus; the male:female difference is greater in earlier preterm pregnancy. Placental or chorion trophoblast cells from pregnancies with a male fetus produced more pro-inflammatory TNFα in response to LPS stimulation and less anti-inflammatory IL-10 and granulocyte colony stimulating factor (G-CSF) than cells from pregnancies with a female fetus, more prostaglandin synthase (PTGS-2) and less prostaglandin dehydrogenase (PGDH). These results suggest that in the presence of a male fetus the trophoblast has the potential to generate a more pro-inflammatory environment. Maturation of the fetal hypothalamic–pituitary–adrenal axis and expression of placental genes, particularly 11β hydroxysteroid dehydrogenase-2 are also expressed in a sex dependent manner, consistent with the sex-biasing influences on gene networks. Sex differences in these activities may affect clinical outcomes of pre- and post-dates pregnancies and fetal/newborn wellbeing. These factors need consideration in studies of placental function and in the development of personalized strategies for the diagnosis of preterm labor and postnatal health.

1. Introduction

Preterm labor is a major problem in obstetric practice. Much of the difficulty in treating this condition arises from our inability to diagnose preterm labor with certainty. The purpose of this article is to review the evidence that the sex of the fetus may need to be considered amongst the known compounding risk factors for threat of preterm labor. We will suggest that fetal genotype influences placental enzyme activities and fetal pituitary adrenal function in a manner that might impact mechanisms leading to the onset of preterm labor.

It is clear that preterm labor is a global problem. The "GAPPS-analysis" shows that this condition affects 13 million babies world-wide each year; that one million babies, many born preterm, die within the first month of life and that death from preterm birth during the first year of life is greater than that ascribed to malaria, HIV/AIDS or tuberculosis [1]. Resolution of these issues is an objective of the United Nations Millennium Goal 13, to reduce mortality of children under 5 by 2/3 by 2015. Despite these lofty objectives, the return on investment for research funding into preterm labor has had only modest success. In the United States, the preterm labor rate between 1998 and 2008 has remained at about 12%, and has even risen slightly over that time. Similar information is available for many other jurisdictions in Western Societies. However, Newnham et al. [2] have shown recently that in Jiangsu province, China, the preterm labor rates are much lower, 2.6% and 2.9% for urban and rural communities respectively. Interestingly, women of Chinese descent, but non-resident in Hong Kong also have low preterm labor rates. In Western Australia, Chinese women who require an interpreter have lower preterm labor rates, 2.5%, than those women of Chinese descent who did not require an interpreter (4.9%). These data imply that the Chinese genotype and/or lifestyle have an important impact on preterm labor rates, which can be modified or lost with integration into western society. Similarly perhaps,

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black migrant women were at lower risk of delivering preterm birth babies than black women born in the USA [3]. At present, the mechanism of this effect is unknown and any influence of the sex of the fetus on the incidence of preterm labor in these populations remains unexplored.

Preterm labor is a complex condition, clearly recognized as a syndrome, with multiple, potentially interacting, causes. Goldenberg [4] has suggested that as much as 40% of preterm labor may be idiopathic, 25% associated with preterm premature rupture of the membranes (PPROM), and the remainder (up to 45–50%) associated with maternal and/or fetal infection. These proportions vary at different gestational ages. In early pregnancy, major factors include immune rejection, infection and inflammation and cervical insufficiency; in later gestation, major factors may include subplacental hemorrhage and bleeding, uterine distention, as in multiple pregnancy, and precocious activation of the maternal or fetal stress axes, accompanied by aberrant expression of the placental 11β hydroxysteroid dehydrogenase (11βHSD-2) enzyme [5]. Maternal risk factors include, body mass index > 25, previous reproductive history, previous abortion, cesarean section, and previous preterm birth and employment in heavy work [6]. Randomized clinical trials (RCT's) designed to test the efficacy of different treatments for preterm labor often overlook this complex and varied etiology, and treat the condition as a single entity, with the result that a single bullet approach to treatment is generally found to be unsuccessful. Future developments in the diagnosis and management of preterm labor are likely to include development of individualized, personalized medicine strategies, with a broad set of biomarkers. We suggest that the sex of the fetus will need to be included in the list of modifying factors that might affect predisposition to preterm birth.

2. Early evidence for a role of fetal sex in the etiology of preterm labor

Zeitlin et al. [7] used random effects meta-analysis of four original data sets and 20 populations extracted from published references, to suggest that there were a higher proportion of male babies delivered preterm overall. Consistently, using data sets from different countries, established over the past 50 years, there were more males among very preterm and preterm births than among term births, and the proportion of male preterm births was higher earlier in gestation and declined with advancing pregnancy. The data for in vitro fertilization (IVF) births conformed to the same pattern, indicating that the finding was not due to differences in the timing of conception. The same trend was reported by Vatten and Skjaerven [8] using data from almost 1.7 million births in the Medical Birth Registry of Norway between 1967 and 1998. The male:female preterm birth ratio was higher (2.48) in the earliest category of gestational age (from 16 weeks), and declined to 1.17 at weeks 37–39. In preeclampsia, the ratio was reversed, an observation substantiated elsewhere (9.10). Brettell et al. [10] and Di Renzo et al. [11] both reported that the male:female preterm birth ratio was higher in very preterm deliveries than later in pregnancy, and was associated with poorer outcome. These findings have been substantiated by others [12,13] but the underlying mechanisms have remained unclear, with suggestions ranging from sex differences in implantation to differences in fetal weight and size. We shall suggest later that pregnancy with a male fetus may favor a more pro-inflammatory intra-uterine environment, linking with a higher incidence of infection/inflammation driven preterm birth earlier in pregnancy. Zeitlin [7] also reported on two populations of black children, born in Cleveland, Ohio, in which the higher ratio of male:female babies at preterm birth was not observed. She commented that understanding the nature of the relationship between fetal sex and preterm birth might be helpful in understanding the etiology of preterm labor.

The EPIPAGE trial of more than 2600 pregnancies in France, published in 2004, confirmed that the incidence of preterm or very preterm birth after spontaneous labor was higher with a male fetus than with a female fetus, but this risk was less in indicated preterm birth, both with or without growth restriction [9]. Later reports also showed the rates of preterm birth were higher in male–male twin pregnancy, than in female–female twin pregnancies or in mixed male–female twin gestations [14]. The risk was higher for twin infants born to black parents compared to mixed race parents [15]. In a retrospective study of 2704 dichorionic twin pregnancies, the risk of preterm delivery was higher in male–male pregnancies than in female–female or mixed twins, which were intermediate. These male neonates had lower birth weight and lower growth rates [16]. One study has reported shorter gestation lengths in mixed twin compared to same sex twin pregnancies, after IVF, although the number of pregnancies was smaller than in most other reports [17].

The mechanism underlying the relationship between the male:female sex ratio with incidence of preterm birth is not understood. Sex differences in responsiveness of various cell types have been reported [18]. Arnold and Lusis [19] have recently described a framework for understanding the so-called sexome, defined as "the sum of all sex specific and sex modulatory interactions between gene products in a network" [19]. Cellular activity, in terms of expression of different gene products in a network reflects the relative influences of sex-biasing genes. Male-biasing factors include the influences of a single X-chromosome, the presence of the Y-chromosome and secretion of testicular steroids and proteins. Female-biasing influences include the two X-chromosomes, ovarian hormones and potential placental endocrine gene products. Importantly, sex-biasing factors can exert either synergistic or antagonistic influences on other genes within the network. In turn, these may interact with environmental cues, such that the final response may be difficult to predict.

More recent work with two large Scandinavian cohorts has described the remarkable observation that exposure to a male fetus in a previous pregnancy increases the risk of preterm birth in a subsequent pregnancy [20]. The mechanism of this effect is not clear, but it is independent of maternal age, or sex of the second infant. This relationship might suggest an acquired immune response from the first pregnancy that results in altered expression of the intra-uterine gene pool in subsequent gestations. It is possible that there is also an association with microchimeras in the mother [21], resulting from passage of fetal stem cells, across the placenta to maternal sites, including the maternal brain and decidua. One might speculate that in decidua, recognition of the fetal antigen in the same or subsequent pregnancy can provoke a later immunological response.

In summary, a large body of epidemiological study supports the view that there is a higher risk of preterm delivery for male infants in both singleton and twin pregnancy, and that this risk is higher early in gestation and progressively declines towards full term.

3. Infection, probiotics and fetal sex

Infection and/or inflammation are major causes of early preterm labor. Goldenberg, Romero and others have described the high incidence of infection with early preterm labor [4,22]. They have suggested the different routes by which intra-uterine infection may arise; an ascending route through the vagina and cervix, across the placenta, along the fallopian tubes and across the uterine wall, at the time of amniocentesis. The locus of infection may lie within the cord as a funisitis, at the chorio-decidual interface or as a chorioamnionitis. Our own in vitro studies have been conducted using