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Promoting a different care for pregnant women according to the fetal sex: where do we stand?

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Summary. Fetal sex represents a fundamental contributor to pregnancy outcomes and maternal health, both in the short and long term. Women carrying a male fetus appear to be at increased risk for cesarean section, preterm labor and the development of gestational diabetes mellitus (GDM). On the other hand, a female fetus negatively affects the development of maternal hypertensive disorders, including pre-eclampsia, and increases the risk of developing diabetes in women with GDM. Ethnic differences in the maternal response to fetal sex have also been noticed. The present review provides evidence that, regardless of the female or male sex, fetal sex dimorphism should be integrated in the risk assessment in pregnancy. The inclusion of fetal sex in future experimental research and clinical investigations would provide useful data for the purposes of reducing the costs of maternal and offspring interventions during pregnancy, upon delivery and after pregnancy.

Key words. Pregnancy-related complications, fetal sex, sexual dimorphism and maternal health, healthcare costs.

Promuovere cure diverse per le donne in gravidanza in base al sesso del feto: a che punto siamo?

Riassunto. Il sesso del feto contribuisce in modo significativo all'esito della gravidanza e alla salute della madre sia a breve che a lungo termine. Il feto di sesso maschile sembra aumentare il rischio di parto pretermine, di ricorrere al parto cesareo e di sviluppare diabete mellito gestazionale (GDM). D'altra parte, il feto femminile influenza negativamente lo sviluppo di ipertensione e patologie associate quali la pre-eclampsia, e in donne con GDM aumenta il rischio di sviluppare il diabete.

È stato osservato che la risposta materna al sesso fetale è influenzata dalle differenze etniche. I dati contenuti in questa review evidenziano che, indipendentemente dal sesso del feto, il dimorfismo sessuale fetale dovrebbe essere integrato nella valutazione dei rischi in gravidanza. L'inserimento del sesso fetale nella ricerca sperimentale e nelle indagini cliniche fornirebbe dati utili al fine di ridurre i costi di intervento sulla madre e sulla la prole durante la gravidanza, al momento del parto e dopo la gravidanza.

Parole chiave. Complicanze legate alla gravidanza, sesso fetale, dimorfismo sessuale e salute materna, costi sanitari.

Introduction

According to the fetal origins of adult disease (FOAD) theorized by David Barker and followed by the Developmental Origins of Health and Disease (DOHaD) theory, it has recently become evident that the intrauterine environment has a significant role in the susceptibility to diseases of the offspring also in their adult life.[1] A growing number of studies confirm this hypothesis[2] and have shown that maternal nutrition impacts fetal growth and development.[3-4] More specifically, it has been observed that maternal malnutrition – both undernutrition and over-nutrition – affects male and female offspring differently,[5-3] suggesting a different sex-related response to the same intrauterine environment.

In this regard, it has been noticed that, at the same gestational age, male fetuses more than female ones are at increased risk of obesity in case of maternal obesity and gestational diabetes mellitus (GDM),[6] and appear to be more vulnerable to prenatal adversity.[7] Moreover, by studying the complex and dynamic interaction between mother and fetus, researchers and clinicians realized that fetal sex can affect pregnancy outcomes and the maternal health in the short and long term,[8-9] with considerable effects on the costs borne by the healthcare system.[10]

In this review, we summarize the latest literature data on the influence of fetal sex on gestational complications and postnatal maternal wellbeing, and we will discuss the need to consider fetal sex in biological and clinical research, in order to better manage pregnancy, related complications and the short- and long-term health status of both offspring and mothers.

Effects of fetal sex on pregnancy outcomes

The effect of fetal sex on pregnancy outcomes and pregnancy-related complications has long been an area of particular interest.[8]

A retrospective study on 574,358 South Australian singleton live births during 1981-2011 showed the existence of a sexual dimorphism for the most adverse pregnancy complications. Pregnancies with a male fe-

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tus have been associated with an increased risk for preterm birth (PTB), pregnancy-induced hypertensive disorders (PIHD), and GDM; and women carrying a female fetus are more at risk for PIHD complicated with PTB.[11] Also, among the total 444,685 singleton births occurred in Austria in the period 2008-2013, significantly more premature births were observed for male fetuses.[12] An analysis of 2,439 women from the Brigham and Women's Hospital in Boston showed that male fetuses (male 13.2% versus 9.6% female) increased the risk of cesarean section (CS)[13] also in primigravidae women with induced labour.[14] Male fetuses slow down the first stage of labor, as was observed in a study conducted on 1,527 term singleton pregnant women enrolled in Teheran between January 2013 and 2014. In addition, the higher rate of CS and the higher birth weight observed in male neonates support the hypothesis of an association between macrosomia and an increased risk of CS in male fetuses.[15] Moreover, it is known that an increased maternal age represents an elevated risk factor for pregnancy complications, and carrying a male fetus may increase such risk. Specifically, in a population study (n = 37,327) on term singleton pregnancies delivered between 2004 and 2008 in Israel, a greater number of CS was observed in women aged ≥40 carrying male fetuses than female ones.[16] In twin pregnancies, also the sex of fetus has a role in the pregnancy outcome. A retrospective study of 2,704 dichorionic twin pregnancies in Israel showed that i) male-male twin pregnancies present an increased risk of premature birth compared to female-female twin pregnancies; ii) in male-female pregnancies, the presence of a female fetus facilitated a higher birth weight of the male; on the other hand, the presence of a male fetus was associated with an increased risk for prematurity and related-morbidity. This study highlights the fact that the presence of a female fetus in twins has positive effects on the pregnancy outcome, and designs a "male-offending factor".[17] All these studies indicate that sexual dimorphism should be taken into consideration in the risk assessment during pregnancy, upon delivery, and at follow-up.

Differences in fetal sex affect maternal glucose tolerance

Increasing evidence indicates that fetal sex may affect maternal glucose metabolism and insulin sensitivity during pregnancy, also in normal glucose tolerance (NGT) pregnant women. In a singleton cohort study, 299 healthy pregnant women were recruited at 24-28 weeks of gestation in three hospitals in Montreal (Canada). By comparing women bearing female vs male fetuses, plasma insulin concentrations were found to be significantly higher (female 66.4 ± 50.5 vs male 51.0 ± 46.1 mU/l) and glucose-to-insulin ratios significantly lower (2.60 ± 2.03 vs 3.77 ± 4.98 mg/dl/mU/l) in women bearing a female fetus, indicating a greater level of insulin resistance during pregnancy.[18]

Conversely, a more recent study carried out at the National Maternity Hospital, Dublin, Ireland, on 582 women enrolled in early pregnancy (12.9 ± 3.0 weeks of gestational age) showed that pregnant women carrying female fetuses were less insulin resistant in early pregnancy (HOMA; B= -0.19, p = 0.01).[19]

In addition, a Chinese study (on 877 healthy pregnant women enrolled at 24-28 weeks) highlighted that the male fetus was associated with a higher level of maternal fasting glucose [4.5 (4.2-4.8) vs 4.4 (4.2-4.7) mmol/l], and a lower basal β-cell function.[20] Moreover, in a population study consisting of 1,074 pregnant women enrolled at 24-34 weeks (Toronto, Ontario, Canada) Retnakaran et al. found an association between the male fetus and a poorer maternal β-cell function, higher postprandial glycemia, and increased risk of GDM.[21] However, a systematic review and meta-analysis of 320 observational studies showed that, among over 2.4 million pregnancies, women carrying a boy have a modest (4%) increase in the risk for GDM than those carrying a girl.[22]

It is well known that women who develop GDM have an increased risk of developing type 2 diabetes (T2D) during their life,[23] and several studies indicate that fetal sex is a factor associated with the maternal diabetic risk. In this regard, a population-based retrospective study (using databases from the Ministry of Health and Long-Term Care of Ontario, Canada) showed that, among 23,363 women with GDM with a singleton live-birth first pregnancy, those who delivered a girl had an increased risk of developing diabetes, compared with those who delivered a boy (adjusted hazard ratio =1.06, 95% CI 1.01-1.12, p = 0.03).[24] A recent study enrolled 327 European primiparous women after a diagnosis of GDM. The data obtained showed that mothers carrying male fetuses needed the insulin therapy more frequently, indicating that male fetal sex may affect the glucose metabolism in the mother (oral glucose tolerance test, OGTT).[25] The authors hypothesized that testosterone might be responsible for the additional insulin resistance in GDM, since a higher level of this hormone was detected in the cord blood of newborns from insulin resistant mothers compared to the ones from insulin sensitive mothers (0.48 ± 0.36 nmol/l vs 0.29 ± 0.18 nmol/l p ≤0.05).[26]

This data indicates that a dynamic metabolic interplay exists between the mother and the fetus affecting each other. Fetal sex is a recent factor that may affect maternal glycemic control, and – along with maternal ethnicity, obesity and gestational age – is associated

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with the maternal diabetic risk during and after pregnancy.

Although further research is necessary to comprehend the molecular mechanisms, sexual dimorphism should be integrated in pregnancy-related investigations, in order to obtain data to support sex-specific diabetes care.

Fetal sex and maternal hypertensive disorders

Observational studies indicate that fetal sex affects the development of hypertensive disorders during pregnancy.[27-28] A Japanese study involving 125 centers and aimed at evaluating the impact of fetal sex in pregnancy-induced hypertension (PIH), showed that i) singleton pregnancy mothers with PIH/preeclampsia (PE) delivered more girls (girls vs male: 5.2% vs 4.6%); and ii) in dichorionic diamniotic twin pregnancies, the mothers carrying female-female fetuses (7.6% vs 6.0%) had an higher incidence of PIH/PE.[27] Although additional studies are needed to clarify the role of fetal gender on the risk of PIH/PE, this large study indicates that female fetal sex is a risk factor for both disorders.

Sexual dimorphism affects the expression of angiogenic markers in pregnancy, as was noticed in a Danish study carried out on 2,874 pregnant women. This study showed that in pregnant women female fetuses are associated with a higher expression of soluble Fms-like kinase 1 (sFlt-1), a predictive factor of PE found at higher level in pregnancies subsequently complicated by PE, in the first and second trimesters.[29] However, taking into account the fact that mortality among male infants born to mothers with PE is higher than among females,[30] the authors speculate that high levels of sFlt-1 in mothers with PE carrying a female fetus may represent a survival mechanism for both mother and fetus.

The results from a large-scale meta-analysis (including 219,575 independent singleton pregnancies) showed that fetal sex-specific differences exist with regard to the risk to develop PE, and a female dominance is observed in preterm – but not term – pregnancies complicated by PE.[31]

However, a recent meta-analysis of 22 studies involving 3,163,735 women highlighted that in the non-Asian population it is the male fetal sex to be associated with an increased maternal risk of pre-eclampsia/eclampsia.[32] It is conceivable that ethnicity, along with the pathophysiology of PE (not well known yet), could explain these conflicting data. It has been hypothesized that fetal genes may influence the maternal metabolism and physiology.[33] Specifically, Petry et al. emphasized that the fetal genome is able to influence maternal blood pressure during pregnancy,[34] and that the development of gestational hypertension can be associated with a specific polymorphic variation of fetal imprinted genes.[35] In consideration of the tremendous impact of PE on the mother's health (i.e., it is the principal cause of maternal morbidity and mortality, and women experiencing PE in pregnancy are at increased risk of hypertension, cardiovascular disease and cognitive decline later in life),[36] fetal sexual dimorphism should also be considered in developing research projects aiming at better understanding the disease mechanisms.

Preterm birth on maternal health

Preterm birth (PTB) is a pregnancy complication causing morbidity and mortality both in the mother and the offspring.[37] Along with obesity, previous abortion and PTB, fetal sex also appears to contribute to the incidence of PTB. Specifically, it seems that carrying a male fetus increases preterm labor (PTL).[38] An analysis of 594 pregnant women confirmed that the majority of women with PTL (between weeks 24 and 34) were pregnant with a male fetus.[39] Also, a larger cohort study (1,736 white European women and 615 singleton births) showed that male fetuses are at increased risk of spontaneous preterm compared with female ones, with a peak between weeks 27 and 31. The basis of this difference is still unclear, although a role of placenta has been hypothesized.[40] However, when women at high risk for preterm delivery (2,505 multicultural women; London, UK) were analyzed, the difference between sexes was abolished. The authors hypothesized that being at high-risk for preterm delivery overcomes other predisposing risk factors accounting for differences between sexes.[37] An important issue that has to be considered in women experiencing preterm delivery is the increased risk of developing mental distress, including depression and post-traumatic stress disorder,[41] as well as a negative feeling with their baby, likely due to delay skin-to-skin contact and breastfeeding soon after birth, compared to the mothers of term babies.[42]

PTB is associated with complications for the infant, and it represents a considerable cost for the healthcare systems; only recently, it became clear that PTB/PTL mothers represent a large burden for individuals, their families and the healthcare systems. A recent study on 2,147 experienced PTL/PTB mothers in Germany described the costs during pregnancy, delivery, and a period up to three years after delivery. The results indicate that, similarly to the costs for the infants, also the costs for the mothers appear to increase with the decrease in the gestational age, both in the short and the long term.[10] Comparable results were observed also in a study on 3,058 Italian PTL/PTB mothers with uncomplicated pregnancies.[43] All these findings indicate that, in plan-

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ning pregnancy services for PTB, it would also be necessary to evaluate the maternal outcomes and related health care costs, taking into account fetal sex differences as an additional risk factor.

Fetal sex affects maternal inflammatory milieu

Pregnancy is characterized by physiological modifications involving neuroendocrine, cardiovascular and immune functions aimed at adapting the maternal body to the developing fetus.[44] However, as regards the changes in inflammatory immune response, the knowledge of the mechanisms involved is still incomplete, also in healthy pregnancy.

In order to shed light on this topic, the authors of a prospective study on 37 black and 39 white healthy pregnant women at the Ohio State University Wexner Medical Center focused their analysis on the in vitro inflammatory response of peripheral blood mononuclear cells (from early, mid-, and late pregnancy and 8-10 weeks postpartum) stimulated with lipopolysaccharide (LPS) for 24 hours. The results revealed a progressive increase, across the entire pregnancy, in the secretion of inflammatory cytokines IL-6, TNF-α, and IL-1β; this production returned to levels comparable to early pregnancy by 8-10 weeks post-partum. Both black and white women displayed a similar inflammatory expression pattern.[44] Interestingly, when these patterns were evaluated taking in account the fetal sex, it was observed that women carrying a female fetus showed higher levels of LPS-stimulated cytokine production of IL-6 ($p = 0.0001$), TNF-α ($p = 0.02$), and IL-1β ($p = 0.001$).[45] These findings suggest that the female fetus might modify the maternal immune milieu, by inducing a greater maternal inflammatory response that should be considered when pregnant women experience adverse events during pregnancy.

In this regard, female fetuses, in early preterm PE (<34 weeks), are associated with higher maternal serum levels of inflammatory TNFβ and IL1β, anti-inflammatory (IL4r) and regulatory cytokines (IL5 and IL10) in the second trimester. The detection of increased levels of the anti-inflammatory cytokine IL-10 in the post-partum period suggests a protective attempt to fight the increased risk for cardiovascular disease later in life in women with PE.[46] Placentas from women with severe PE carrying male fetuses had greater levels ($p < 0.05$) of TNFα, IL-8 and IL-6 compared to female fetuses. Although both male and female placentas displayed an increased activation of the inflammatory transcription factor NFkB, the male ones had a higher expression of the p65 subunit. Sexual dimorphism was observed also for placental apoptosis; male placentas displayed an increased apoptosis, in association with elevated expression of pro-apoptotic molecules PUMA and Bax, compared to females.[47] The placenta is a feto-maternal multifunctional organ, with a central role in the fetal growth and development; it regulates maternal-fetal nutrient transport, gas exchange and immune tolerance, and, as an endocrine organ, it secretes various hormones and cytokines. The identification of sex-dependent differences in the transcriptomic profile in human placenta indicated that sexual dimorphism may affect all the aforementioned placental activities.[48] In this context, it has been observed, by a microarray-based approach, that the human placenta related to female fetuses displayed a higher expression of immune-regulating genes, such as *JAK1*, *IL2RB*, *Clusterin*, *LTBP*, *CXCL1*, and *IL1RL1*, suggesting a better response to possible infections in the mother.[49] A more recent study highlighted that placentas from male fetuses showed an increased expression of transcripts involved in graft-versus-host disease, and immune and inflammatory response (*HLA-DQB1*, *HLA-DQA1*, *HCP5*, *NOS1*, *FSTL3*, *PAPPA*, *SPARCL*, *FCGR2C*, *CD34*, *HLA-F*, and *BCL2*), supporting the hypothesis of a reduced maternal-fetal compatibility for male fetuses, as well as an increased adverse pregnancy outcome.[50] Fetal sex-dependent maternal immunologic differences are recognizable already in the early pregnancy. The expression pattern of mRNAs in the decidual tissue (10-12 weeks) from healthy pregnancies showed an increased expression of *FOXP3* ($p <0.01$) in the tissue from pregnancies with a male fetus, and a higher expression of *IFNγ* ($p <0.05$) in pregnancies with a female fetus. Since *FOXP3* is a marker of the T-regulatory cells (Tregs) involved in the immune tolerance in the early pregnancy, the authors hypothesized that its reduction in the pregnancies with a male fetus might contribute to the higher risk of pregnancy complications. On the contrary, IFNγ – that has a positive role in implantation and placentation –might account for the more successful female pregnancy outcome.[51] The placental oxidative stress and antioxidant activity are also impacted by sexual dimorphism. Specifically, placentas from lean healthy women with a male fetus showed a higher superoxide dismutase (SOD; $p <0.05$) activity and total antioxidant capacity (TAC; $p <0.05$), compared to those from women with a female fetus, thus indicating increased antioxidant defenses.[52] Decreased SOD, catalase and TAC activities were observed in placentas from obese mothers; these features are associated with increased glutathione peroxidase and thioredoxin reductase activity only in placentas from male fetuses.[52]

These findings provide evidence that fetal sex impacts the maternal immune-regulation both during pregnancy and after delivery, and indicate that fetal sexual di-

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morphism should be considered in the evaluation of pregnancy outcomes and the mother's health, both in healthy and complicated pregnancies.

Sex specific health care policy

For a long time an under-representation of women in clinical trials and in study designs has slowed down the awareness of a sex-gender difference in term of prevention, recurrence and occurrence of diseases, treatments and outcomes.[53] Now, in the era of precision and personalized medicine, a stratification is crucial that takes into account both biological (sex) and socio-cultural factors (gender), in order to optimize the healthcare system.[54-55] Good evidence of this can be found in the National Institutes of Health (NIH) policies that require applicants to consider sex as a variable in biomedical research,[56] as well as in the Italian National Healthcare Service, with a law regulating the implementation of gender-specific medicine in Italy.[57] Another major step forward in reducing sex and gender disparities in healthcare would be to introduce the principles of sex- and gender-based differences[58] into the medical and interprofessional education, through adequate programs and approaches, as some countries are already doing.[59] Moreover, efforts have been made to implement the common rules necessary to improve clinical trials with a sex-gender approach.[53] With regard to the evaluation of sexual dimorphism in pregnancy, we are still in the early stages, although it is becoming increasingly evident that fetal sex is a critical factor both for pregnancy outcomes and the maternal health.

Key messages

- Women carrying a male fetus are at increased risk for preterm birth, caesarean section, hypertension disorders and gestational diabetes.
- In dichorionic twin pregnancies, the presence of a male fetus appears to be associated with increased risk for prematurity and related-morbidity.
- The risk to develop preeclampsia is associated to female or male fetus depending on maternal ethnicity.
- Fetal sex differently influences maternal inflammatory patterns and metabolic profiles.
- This suggests that fetal sex should be included in pregnancy management, as well as in future pregnancy-related experimental research and clinical investigations.

Conclusions

The importance of sex and gender in health and medicine is clear, even more so in the era of personalized medicine. In pregnancy, a dynamic interplay connects the fetus and the mother through a mutual influence, and an increasing evidence emphasizes the role of fetal sexual dimorphism on pregnancy outcomes and the maternal health. More efforts need to be made to comprehend why caesarean section, hypertension, preeclampsia, and increased inflammation occur with a different risk profile, depending on fetal sex. A better definition of the mechanisms responsible of these differences will provide useful information in order to design appropriate pregnancy services, in term of disease prevention, treatment and follow-up, with the aim of reducing individual and collective healthcare costs.

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