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Gender-related differences in neonatal age

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Summary. Men and women are significantly different in their body system, and this difference has been studied in various fields of medicine. Medical research has identified a substantial group of gender-specific adult diseases, but biological differences between sexes are evident even from the beginning of pregnancy. The evaluation of gender specificities has been also extended to newborns, infants, children and adolescents. Gender-specific medicine deals with the differences between men and women both in health and diseases.

Male and female fetuses react differently to the same intrauterine environment, suggesting biological variation at cellular and molecular level. Male sex is a risk factor for adverse pregnancy outcomes. There are significant sex-related differences in relation to different outcomes in preterm newborns and in the neonatal age, as well as in the incidence of congenital malformations, response to drugs during infancy, neurological and respiratory diseases. The functional and structural development of the lungs occurs earlier in females, especially in preterm newborns.

In this narrative review, we describe how the sex of the fetus and the newborn can affect morbidity and mortality, both during pregnancy and after birth. Gender-related medicine can be applied to the neonatal age to evaluate disease-related sex differences. This could possibly allow for the application of preventive strategies and/or specific treatments, with a great impact on public health.

Key words. Gender-related medicine, sex differences, pregnancy, prematurity, newborn.

Differenze genere-specifiche nell'età neonatale

Riassunto. Vi sono significative differenze legate al sesso a livello dei diversi apparati dell'organismo umano, differenze che rappresentano un campo di studio in continua evoluzione. La ricerca medica ha identificato un gruppo significativo di patologie dell'adulto sesso-correlate, ma differenze biologiche tra i sessi sono evidenti già nel feto e poi nel neonato, nel bambino e nell'adolescente. La medicina di genere è lo studio di come fisiologia e patologia differiscano tra uomini e donne.

I feti maschi e femmine rispondono in modo diverso allo stesso ambiente intrauterino, suggerendo una differenza biologica fondamentale a livello cellulare e molecolare. Il sesso maschile rappresenta un fattore di rischio per esiti avversi in gravidanza. Vi sono differenze significative legate al sesso nel periodo neonatale e per gli esiti dei neonati pretermine, così come per l'incidenza di malattie neurologiche, malformazioni congenite e malattie respiratorie, nonché nella risposta individuale ai farmaci durante l'infanzia. Lo sviluppo funzionale e strutturale dell'apparato respiratorio è superiore nelle femmine, specialmente nei neonati pretermine.

In questa review descriviamo come il sesso del feto e del neonato possano influenzare la morbilità e la mortalità durante la gravidanza e dopo la nascita. La medicina di genere ha un suo ruolo già nel periodo neonatale per valutare le differenze sesso-correlate. Questo approccio potrebbe rendere possibile applicare strategie preventive e/o trattamenti specifici con grande impatto sulla salute pubblica.

Parole chiave. Differenze genere-specifiche, differenze sessuali, gravidanza, prematurità, neonato.

Background

Men and women are significantly different in their body system, and this difference has been studied in various fields of medicine. Historically, most of the people who heard the term gender-specific assumed it meant "women's medicine", a still common misperception; gender-specific medicine, however, is the study of how normal function and disease experience differ between men and women.[1]

Medical research has identified a substantial group of gender-specific adult diseases, but the evaluation of gender specificities has been extended also to newborns, infants, children and adolescents.

The application of gender medicine in childhood could help to evaluate disease-related sex differences and possible preventive strategies and/or treatments, with a consequent great impact on public health.

The concept of gender medicine in the neonatal age traces back to the 1970s, when it was introduced by Naeye as the "hypothesis of the male disadvantage", to describe the increased perinatal mortality in males compared with females.[2]

In 1997, the male/female ratio at birth was found to be 1.06%,[3] thus postulating that gender-related differences begin soon after conception. The human sex ratio is thought to be the result of two processes: first, the sex of the zygotes is significantly affected by the hormonal

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activity of the progenitors during the periconceptional period and, second, maternal stress stimulates the adrenal androgens synthesis, leading to a selective spontaneous abortion of male sex embryos, probably because male embryos are less resistant to maternal stress than female, and therefore they die early.

The sex ratio at conception – primary sex ratio (PSR) – in humans remains unknown. In previous studies, PSR estimates gave a result approximately equal to 0.56 (proportion of males), or even greater. Interestingly, male abnormal embryos outnumber female ones, while as for normal embryos female sex prevails. During gestation, sex ratio varies. After an initial increase in male mortality, female mortality increases thereafter, finally overcoming male mortality at the end of gestation. This would explain why secondary sex ratio for males is greater that for females.[4]

After birth, the overall infant mortality rate for male infants was 21% higher than the rate for female infants,[5] also because the "male disadvantage" refers to the higher incidence of diseases, such as respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), chronic lung disease (CLD) and brain haemorrhage.[5]

The exact mechanisms involved in the male biologic disadvantages remain unclear; however, a body of evidence reveals that obstetric risk factors such as hypoxia, influence of sex hormones, alterations in cell death pathways, and sensitivity to inflammation and excitotoxins – as well as sex differences in the autonomic and endocrine stress responses – play a key role.[6]

Objective

The aim of this narrative review is to describe how gender-related medicine applies to the neonatal age, providing an in-depth insight on how the fetal sex affects morbidity and mortality during pregnancy and after birth.

Materials and methods

An exhaustive search for eligible studies was performed, using the PubMed database as a data source. The following subject or MeSH headings were used: 'Sex' [Mesh], 'Infant, Newborn' [Mesh], Pregnancy, Maternal glucose intolerance, Gestational diabetes mellitus, Maternal hypertension, Prematurity, Respiratory diseases, Congenital malformations and Neurodevelopment. Furthermore, free text and proper Boolean operators 'AND' and 'OR' were included, in order for the search to be as comprehensive as possible. Additional studies were sought using the references contained in the articles obtained from the searches. Search limits were set for articles published in English.

Results and discussion

Pregnancy, nutrition and programming

The biological differences between sexes become evident since the early pregnancy, and the fetal sex may affect several maternal and obstetric outcomes.[7] Pregnancy of a male fetus has been associated with an increased risk of pregnancy complications and adverse obstetrical outcomes.

Sheiner et al.[8] showed that male fetuses have higher rates of macrosomia and cesarean section (CS), as a possible result of the interaction between sex hormones, fetal insulin and genetic factors. Male fetuses are also more likely to show non-reassuring fetal heart rate patterns, failure to progress during the first and second stages of labor, cord prolapse, nuchal cord, true umbilical cord knots or low Apgar scores at 5 min, so that male sex may even be considered an independent risk factor for adverse pregnancy outcomes.

Placenta

The placentas of male and female fetuses have different protein and gene expressions, especially in adverse conditions, like preterm labor. Sex-specific placental, hormonal and maternal anthropometrics, and several still unknown factors, also appear to interact in complex ways, affecting fetal growth.

Male and female fetuses show different responses to the same intrauterine environment, suggesting differences at both cellular and molecular level.[9]

Sex-specific differences in fetal growth start quite early in pregnancy. The growth of the male fetuses appears to be greater than in females from the very early stages of gestation,[9] and therefore mean birth weight is higher in boys than girls.[10]

Sex-specific differences of placental function might affect fetal growth and fetal programming, or fetal sex itself influence placental function. The levels of fetal sex-specific placental biomarkers, such as the pro-angiogenic placental growth factor (PIGF) and the anti-angiogenic soluble Fms-like tyrosine kinase 1 (s-Flt1), are higher in female fetuses during the first trimester of pregnancies.[11]

Maternal glucocorticoids (GC) play an important role in fetal growth and organ maturation. An excess of glucocorticoids affect growth, but their action may also be sex-specific, probably mediated through the glucocorticoids receptors (GR) of the placenta. An excess of maternal GCs has shown to lead to reduced placental capillary length exclusively in male fetuses.[12] Other studies have shown that GCs may preferentially increase the production of reactive oxygen species in the placentas of male fetuses.[13,14]

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Evidence suggests that the placentas of female fetuses inactivate maternal GCs more efficiently compared to male ones, through the action of placental 11 beta-HSD2. A decreased activity of this enzyme in placenta occurs in male fetuses and it is associated with higher levels of fetal cortisol. This higher intrinsic exposure to GCs *in utero* may explain why male fetuses have reduced responses compared to females, in cases of any maternal stress-associated complications.[15]

Intrauterine environment

To determine whether the fetal sex or genotype may influence the adaptive response to the intrauterine environment, Cogollos et al.[16] studied the maternal malnutrition effects on developmental patterns, adiposity level, and fatty-acid composition, according to fetal sex. A better adaptive response was observed in the female offspring, and this was modulated by their genotype. Female fetuses faced with prenatal undernutrition are able to promote the growth of some organs (liver, brain, kidneys, lungs and intestine), at the expense of bone tissue and muscle mass.

Mandò et al.[17] found a significant interaction between maternal BMI and fetal sex on the placental weight. They reported a difference in placental adaptation depending on fetal sex, with significant changes only in female fetuses. This is significant, because it can explain why female fetuses have a better survival than males.

Another study conducted in the United States[18] examined placental histopathology, i.e. placental disc weight >the 90th percentile, decreased placental effectiveness, chronic villitis (CV), fetal thrombosis, and normoblastemia, and inflammatory markers. Fetal thrombosis and higher rates of CV were observed in female fetuses of obese mothers, but the extent of CV was significantly associated with obesity and BMI, but not with fetal sex. However, they showed for the first time that the effect of maternal obesity on placental inflammation is not related to both maternal hypertension and diabetes, but to fetal sex.

Fetal growth and birth weight

Sex differences in fetal growth can be present as early as at 15 weeks of gestation[19-21] and they were used to obtain different fetal growth charts, based on fetal sex.[22] The following fetal measurements were obtained: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). Parents' height, weight, parity, and ethnicity were significantly related to these fetal biometric parameters, but they were considered independently from fetal sex. Fetal sex was a significant covariate for BPD, HC and AC, with higher values for male fetuses, whereas minimal differences for FL were found among sexes. The use of sex-specific fetal growth charts may offer the advantage of a more accurate detection of abnormal fetal growth. Preeclamptic pregnancies have higher serum leptin levels than normal ones,[23] and leptin levels were found to be higher in the amniotic fluid in IUGR female fetuses than in IUGR male fetuses.[24] A higher incidence of preeclampsia in women carrying female fetuses is one explanation of the lower weight of the latter.[7,25]

Muhihi et al.[26] analyzed birth outcome data from singleton infants enrolled in a large, randomized, double-blind, placebo-controlled trial of neonatal vitamin A supplementation, conducted in Tanzania. Among the 19,269 singleton Tanzanian newborns included in this analysis, 68.3% were term deliveries, and appropriate for their gestational age (AGA), 15.8% were also term deliveries, but small for their gestational age (SGA, defined as birth weight lower than the 10th percentile), 15.5% were preterm deliveries and AGA, and 0.3% were preterm and SGA. In their multivariate analyses, the Authors found that male sex was a significant risk factors for being term-SGA ($p < 0.05$).

Interestingly, Morley et al. assessed the neurodevelopmental outcomes of SGA children fed an enriched formula. The Authors reported that SGA children who were fed an enriched formula showed enhanced growth in both sexes. However, the use of the enriched formula was not related to any neurodevelopmental advantage. This finding was more obvious at 9 months in SGA girls, who had a significant developmental disadvantage, although this was not confirmed at 18 months.[27]

Diabetes during pregnancy

High maternal blood glucose during pregnancy carries maternal and fetal risks, so careful blood sugar control is needed to reduce fetal complications.

Studies examining an association between fetal sex and impaired maternal glucose metabolism have given conflicting results. One study found that the female fetus may be associated with a greater maternal insulin resistance during pregnancy, while Verburg et al.[28] and Sheiner et al.[8] demonstrated more cases of gestational diabetes mellitus (GDM) in pregnancy with male fetuses.[29]

Another study found that carrying a male fetus is a risk factor of GDM during the first and second pregnancy.[30] However, mothers with a history of GDM showed an increased risk of developing type 2 diabetes mellitus (T2DM) before a second pregnancy if they delivered a girl, although the recurrence of GDM was not found to be affected by fetal sex.

One suggested mechanism is that women carrying a male fetus have a poorer beta cell function, as measured

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by the insulinogenic index (IGI) divided by the homeostatic model assessment (HOMA) of insulin resistance.[30]

A study from Ireland[31] found a greater insulin resistance among female fetuses, with higher leptin and C-peptide concentrations in their cord blood, despite a reduced birth weight. These findings are consistent with the growing body of evidence suggesting that girls are intrinsically more insulin resistant than boys, both during childhood and adolescence.

Similarly, Shields et al.[32] also found that, despite being smaller, female newborns have higher insulin and proinsulin levels, probably because of their higher intrinsic insulin resistance.

Eder et al.[33] found that the fat deposit in female neonates seems less affected by insulin compared to males, another effect of a greater insulin resistance in females.

Hypertensive disorders in pregnancy

Some studies suggest that fetal sex can be a risk factor for the development of hypertensive disorders in pregnancy.

Shiozaki et al.[25] found that female sex was a risk factor for both pregnancy-induced hypertension (PIH) and preeclampsia.

High levels of beta human chorionic gonadotropin (β-hCG) are a well-known risk factor for hypertensive disorders in pregnancy and, apparently, there is a female preponderance in hypertensive pregnancies with elevated β-hCG levels.[34]

In pregnancies with female fetuses, hCG levels in maternal blood are significantly higher at 35 weeks than at 16, while in pregnancies with male fetuses the levels are the highest at 16 weeks. Since most cases of PIH develop in the third trimester, these findings suggest that carrying a female fetus is a further risk factor for the development of hypertensive diseases.[35]

The renin-angiotensin system during early gestation shows sex-related differences. Sykes et al.[36] found that women carrying a female fetus and subsequently developing preeclampsia or gestational hypertension had elevated levels of angiotensin-(1-7) at 15 weeks of gestation, compared with women with normotensive pregnancies.

Fetal sex seems to affect not only gestational hypertension, but also its response to treatment.

In New Zealand, Gray et al.[37] examined the effects of magnesium sulfate on the vascular tone in male and female placental vessels from term and preterm deliveries. They found that, in preterm female pregnancies, the placental bed responds better to magnesium sulfate, with an improved fetal nutrient delivery and gas exchange during the peripartum period and higher overall neuroprotective effects.

Fetal heart rate monitoring

According to Kim et al.,[38] the cardiovascular system of female fetuses develops earlier, and females show greater heart rate dynamics in the early gestational periods, while male fetuses undergo a compensatory period of rapid changes, to catch up with females at term.

Most studies failed to demonstrate any significant sex differences during the perinatal period.[39,40] Dawes et al.[41] found that the fetal heart rate (FHR) is significantly higher in female fetuses, but these sex differences are found 6-7 hrs before delivery and during the first stage of labor, while no difference are observed before the onset of labor. Di Pietro et al.[42] found a higher heart rate variability throughout gestation in males, and Bernardes et al.[43] suggested sex differences in the activity of the autonomic nervous system, with evidence of less complex fetal heart rate activity in males. Amorim-Costa et al.[44] provided reference values for CTG parameters, with different centile charts according to sex. In a prospective study of abnormal FHR patterns during the second stage of labor, male gender was found to be an independent risk factor for abnormal second-stage FHR patterns (OR 1.5; 95% CI: 1.01-2.2).[45] Another study showed that male fetuses have a higher rate of deceleration episodes and an increased risk for both repetitive variable decelerations and prolonged decelerations,[46] probably due to lower levels of catecholamines in response to the asphyxia seen in male fetuses.[47]

Stillbirth risk

Sex difference in the birth rate was initially reported as an observational finding, and only lately this finding was associated with sex-related characteristics of both the placenta and the feto-placental hormonal milieu. Differences in placental metabolism and in the response to nutritional factors between the male and female placentas have been considered as causative factors.

According to the large systematic review conducted by Mondal et al.,[48] the stillbirth risk is 10% higher in male fetuses, with no differences if the limit of the gestational age is 20 or 28 weeks, but different data have also reported no sex-differences[49] or a higher number of cases in female pregnancies,[50] although cultural factors promoting male births in these countries could be a bias.[48] Further studies are needed to establish a clear causal relationship between fetal sex and stillbirth rate.

Congenital malformations

Congenital malformations (CMs) are structural or chromosomal alterations with a significant impact on the health and development of a child.[51] Congenital mal-

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formations are one of the most common cause of infant mortality, especially in the first year of life, and are significantly influenced by gestational-age and sex.

Sex differences in several specific congenital anomalies have been documented as far back as the 1940s. Studies reported conditions such as cleft lip and polydactyly to be more common in males,[52] whereas neural tube defects[53] and cleft palate[54] were more common in females.

In 2014, a UK-based population meta-analysis showed that the prevalence of congenital anomalies was higher in males than in females.[55] In this study, congenital malformations with greater predominance in male sex show a higher sex-specific risks, whereas conditions with female dominance have a smaller risk differences between sexes. These results were highly consistent with those from previous studies.[56-59]

In 2014, in a population-based cross-sectional study which analyzed the effect of sex and prematurity, Egbe et al. showed that the risk of CMs was significantly higher for an isolated malformation in preterm and in males, although there was no difference in the overall risk of CMs. The prevalence of isolated non-syndromic congenital malformations was higher in males than in females, but no sex differences were found for the prevalence of syndromic CMs, multiple non-syndromic CMs, and overall congenital malformations.[60]

Gastrointestinal malformations (such as tracheoesophageal fistula or Hirschsprung disease), cardiac malformations (aortic stenosis, aortic arch anomaly, hypoplastic left heart syndrome – HLHS, complete transposition of great arteries), cleft lip, and cleft lip-palate seem to be more common in males, while respiratory and musculoskeletal malformations are more common in females.[60]

Sex differences in the prevalence of several human birth defects (eg., anencephaly, cleft lip with or without cleft palate, polydactyly, congenital dislocation of the hip) have often been reported, but the real extent of sex differences for most birth defects is unknown.[56]

A number of major birth defects can be detected by prenatal diagnostic procedures, and fetuses with these defects may be subjected to high rates of elective termination of pregnancy.[61,62] Prenatal diagnosis and elective termination can thus have a substantial impact on the prevalence of birth defects, since in most CM registers only live-born/stillborn infants of ≥20 weeks of gestation are included. There is no evidence that the prenatal diagnosis is more accurate in one sex than in the other, and it is unlikely that fetuses with malformations are selected for termination on the basis of sex. Because the impact of prenatal diagnosis and elective termination is expected to be non-differential with respect to sex, it should have no impact on the male-female relative risk of a defect at birth.[56]

Moreover, for some defects, prenatal mortality rate may be different between sexes, leading to a sex difference in prevalence at birth.[63]

Several different mechanisms may account for the sex differences in the prevalence of birth defects. For many years now some authors have been speculating that differences in urogenital morphogenesis or the differences in sex hormones could account for the sex differences in the prevalence of some defects.[64]

It is known that male gonads begin to differentiate during the 7th week of development, and the testes begin to secrete testosterone during the 8th week of development, while female gonads do not begin to differentiate until the 12th week of gestation. Since from the 8th week of development testosterone levels are much higher in the male fetus than in the female fetus,[65,66] it is likely that the abnormal levels of testosterone and other hormones produced by the male reproductive tract after testicular differentiation account for the large excess of defects of the male reproductive system compared with the female's. Higher levels of these hormones in the male fetus after testicular differentiation could affect the development of organs and tissues of other systems as well, leading to sex differences in the prevalence of some defects.[56]

The high prevalence of defects of the reproductive system among males compared with females may be attributable to the greater complexity of the male reproductive development, with a consequently greater chance for organogenesis and histogenesis alterations. These errors originate during or after the expression of the SRY gene on the Y chromosome, during the 7th week of gestation, which subsequently controls the development of male gonads, genital ducts, and external genitalia.

Sex differences in the prevalence of the human birth defects arising before gonadal differentiation are determined by X-linked or Y-linked genes, which influence the morphogenetic processes, either directly or in a multifactorial manner. X-linked or Y-linked genes (different from SRY) may also contribute to sex differences in some CMs.[56]

Sex hormone interaction and system development have been cited as two possible causes of sex differences in some anomalies, including cleft palate and lip.[67] Other theories for sex differences include one according to which the earlier the male reproductive organs develop, the more hormone levels may be responsible for their susceptibility to urinary and reproductive defects,[56,68] although there is little evidence to support this theory.

In conclusion, the risk of major CMs seems to be higher in males, but these differences are still not fully explained. Future genetic research on candidate genes on the sex chromosomes should give some clues about the causes and the pathogenesis of the sex differences related to the incidence of specific birth defects.

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Response to drugs

It has not been long since sex was taken into account in the evaluation of the response to drugs.[69] Experimental studies on the effectiveness of vasoactive drugs to counteract the loss of cerebral autoregulation in a traumatic brain injury piglet model showed significant differences between sexes. Apparently, the protective autoregulation response to drugs such as phenylephrine, norepinephrine, and dopamine was age- and sex-dependent, therefore it was concluded that a specific pharmacotherapy, targeted to both postnatal age and sex, should be sought.[70]

To date, only few clinical studies have reported sex differences in drug response during the neonatal period.

In a subset analysis of a multicenter randomized controlled trial in ELBW infants, the prophylactic use of indomethacin was found to slightly increase the development of severe IVH (grades III and IV) in males.[71]

In a recent study, the human umbilical artery smooth muscle cells isolated from healthy male and female newborn umbilical cords were employed to analyze sex differences in basal and drug-induced autophagy. Constitutive autophagy was similar in both sexes; nonetheless, autophagy increased after starvation in both sexes, but was significantly higher in females. Furthermore, the response to rapamycin was exclusively present in females, whereas no sex differences were found in the response to verapamil.[72]

Prematurity and related diseases

Premature birth is more common in male fetuses, compared to female.[73] Although significant new strategies have improved the outcomes for very preterm infants, males experience higher rates of mortality and complications than females, including lower Apgar scores, a greater need for supplemental oxygen, higher rates of respiratory distress syndrome, more pulmonary interstitial emphysema, and higher overall perinatal mortality rates.[74-78] The higher levels of androgens in male fetuses do interfere with surfactant production, resulting in an increased rate of respiratory distress syndrome (RDS) in male neonates, compared to female neonates of the same gestational age.

Since the 1980s, researchers demonstrated that fetal pulmonary maturity was greater in females, and that androgens may inhibit surfactant production.[49,79] Male fetuses are exposed to higher levels of androgen and Mullerian inhibiting substance, which both adversely affect surfactant production,[80,81] so that the functional lung immaturity in premature newborns can contribute to their poorer outcomes.

Studies conducted on the indices of pulmonary maturity (such as lecithin/sphingomyelin ratios, percent of desaturated lecithin, phosphatidylglycerol, and phosphatidylinositol) showed that male fetuses have less mature lungs than the females by approximately 1 week.[82] The introduction of antenatal corticosteroids and postnatal surfactant has been associated with a substantial improvement in the survival rate, but[83] male sex still represents a risk factor for poorer lung function,[84] increased respiratory morbidity[85] and poorer neurological function overall,[86] and the gap in mortality rates between boys and girls has not narrowed yet.[77] Survival differences in the population of very-low-birth-weight infants (VLBWI) ranged from 14% in 1980-82 in London[74] to 7% in 1991-1993 in the United States.[75]

A more recent, large study (EPICure) on extremely preterm infants (23-25 weeks of gestational age) hospitalized in neonatal units in UK and in the Republic of Ireland also showed a greater mortality for male newborns.[76]

In 2012 Peacock et al. studied 797 preterm infants, showing that male sex was significantly associated with higher birth weight, death rates or oxygen dependency, hospital stay, pulmonary hemorrhage, postnatal steroids, and major cranial ultrasound abnormality. The differences remained significant even after adjusting for birth weight and gestational age. At the follow-up visits, disability, cognitive delay and the use of inhalers remained significantly higher in male infants, after further adjustment.[78]

Gender differences in lung function have been demonstrated in term[87] and preterm[88] infants, with a worse outcome in the male sex. Although the modern advances in technology and medications (in particular antenatal steroids, surfactant and ventilation) have significantly decreased the incidence of RDS, a difference still persists, because female fetuses produce surfactant earlier, move their mouths more, develop larger airways, which are less reactive to insult, and develop more mature parenchyma.

Not only the risk of respiratory distress syndrome (RDS), but also that of subsequent chronic lung disease (CLD) of prematurity is higher in males, and this higher risk may be independent of the earlier RDS,[89] but be affected by the narrow airways and the increased airway reactivity in males.[90,91]

Sex-related differences have been demonstrated also for the neurological outcome, which has been reported to be worse in males.[75,78] In 2005, the EPICure Study Group showed that severe disability and cerebral palsy were more common in boys,[92] and also cognitive delay appears to be significantly more common in male preterms.[78]

In 2005, Marlow et al. showed that the neurological and developmental disability at 6 years of age in infants born before the 26 weeks of gestational age is more common in boys than in girls.

In particular, a very recent study of Kozhemiako et al. shows better cognitive and behavioral outcomes for

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very preterm females compared to males, probably because very preterm boys have greater alterations in the resting neurophysiological network communication than girls. Stronger connectivity alterations might contribute to the male vulnerability in the long-term behavioral and cognitive outcome.[93]

No definitive perinatal, neonatal, or postnatal causative factors have been identified up to date.[94]

Patent ductus arteriosus (PDA) is a common problem in preterm infants, as well as one of the most frequent congenital heart malformations. Some studies showed that many different perinatal factors are associated with PDA, such as birth weight, gestational age, Apgar scores at 1 and 5 minutes, and also female gender.[95]

In some studies, the female-to-male PDA ratio was close to 2:1,[96,97] but this finding was not confirmed by more recent studies.[98] The gender difference relates to the incidence of PDA, but also to the response of PDA to medical treatment.[95] Many studies conducted in adults reported gender differences in drug response, both in pharmacodynamics and pharmacokinetics,[99,100] therefore gender differences in preterm neonates also cannot be underestimated. PDA frequently needs to be treated with drugs to avoid complications and, in case of no response, surgical intervention can be indicated.

Further studies are needed to understand which mechanisms relate to drug response, in order to improve the effectiveness of PDA treatment in preterm infants.

In very preterm infants, male sex is certainly an important risk factor for poor neonatal outcomes and poor neurological and respiratory outcomes at follow-up.

The biological mechanisms responsible for these sex differences remain to be fully understood, and further research is needed.

Perinatal and neonatal asphyxia

Perinatal asphyxia is one of the most important factors causing neonatal neurologic morbidity and mortality. It is also the leading cause of long-term neurocognitive and sensorial dysfunction among survivors. The prevalence of hypoxic-ischemic encephalopathy (HIE) among term neonates is 1-4/1,000 in the industrialized countries, but can reach a significantly higher incidence in low-income countries. Around 20-50% of infants with severe HIE will die in the early neonatal period, and 25-60% of the survivors will suffer from long-lasting neurologic disabilities, including cerebral palsy (CP), seizures and behavioural and learning defects.[101]

Mohamed and Aly compared birth asphyxia in males and females by assessing >9 million births. They found that the OR for severe asphyxia in male newborn was 1.16 (CI: 1.12-1.20; p <0.001).[102] Recently, a meta-analysis showed that male infants have greater long-term IQ impairment than females with a similar degree of HIE.[103] One of the most relevant complications of birth asphyxia is CP, whose European prevalence is 2-3 per 1,000 live births,[104] with a male/female ratio of 1.2.[105]

Experimental research on neonatal hypoxia ischemia (HI) performed in rat models revealed that males are more susceptible to behavioural and neurocognitive deficits compared to females, after a similar degree of brain damage. Moreover, proapoptotic signalling pathways and caspase-independent cell death tendency are markedly different between males and females.[106]

Reactive species of oxygen (ROS) have been linked to several neonatal diseases.[107,108] Recent experimental studies have shown that the mitochondrial respiratory activity is significantly more damaged in males than in females in response to HI. Furthermore, males' endogenous glutathione (the most relevant cytoplasmic non-enzymatic antioxidant) stores were substantially lower, and males have a decreased glutathione peroxidase activity following HI injury. Under these circumstances, male rats were significantly more susceptible to HI, as shown by the increased content of oxidation by-products, such as protein carbonyl, in different areas of the brain.[109] Of note, in response to HI, female rats highly express the mitochondrial biogenesis-associated transcription factor Nrf2/GABPα, while males do not. In the presence of free radicals, Nrf2 enhances the expression of multiple anti-oxidant defense-related genes.[107] Consequently, there is an increase in the electron transport chain proteins, that could partially explain the increased resistance of females to respiratory impairment and secondary neuronal damage.[110]

Moreover, in clinical studies males and females show a different predisposition to certain types of seizures. Bilateral infusions of the GABA receptor agonist muscimol identified distinct roles of the anterior or posterior rat SNR in the flurothyl seizure control that follow sex-specific maturational patterns during development. These studies indicate that: the regional functional compartmentalization of the SNR appears only after the third week of life; only the male SNR exhibits muscimol-sensitive proconvulsant effects which, in older animals, are confined to the posterior SNR; the expression of the muscimol-sensitive anticonvulsant effects becomes apparent earlier in females than in males.[111]

Respiratory diseases

There are sex-related differences in many lung diseases in newborns, infants, and young children: there are not only prematurity-related conditions, such as

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respiratory distress syndrome and chronic lung disease, but also lower respiratory tract illnesses, wheezing, asthma, diffuse and interstitial lung diseases, and cystic fibrosis.

The factors responsible for the male/female differences in pediatric respiratory illnesses are not well-known, although there have been many hypotheses.

Anatomic and physiologic mechanisms may explain some of these sex differences, such as airway size, airway muscle bulk, airway reactivity, and airway tone.[90]

Sex differences in lung development start at the beginning of gestation. At the same gestational age, female fetuses present more structurally advanced lungs, and have earlier and more extensive mouth movements, which are thought to be breathing and/or swallowing motions, and which may be linked to lung development.[90,112]

Furthermore, intrauterine environment, infection or maternal smoking affect the sexes differently.

For example, chorioamnionitis reduces forced expiratory flows in preterm females when compared to unexposed females, whereas this difference is not seen in male infants.[113]

Maternal smoking affects both the male and female lung development[114-117] with significant differences between the two sexes. Female fetuses exposed to maternal smoking have greater airway resistance than non-exposed female fetuses, leading to the hypothesis that smoke exposure could cause the 'masculinization' of the airways of the female fetus, with a decrease in airflow rates to levels comparable to males. The effects of maternal smoke exposition on the fetus airways depend also on the genetic differences in detoxifying enzymes[118] and on the underlying genetic predisposition to asthma, with a more significant effect in male fetuses predisposed to asthma (large deficits in lung volume and forced flow rates) compared to female predisposed fetuses (only small deficits in flow rates).[119]

Sex differences are also evident in the morphology, maturation, and growth patterns of the airways and the lung parenchyma. Lung parenchymal growth is the best determinant of airway growth in males. Other factors, such as the genetic ones, appear to be more important for airway growth in females.[120]

Even if males have larger lung volumes, they present decreased forced expiratory flows, especially when corrected for lung volume, since birth. The decrease in the expiratory flow rates in males is evident before any lower respiratory tract illness[121,122] and is probably due to an increased smooth muscle and to thicker airway walls.[123] Higher forced expiratory flows in females could be due to larger central airways, with lower specific airways resistance,[124] which increases faster in males than in females.[125]

The most important sex-related differences have been reported in lower respiratory tract infections, wheezing, asthma and cystic fibrosis.

Males are more frequently hospitalized for lower respiratory tract infections (LRTI), such as bronchiolitis and pneumonia.[126,127]

Many studies showed that the infection rates are similar in the two sexes,[128-130] but males have a smaller airway diameter and an increased airway reactivity, so that common viral infections – i.e. respiratory syncytial virus or rhinovirus – have a more serious course in male infants and children.

Wheezing is often a major clinical finding in children with moderate to severe LRTI in the first years of life, and it appears more common in young males,[131] again because of the smaller airways and the greater bronchial reactivity.

Larger central airways and a decreased airway reactivity in females seem to be protective against severe croup, but females affected by pertussis show increased morbidity and mortality, an issue that should be further investigated.[132-134]

Increased baseline airway reactivity and narrow airways – together with increased IgE levels[135] and higher finding of positive skin tests[136] in young healthy and asymptomatic males – explain why male sex has an increased risk for developing asthma.

Young males also show a greater response to bronchodilators compared to females,[137] suggesting an increased airway tone in males, although such increased airway tone may be dangerous, because a lung insult provoke wheezing easily, by preventing the dilation of the airways, with a subsequent greater risk for more severe attacks.

It is very important to consider that these physiologic differences in asthmatics subjects can suggest the possibility that males and females may respond differently to various drugs.[138,139]

The "gender gap" in cystic fibrosis (CF) differs from the sex differences observed with other childhood respiratory illnesses. After the first year of life, females present an increased mortality compared to males, with a decreased FEV1 and a faster rate of decline in FEV1.[140]

Many studies showed that females are often diagnosed late (4-18 months later than the male patients),[141] and such delayed diagnosis can lead to an increased malnutrition, with a late start of therapies, and with a bad effect on the prognosis for female patients.

Moreover, we can postulate that young females with CF must develop a more severe airway disease before they reach the symptom threshold (and possibly any decrease in lung function) compared to males, since young females have larger airways and a decreased airway reactivity.[142]

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We can speculate that females with CF may tend to develop occult lung involvement (without any treatment), subsequently resulting in a more serious lung disease and a worse prognosis.

It appears evident that males are more vulnerable to most respiratory pediatric diseases, while females are at a greater risk for cystic fibrosis.

A better understanding of these sex-related lung differences could help implement personalized respiratory treatments.

Conclusion

Although the sex ratio at conception is equal in male and female embryos, there is a tendency toward an increased survival of males fetuses.

Male sex is an independent risk factor for adverse pregnancy outcomes, ranging from higher rates of non-reassuring FHR patterns, to increased rates of CS and low Apgar scores. Several adverse events (eg., gestational diabetes, labor dystocia, cord prolapse, nuchal cord, true umbilical cord knots, fetal macrosomia and shoulder dystocia) appear to be more common in male pregnancies. However, the functional and structural development of the lungs and the regulation of cardiorespiratory circulation are substantially more mature in females, therefore the latter are capable to better face fetal-to-neonatal transition and postnatal adaptation. This is particularly true for preterm newborns.

Overall, an intact survival in the neonatal period is significantly higher in female than in male infants.

Despite the evidence of an intrinsic 'weakness' of the male newborn, geographic factors, antenatal care, and gestational age at birth need to be taken into account.

After the neonatal period, morbidity in both ex-preterm and term infants seems to be higher in male sex, mainly during the first year of life, when the rates of respiratory tract infections and trauma are significant higher compared to females.

At present, further studies are needed to determine the appropriate interventions to improve the understanding of gender differences, thus integrating all the best resources for the health of newborns and children.

Key messages

- Sex ratio at conception is equal in male and female embryos, but there is a tendency toward an increase in the survival of males in uterus.
- Premature birth is more common in male fetuses. Although the progresses of neonatal care have improved the outcomes in the very preterm infants, males show greater mortality and morbidity than females.
- Females better counteract the possible difficulties of birth transition and postnatal adaptation, therefore intact survival rate in the neonatal period is significantly higher in female than in male infants.
- Male sex is also a risk factor for adverse pregnancy outcomes, from higher rates of non-reassuring FHR patterns to increased rates of cesarean sections and low Apgar scores. Several adverse events (eg., gestational diabetes, labor dystocia, fetal macrosomia) are more common in male pregnancies.
- Differences between sexes have also been shown in the incidence of childhood respiratory diseases, neurological diseases, and response to drugs during infancy.

Abbreviations

AC: Abdominal circumference
AGA: Appropriate for gestational age
β-Hcg: Beta human chorionic gonadotropin
BMI: Body mass index
BPD: Biparietal diameter
CF: Cystic fibrosis
CLD: Chronic lung disease
CM: Congenital malformation
CP: Cerebral palsy
CS: Cesarean section
CTG: Cardiotocography
CUS: Cerebral ultrasound
CV: Chronic villitis
EFM: Electronic fetal monitoring
ELBW: Extremely low birth weight
FHR: Fetal heart rate
FL: Femur length
GC: Glucocorticoids
GDM: Gestational diabetes mellitus
GR: Glucocorticoids receptors
HC: Head circumference
HI: Hypoxia ischemia

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