

## Gender-related differences in neonatal age

Nicola Laforgia, Manuela Capozza, Antonio Di Mauro, Federico Schettini, Raffaella Panza, Maria Elisabetta Baldassarre

Department of Biomedical Science and Human Oncology, Neonatology and Neonatal Intensive Care Section, University of Bari 'Aldo Moro', Policlinico Hospital, Bari, Italy

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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.<sup>1</sup>

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.<sup>2</sup>

In 1997, the male/female ratio at birth was found to be 1.06%,<sup>3</sup> 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

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 than that for females.<sup>4</sup>

After birth, the overall infant mortality rate for male infants was 21% higher than the rate for female infants,<sup>5</sup> 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.<sup>5</sup>

The exact mechanisms involved in the male biological 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.<sup>6</sup>

## 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 fetus 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 fetus sex may affect several maternal and obstetric outcomes.<sup>7</sup> Pregnancy of a male fetus has been associated with an increased risk of pregnancy complications and adverse obstetrical outcomes.

Sheiner et al.<sup>8</sup> 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.<sup>9</sup>

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,<sup>9</sup> and therefore mean birth weight is higher in boys than girls.<sup>10</sup>

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 (PlGF) and the anti-angiogenic soluble Fms-like tyrosine kinase 1 (s-Flt1), are higher in female fetuses during the first trimester of pregnancies.<sup>11</sup>

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.<sup>12</sup> Other studies have shown that GCs may preferentially increase the production of reactive oxygen species in the placentas of male fetuses.<sup>13,14</sup>

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.<sup>15</sup>

### Intrauterine environment

To determine whether the fetus sex or genotype may influence the adaptive response to the intrauterine environment, Cogollos et al.<sup>16</sup> 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.<sup>17</sup> 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<sup>18</sup> examined placental histopathology, i.e. placental disc weight >the 90<sup>th</sup> 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<sup>19-21</sup> and they were used to obtain different fetal growth charts, based on fetal sex.<sup>22</sup> 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,<sup>23</sup> and leptin levels were found to be higher in the amniotic fluid in IUGR female fetuses than in IUGR male fetuses.<sup>24</sup> A higher incidence of preeclampsia in women carrying female fetuses is one explanation of the lower weight of the latter.<sup>7,25</sup>

Muhihi et al.<sup>26</sup> 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 10<sup>th</sup> 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.<sup>27</sup>

### 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.<sup>28</sup> and Sheiner et al.<sup>8</sup> demonstrated more cases of gestational diabetes mellitus (GDM) in pregnancy with male fetuses.<sup>29</sup>

Another study found that carrying a male fetus is a risk factor of GDM during the first and second pregnancy.<sup>30</sup> 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

by the insulinogenic index (IGI) divided by the homeostatic model assessment (HOMA) of insulin resistance.<sup>30</sup>

A study from Ireland<sup>31</sup> 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.<sup>32</sup> 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.<sup>33</sup> 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.<sup>25</sup> found that female sex was a risk factor for both pregnancy-induced hypertension (PIH) and preeclampsia.

High levels of beta human chorionic gonadotropin ( $\beta$ -hCG) are a well-known risk factor for hypertensive disorders in pregnancy and, apparently, there is a female preponderance in hypertensive pregnancies with elevated  $\beta$ -hCG levels.<sup>34</sup>

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.<sup>35</sup>

The renin-angiotensin system during early gestation shows sex-related differences. Sykes et al.<sup>36</sup> 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.<sup>37</sup> 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.,<sup>38</sup> 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.<sup>39,40</sup> Dawes et al.<sup>41</sup> 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.<sup>42</sup> found a higher heart rate variability throughout gestation in males, and Bernardes et al.<sup>43</sup> 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.<sup>44</sup> 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).<sup>45</sup> 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,<sup>46</sup> probably due to lower levels of catecholamines in response to the asphyxia seen in male fetuses.<sup>47</sup>

### 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 fetoplacental 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.,<sup>48</sup> 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<sup>49</sup> or a higher number of cases in female pregnancies,<sup>50</sup> although cultural factors promoting male births in these countries could be a bias.<sup>48</sup> 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.<sup>51</sup> Congenital mal-



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,<sup>52</sup> whereas neural tube defects<sup>53</sup> and cleft palate<sup>54</sup> 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.<sup>55</sup> 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.<sup>56-59</sup>

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.<sup>60</sup>

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.<sup>60</sup>

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.<sup>56</sup>

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.<sup>61,62</sup> 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  $\geq 20$  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.<sup>56</sup>

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

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.<sup>64</sup>

It is known that male gonads begin to differentiate during the 7<sup>th</sup> week of development, and the testes begin to secrete testosterone during the 8<sup>th</sup> week of development, while female gonads do not begin to differentiate until the 12<sup>th</sup> week of gestation. Since from the 8<sup>th</sup> week of development testosterone levels are much higher in the male fetus than in the female fetus,<sup>65,66</sup> 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.<sup>56</sup>

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 7<sup>th</sup> 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.<sup>56</sup>

Sex hormone interaction and system development have been cited as two possible causes of sex differences in some anomalies, including cleft palate and lip.<sup>67</sup> 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,<sup>56,68</sup> 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.

### *Response to drugs*

It has not been long since sex was taken into account in the evaluation of the response to drugs.<sup>69</sup> 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.<sup>70</sup>

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.<sup>71</sup>

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.<sup>72</sup>

### *Prematurity and related diseases*

Premature birth is more common in male fetuses, compared to female.<sup>73</sup> 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.<sup>74-78</sup> 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.<sup>49,79</sup> Male fetuses are exposed to higher levels of androgen and Mullerian inhibiting substance, which both adversely affect surfactant production,<sup>80,81</sup> 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 phos-

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

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.<sup>76</sup>

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.<sup>78</sup>

Gender differences in lung function have been demonstrated in term<sup>87</sup> and preterm<sup>88</sup> 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,<sup>89</sup> but be affected by the narrow airways and the increased airway reactivity in males.<sup>90,91</sup>

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

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

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.<sup>93</sup>

No definitive perinatal, neonatal, or postnatal causative factors have been identified up to date.<sup>94</sup>

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.<sup>95</sup>

In some studies, the female-to-male PDA ratio was close to 2:1,<sup>96,97</sup> but this finding was not confirmed by more recent studies.<sup>98</sup> The gender difference relates to the incidence of PDA, but also to the response of PDA to medical treatment.<sup>95</sup> Many studies conducted in adults reported gender differences in drug response, both in pharmacodynamics and pharmacokinetics,<sup>99,100</sup> 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.<sup>101</sup>

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 new-

born was 1.16 (CI: 1.12-1.20;  $p < 0.001$ ).<sup>102</sup> Recently, a meta-analysis showed that male infants have greater long-term IQ impairment than females with a similar degree of HIE.<sup>103</sup> One of the most relevant complications of birth asphyxia is CP, whose European prevalence is 2-3 per 1,000 live births,<sup>104</sup> with a male/female ratio of 1.2.<sup>105</sup>

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.<sup>106</sup>

Reactive species of oxygen (ROS) have been linked to several neonatal diseases.<sup>107,108</sup> 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.<sup>109</sup> Of note, in response to HI, female rats highly express the mitochondrial biogenesis-associated transcription factor Nrf2/GABP $\alpha$ , while males do not. In the presence of free radicals, Nrf2 enhances the expression of multiple anti-oxidant defense-related genes.<sup>107</sup> 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.<sup>110</sup>

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 anti-convulsant effects becomes apparent earlier in females than in males.<sup>111</sup>

### *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

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.<sup>90</sup>

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.<sup>90,112</sup>

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.<sup>113</sup>

Maternal smoking affects both the male and female lung development<sup>114-117</sup> 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 air-flow 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<sup>118</sup> 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).<sup>119</sup>

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.<sup>120</sup>

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<sup>121,122</sup> and is probably due to an increased smooth muscle and to thicker airway walls.<sup>123</sup> Higher forced expiratory flows in females could be due to larger central airways, with lower specific airways resistance,<sup>124</sup> which increases faster in males than in females.<sup>125</sup>

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.<sup>126,127</sup>

Many studies showed that the infection rates are similar in the two sexes,<sup>128-130</sup> 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,<sup>131</sup> 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.<sup>132-134</sup>

Increased baseline airway reactivity and narrow airways – together with increased IgE levels<sup>135</sup> and higher finding of positive skin tests<sup>136</sup> 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,<sup>137</sup> 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.<sup>138,139</sup>

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.<sup>140</sup>

Many studies showed that females are often diagnosed late (4-18 months later than the male patients),<sup>141</sup> 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.<sup>142</sup>



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 cardio-respiratory 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

## References

- Legato MJ. Preface. *Princ Gend-Specif. Med.* 2010.
- Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. *Pediatrics.* 1971;48(6):902-6.
- Maconochie N, Roman E. Sex ratios: are there natural variations within the human population? *BJOG Int J Obstet Gynaecol.* 1997;104(9):1050-3.
- Lorente-Pozo S, Parra-Llorca A, Torres B, Torres-Cuevas I, Nuñez-Ramiro A, Cernada M et al. Influence of sex on gestational complications, fetal-to-neonatal transition, and postnatal adaptation. *Front Pediatr.* 2018;6.
- Mathews TJ, MacDorman MF. Infant mortality statistics from the 2009 period linked birth/infant death data set. *Natl Vital Stat Rep.* 2013;61(8):1-27.
- Bennet L. Sex, drugs and rock and roll: tales from preterm fetal life: preterm fetal responses to asphyxia. *J Physiol.* 2017;595(6):1865-81.
- Al-Qaraghoul M, Fang YMV. Effect of fetal sex on maternal and obstetric outcomes. *Front Pediatr.* 2017;5:1-10.
- Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. *Fetal Diagn Ther.* 2004;19(4):366-9.
- Alur P. Sex differences in nutrition, growth, and metabolism in preterm infants. *Front Pediatr.* 2019;7.
- Centre for longitudinal studies 2006 the millennium studies [Internet]. Available from: <http://www.cls.ioe.ac.uk/studies.asp?section=000100020001>.
- Broere-Brown ZA, Baan E, Schalekamp-Timmermans S, Verburg BO, Jaddoe VWV, Steegers EAP. Sex-specific differences in fetal and infant growth patterns: a prospective population-based cohort study. *Biol Sex Differ.* 2016; 7(1).
- Mayhew TM, Jenkins H, Todd B, Clifton VL. Maternal asthma and placental morphometry: effects of severity, treatment and fetal sex. *Placenta.* 2008;29(4):366-73.
- Stark MJ, Hodyl NA, Wright IMR, Clifton V. The influence of sex and antenatal betamethasone exposure on vasoconstrictors and the preterm microvasculature. *J Matern Fetal Neonatal Med.* 2011;24(10):1215-20.
- Stark MJ, Hodyl NA, Wright IMR, Clifton VL. Influence of sex and glucocorticoid exposure on preterm placental pro-oxidant-antioxidant balance. *Placenta.* 2011;32(11): 865-70.
- Bivol S, Owen SJ, Rose-Meyer RB. Glucocorticoid-induced changes in glucocorticoid receptor mRNA and protein expression in the human placenta as a potential factor for altering fetal growth and development. *Reprod Fertil Dev.* 2017;29(5):845.
- Cogollos L, Garcia-Contreras C, Vazquez-Gomez M, Astiz S, Sanchez-Sanchez R, Gomez-Fidalgo E et al. Effects of fetal genotype and sex on developmental response to maternal malnutrition. *Reprod Fertil Dev.* 2017;29(6):1155-68.
- Mandò C, Calabrese S, Mazzocco MI, Novielli C, Anelli GM, Antonazzo P et al. Sex specific adaptations in placental biometry of overweight and obese women. *Placenta.* 2016;38:1-7.
- Leon-Garcia SM, Roeder HA, Nelson KK, Liao X, Pizzo DP, Laurent LC et al. Maternal obesity and sex-specific differences in placental pathology. *Placenta.* 2016;38: 33-40.
- Schwärzler P, Bland JM, Holden D, Campbell S, Ville Y. Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15-40 weeks of gestation. *Ultrasound Obstet Gynecol.* 2004;23(1):23-9.
- Lampl M, Gotsch F, Kusanovic JP, Gomez R, Nien JK, Frongillo EA et al. Sex differences in fetal growth responses to maternal height and weight. *Am J Hum Biol.* 2010;22(4):431-43.
- Melamed N, Meizner I, Mashiach R, Wiznitzer A, Glezerman M, Yogev Y. Fetal sex and intrauterine growth patterns. *J. Ultrasound Med.* 2013;32(1):35-43.
- Rizzo G, Prefumo F, Ferrazzi E, Zanardini C, Di Martino D, Boito S et al. The effect of fetal sex on customized fetal growth charts. *J. Matern. Fetal Neonatal Med.* 2016;29(23):3768-75.
- Acromite M, Ziotopoulou M, Orlova C, Mantzoros C. Increased leptin levels in preeclampsia: associations with BMI, estrogen and SHBG levels. *Hormones.* 2004;3(1): 46-52.
- Cagnacci A, Arangino S, Caretto S, Mazza V, Volpe A. Sexual dimorphism in the levels of amniotic fluid leptin in pregnancies at 16 weeks of gestation: relation to fetal growth. *Eur J Obstet Gynecol Reprod Biol.* 2006;124(1): 53-7.
- Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. *J Reprod Immunol.* 2011;89(2):133-9.
- Muhihi A, Sudfeld CR, Smith ER, Noor RA, Mshamu S, Briegleb C et al. Risk factors for small-for-gestational-age and preterm births among 19,269 Tanzanian newborns. *BMC Pregnancy Childbirth.* 2016;16(1).
- Morley R, Fewtrell MS, Abbott RA, Stephenson T, MacFadyen U, Lucas A. Neurodevelopment in children born small for gestational age: a randomized trial of nutrient-enriched versus standard formula and comparison with a reference breastfed group. *Pediatrics.* 2004;113(3 Pt 1):515-21.
- Verburg PE, Tucker G, Scheil W, Erwich JJHM, Dekker GA, Roberts CT. Sexual dimorphism in adverse pregnancy outcomes. A retrospective Australian population study 1981-2011. *PloS One.* 2016;11(7):e0158807.
- Xiao L, Zhao JP, Nuyt AM, Fraser WD, Luo ZC. Female fetus is associated with greater maternal insulin resistance in pregnancy. *Diabet Med.* 2014;31(12):1696-701.
- Retnakaran R, Shah BR. Fetal sex and the natural history of maternal risk of diabetes during and after pregnancy. *J Clin Endocrinol Metab.* 2015;100(7):2574-80.
- Walsh JM, Segurado R, Mahony RM, Foley ME, McAuliffe FM. The effects of fetal gender on maternal and fetal insulin resistance. *PloS One.* 2015;10(9):e0137215.
- Shields BM, Knight B, Hopper H, Hill A, Powell RJ, Hattersley AT et al. Measurement of cord insulin and insulin-related peptides suggests that girls are more insulin resistant than boys at birth. *Diabetes Care.* 2007;30(10): 2661-6.

33. Eder M, Csapo B, Wadsack C, Haas J, Catalano PM, Desoye G et al. Sex differences in the association of cord blood insulin with subcutaneous adipose tissue in neonates. *Int J Obes.* 2016;40(3):538-42.
34. Zheng Q, Deng Y, Zhong S, Shi Y. Human chorionic gonadotropin, fetal sex and risk of hypertensive disorders of pregnancy: a nested case-control study. *Pregnancy Hypertens.* 2016;6(1):17-21.
35. Steier JA, Myking OL, Bergsjø PB. Correlation between fetal sex and human chorionic gonadotropin in peripheral maternal blood and amniotic fluid in second and third trimester normal pregnancies. *Acta Obstet Gynecol Scand.* 1999;78(5):367-71.
36. Sykes SD, Pringle KG, Zhou A, Dekker GA, Roberts CT, Lumbers ER. Fetal sex and the circulating renin-angiotensin system during early gestation in women who later develop preeclampsia or gestational hypertension. *J Hum Hypertens.* 2014;28(2):133-9.
37. Gray C, Vickers MH, Dyson RM, Reynolds CM, Berry MJ. Magnesium sulfate has sex-specific, dose-dependent vasodilator effects on preterm placental vessels. *Biol Sex Differ.* 2015;6(1):22.
38. Kim KN, Park Y-S, Hoh J-K. Sex-related differences in the development of fetal heart rate dynamics. *Early Hum Dev.* 2016;93:47-55.
39. Druzin ML, Hutson JM, Edersheim TG. Relationship of baseline fetal heart rate to gestational age and fetal sex. *Am J Obstet Gynecol.* 1986;154(5):1102-3.
40. Ogueh O, Steer P. Gender does not affect fetal heart rate variation. *BJOG Int J Obstet Gynaecol.* 1998;105(12):1312-4.
41. Dawes NW, Dawes GS, Moulden M, Redman CWG. Fetal heart rate patterns in term labor vary with sex, gestational age, epidural analgesia, and fetal weight. *Am J Obstet Gynecol.* 1999;180(11):181-7.
42. DiPietro JA, Costigan KA, Shupe AK, Pressman EK, Johnson TR. Fetal neurobehavioral development: associations with socioeconomic class and fetal sex. *Dev Psychobiol.* 1998;33(1):79-91.
43. Bernardes J, Gonçalves H, Ayres-de-Campos D, Rocha AP. Linear and complex heart rate dynamics vary with sex in relation to fetal behavioural states. *Early Hum Dev.* 2008;84(7):433-9.
44. Amorim-Costa C, Cruz J, Ayres-de-Campos D, Bernardes J. Gender-specific reference charts for cardiocardiographic parameters throughout normal pregnancy: a retrospective cross-sectional study of 9701 fetuses. *Eur J Obstet Gynecol Reprod Biol.* 2016;199:102-7.
45. Sheiner E, Hadar A, Hallak M, Katz M, Mazor M, Shoham-Vardi I. Clinical significance of fetal heart rate tracings during the second stage of labor. *Obstet Gynecol.* 2001;97(5 Pt 1):747-52.
46. Porter AC, Triebwasser JE, Tuuli M, Caughey AB, Macones GA, Cahill AG. Fetal sex differences in intrapartum electronic fetal monitoring. *Am J Perinatol.* 2016;33(8):786-90.
47. Greenough A, Lagercrantz H, Pool J, Dahlin I. Plasma catecholamine levels in preterm infants. Effect of birth asphyxia and Apgar score. *Acta Paediatr Scand.* 1987;76(1):54-9.
48. Mondal D, Galloway TS, Bailey TC, Mathews F. Elevated risk of stillbirth in males: systematic review and meta-analysis of more than 30 million births. *BMC Med.* 2014;12:220.
49. Nielsen BB, Liljestrand J, Hedegaard M, Thilsted SH, Joseph A. Reproductive pattern, perinatal mortality and sex preference in rural Tamil Nadu, South India: community based, cross sectional study. *Br Med J.* 1997;314(7093):1521-4.
50. Xu B, Rantakallio P, Järvelin MR, Fang XL. Sex differentials in perinatal mortality in China and Finland. *Soc Biol.* 1997;44(3-4):170-8.
51. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE et al. for the National birth defects prevention network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birt Defects Res A Clin Mol Teratol.* 2010;88(12):1008-16.
52. Hay S. Sex differences in the incidence of certain congenital malformations: a review of the literature and some new data. *Teratology.* 1971;4(3):277-86.
53. Deak KL, Siegel DG, George TM, Gregory S, Ashley-Koch A, Speer MC et al. Further evidence for a maternal genetic effect and a sex-influenced effect contributing to risk for human neural tube defects. *Birt Defects Res A Clin Mol Teratol.* 2008;82(10):662-9.
54. Natsume N, Kawai T, Ogi N, Yoshida W. Maternal risk factors in cleft lip and palate: case control study. *Br J Oral Maxillofac Surg.* 2000;38(1):23-5.
55. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. *Birt Defects Res A Clin Mol Teratol.* 2014;100(2):79-91.
56. Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. *Teratology.* 2001;64(5):237-51.
57. Shaw GM, Carmichael SL, Kaidarova Z, Harris JA. Differential risks to males and females for congenital malformations among 2.5 million California births, 1989-1997. *Birt Defects Res A Clin Mol Teratol.* 2003;67(12):953-8.
58. Rittler M, López-Camelo J, Castilla EE. Sex ratio and associated risk factors for 50 congenital anomaly types: clues for causal heterogeneity. *Birt Defects Res A Clin Mol Teratol.* 2004;70(1):13-9.
59. Tennant PWC, Samarasekera SD, Pless-Mulloli T, Rankin J. Sex differences in the prevalence of congenital anomalies: a population-based study. *Birt Defects Res A Clin Mol Teratol.* 2011;91(10):894-901.
60. Egbe A, Uppu S, Lee S, Stroustrup A, Ho D, Srivastava S. Congenital malformations in the newborn population: a population study and analysis of the effect of sex and prematurity. *Pediatr Neonatol.* 2015;56(1):25-30.
61. Cragan JD, Roberts HE, Edmonds LD, Khoury MJ, Kirby RS, Shaw GM et al. Surveillance for anencephaly and spina bifida and the impact of prenatal diagnosis-United States, 1985-1994. *MMWR CDC Surveill Summ.* 1995;44(4):1-13.

62. Forrester MB, Merz RD, Yoon PW. Impact of prenatal diagnosis and elective termination on the prevalence of selected birth defects in Hawaii. *Am J Epidemiol.* 1998;148(12):1206-11.
63. Hook EB, Regal RR. Conceptus viability, malformation, and suspect mutagens or teratogens in humans. The Yule-Simpson paradox and implications for inferences of causality in studies of mutagenicity or teratogenicity limited to human livebirths. *Teratology.* 1991;43(1):53-9.
64. Fernando J, Arena P, Smith DW. Sex liability to single structural defects. *Am J Dis Child.* 1978;132(10):970-2.
65. Reyes FI, Boroditsky RS, Winter JS, Faiman C. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. *J Clin Endocrinol Metab.* 1974;38(4):612-7.
66. Winter JS, Faiman C, Reyes FI. Sex steroid production by the human fetus: its role in morphogenesis and control by gonadotropins. *Birth Defects Orig Artic Ser.* 1977;13(2):41-58.
67. Nagase Y, Natsume N, Kato T, Hayakawa T. Epidemiological analysis of cleft lip and/or palate by cleft pattern. *J Maxillofac Oral Surg.* 2010;9(4):389-95.
68. Lubinsky MS. Classifying sex biased congenital anomalies. *Am J Med Genet.* 1997;69(3):225-8.
69. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacol Res.* 2007;55:81-95.
70. Curvello V, Hekierski H, Riley J, Vavilala M, Armstead WM. Sex and age differences in phenylephrine mechanisms and outcomes after piglet brain injury. *Pediatr Res.* 2017;82(1):108-13.
71. Ohlsson A, Roberts RS, Schmidt B, Davis P, Moddeman D, Saigal S et al. Male/female differences in indomethacin effects in preterm infants. *J Pediatr.* 2005;147(6):860-2.
72. Campesi I, Occhioni S, Capobianco G, Fois M, Montella A, Dessole S et al. Sex-specific pharmacological modulation of autophagic process in human umbilical artery smooth muscle cells. *Pharmacol Res.* 2016;113(Pt A):166-74.
73. Zeitlin J, Saurel-Cubizolles M-J, De Mouzon J, Rivera L, Ancel P-Y, Blondel B et al. Fetal sex and preterm birth: are males at greater risk? *Hum Reprod Oxf Engl.* 2002;17(10):2762-8.
74. Brothwood M, Wolke D, Gamsu H, Benson J, Cooper D. Prognosis of the very low birthweight baby in relation to gender. *Arch Dis Child.* 1986;61(6):559-64.
75. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. *Arch Dis Child Fetal Neonatal Ed.* 2000;83(3):F182-5.
76. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics.* 2000;106(4):659-71.
77. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. *Early Hum Dev.* 1999;53(3):193-218.
78. Peacock JL, Marston L, Marlow N, Calvert SA, Greenough A. Neonatal and infant outcome in boys and girls born very prematurely. *Pediatr Res.* 2012;71(3):305-10.
79. Torday JS, Nielsen HC, Fencel M de M, Avery ME. Sex differences in fetal lung maturation. *Am Rev Respir Dis.* 1981;123(2):205-8.
80. Catlin EA, Powell SM, Manganaro TE, Hudson PL, Ragin RC, Epstein J et al. Sex-specific fetal lung development and müllerian inhibiting substance. *Am Rev Respir Dis.* 1990;141(2):466-70.
81. McMillan EM, King GM, Adamson IY. Sex hormones influence growth and surfactant production in fetal lung explants. *Exp Lung Res.* 1989;15(2):167-79.
82. Fleisher B, Kulovich MV, Hallman M, Gluck L. Lung profile: sex differences in normal pregnancy. *Obstet Gynecol.* 1985;66(3):327-30.
83. Jones HP, Karuri S, Cronin CMG, Ohlsson A, Peliowski A, Synnes A et al. Actuarial survival of a large canadian cohort of preterm infants. *BMC Pediatr.* 2005;5:40.
84. Thomas MR, Marston L, Rafferty GF, Calvert S, Marlow N, Peacock JL et al. Respiratory function of very prematurely born infants at follow up: influence of sex. *Arch Dis Child Fetal Neonatal Ed.* 2006;91(3):F197-201.
85. Greenough A, Limb E, Marston L, Marlow N, Calvert S, Peacock J. Risk factors for respiratory morbidity in infancy after very premature birth. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(4):F320-3.
86. Marlow N, Greenough A, Peacock JL, Marston L, Limb ES, Johnson AH et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed.* 2006;91(5):F320-6.
87. Jones M, Castile R, Davis S, Kisling J, Filbrun D, Flucke R et al. Forced expiratory flows and volumes in infants. Normative data and lung growth. *Am J Respir Crit Care Med.* 2000;161(2 Pt 1):353-9.
88. Hoo AF, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. *Am J Respir Crit Care Med.* 1998;158(3):700-5.
89. Martinez A, Dargaville P, Taeusch H. *Epidemiology of bronchopulmonary dysplasia: clinical risk factors and associated clinical conditions.* 1st ed. New York, NY: Marcel Dekker; 2000.
90. Liptzin DR, Landau LI, Taussig LM. Sex and the lung: observations, hypotheses, and future directions. *Pediatr Pulmonol.* 2015;50(12):1159-69.
91. Naeye RL, Freeman RK, Blanc WA. Nutrition, sex, and fetal lung maturation. *Pediatr Res.* 1974;8(3):200-4.
92. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR et al. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(2):F134-40.
93. Kozhemiako N, Nunes AS, Vakorin VA, Chau CMY, Moiseev A, Ribary U et al. Sex differences in brain connectivity and male vulnerability in very preterm children. *Hum Brain Mapp.* 2020;41(2):388-400.



94. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD, Nichd Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. *Acta Paediatr.* 2006;95(10):1239-48.
95. Pourarian S, Farahbakhsh N, Sharma D, Cheriki S, Bijanzadeh F. Prevalence and risk factors associated with the patency of ductus arteriosus in premature neonates: a prospective observational study from Iran. *J Matern Fetal Neonatal Med.* 2017;30(12):1460-4.
96. Schneider DJ, Moore JW. Patent ductus arteriosus. *Circulation.* 2006;114(17):1873-82.
97. Forsey JT, Elmasry OA, Martin RP. Patent arterial duct. *Orphanet J Rare Dis.* 2009;4:17.
98. Chen Y-Y, Wang H-P, Chang J-T, Chiou Y-H, Huang Y-F, Hsieh K-S et al. Perinatal factors in patent ductus arteriosus in very low-birthweight infants: influence of hemoglobin on Pda in Vlb. *Pediatr Int.* 2014;56(1):72-6.
99. Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. *J Biomed Biotechnol.* 2011;2011:187103.
100. Whitley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician.* 2009;80(11):1254-8.
101. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(4):F346-58.
102. Mohamed MA, Aly H. Impact of race on male predisposition to birth asphyxia. *J Perinatol.* 2014;34(6):449-52.
103. Smith AL, Alexander M, Rosenkrantz TS, Sadek ML, Fitch RH. Sex differences in behavioral outcome following neonatal hypoxia ischemia: Insights from a clinical meta-analysis and a rodent model of induced hypoxic ischemic brain injury. *Exp Neurol.* 2014;254:54-67.
104. Surveillance of cerebral palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol.* 2000;42(12):816-24.
105. Gowda VK, Kumar A, Shivappa SK, Srikanteswara PK, Shivananda S, Mahadeviah MS. Clinical profile, predisposing factors, and associated co-morbidities of children with cerebral palsy in South India. *J Pediatr Neurosci.* 2015;10(2):108-13.
106. Hill CA, Fitch RH. Sex differences in mechanisms and outcome of neonatal hypoxia-ischemia in rodent models: implications for sex-specific neuroprotection in clinical neonatal practice. *Neurol Res Int.* 2012;2012:867531.
107. Torres-Cuevas I, Parra-Llorca A, Sánchez-Illana A, Nuñez-Ramiro A, Kuligowski J, Cháfer-Pericás C et al. Oxygen and oxidative stress in the perinatal period. *Redox Biol.* 2017;12:674-81.
108. Laforgia N, Di Mauro A, Guarnieri GF, Varvara D, De Cosmo L, Panza R et al. The role of oxidative stress in the pathomechanism of congenital malformations. *Oxid Med Cell Longev.* 2018;2018.
109. Demarest TG, Schuh RA, Waite EL, Waddell J, McKenna MC, Fiskum G. Sex dependent alterations in mitochondrial electron transport chain proteins following neonatal rat cerebral hypoxic-ischemia. *J Bioenerg Biomembr.* 2016;48(6):591-8.
110. Demarest TG, Schuh RA, Waddell J, McKenna MC, Fiskum G. Sex-dependent mitochondrial respiratory impairment and oxidative stress in a rat model of neonatal hypoxic-ischemic encephalopathy. *J Neurochem.* 2016;137(5):714-29.
111. Giorgi FS, Galanopoulou AS, Moshé SL. Sex dimorphism in seizure-controlling networks. *Neurobiol Dis.* 2014;72(PB):144-52.
112. Hepper PG, Shannon EA, Dornan JC. Sex differences in fetal mouth movements. *Lancet Lond Engl.* 1997;350(9094):1820.
113. Jones MH, Corso AL, Tepper RS, Edelweiss MIA, Friedrich L, Pitrez PMC et al. Chorioamnionitis and subsequent lung function in preterm infants. *PloS One.* 2013;8(12):e81193.
114. Gilliland FD, Berhane K, Li Y-F, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med.* 2003;167(6):917-24.
115. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H et al. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis.* 1992;145(5):1129-35.
116. Milner AD, Marsh MJ, Ingram DM, Fox GE, Susiva C. Effects of smoking in pregnancy on neonatal lung function. *Arch Dis Child Fetal Neonatal Ed.* 1999;80(1):F8-14.
117. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet Lond Engl.* 1996;348(9034):1060-4.
118. Cutolo M, Brizzolara R, Atzeni F, Capellino S, Straub RH, Puttini PCS. The immunomodulatory effects of estrogens: clinical relevance in immune-mediated rheumatic diseases. *Ann N Y Acad Sci.* 2010;1193:36-42.
119. Li YF, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB et al. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. *Am J Respir Crit Care Med.* 2000;162(6):2097-104.
120. Pagtakhan RD, Bjelland JC, Landau LI, Loughlin G, Kaltenborn W, Seeley G et al. Sex differences in growth patterns of the airways and lung parenchyma in children. *J Appl Physiol.* 1984;56(5):1204-10.
121. Martinez FD, Morgan WJ, Wright AL, Holberg C, Tauszig LM. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. *Group Health Medical Associates. Am Rev Respir Dis.* 1991;143(2):312-6.
122. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Tauszig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med.* 1988;319(17):1112-7.
123. McKay K. Gender differences in airway wall structure in infant lungs. *Am J Respir Crit Care Med.* 2000;161:A111.
124. Doershuk CF, Fisher BJ, Matthews LW. Specific airway resistance from the perinatal period into adulthood. Alterations in childhood pulmonary disease. *Am Rev Respir Dis.* 1974;109(4):452-7.

125. Belgrave DCM, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med.* 2014;189(9):1101-9.
126. Glezen WP, Loda FA, Clyde WA, Senior RJ, Sheaffer CI, Conley WG et al. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J Pediatr.* 1971;78(3):397-406.
127. Kaneko M, Watanabe J, Ueno E, Hida M, Sone T. Risk factors for severe respiratory syncytial virus-associated lower respiratory tract infection in children. *Pediatr Int.* 2001;43(5):489-92.
128. Glezen P, Denny FW. Epidemiology of acute lower respiratory disease in children. *N Engl J Med.* 1973;288(10):498-505.
129. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson children's respiratory study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol.* 1989;129(6):1232-46.
130. Parrott RH, Kim HW, Arrobio JO, Hodes DS, Murphy BR, Brandt CD et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. *Am J Epidemiol.* 1973;98(4):289-300.
131. Wright AL, Stern DA, Kauffmann F, Martinez FD. Factors influencing gender differences in the diagnosis and treatment of asthma in childhood: the Tucson children's respiratory study. *Pediatr Pulmonol.* 2006;41(4):318-25.
132. Halperin SA, Wang EE, Law B, Mills E, Morris R, Déry P et al. Epidemiological features of pertussis in hospitalized patients in Canada, 1991-1997: report of the immunization monitoring program-active (Impact). *Clin Infect Dis.* 1999;28(6):1238-43.
133. Mikelova LK, Halperin SA, Scheifele D, Smith B, Ford-Jones E, Vaudry W et al. Predictors of death in infants hospitalized with pertussis: a case-control study of 16 pertussis deaths in Canada. *J Pediatr.* 2003;143(5):576-81.
134. Pertussis Deaths-United States, 2000 [Internet]. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5128a2.htm>.
135. Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. *Clin Exp Allergy.* 1991;21(2):235-41.
136. Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood. I. Gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy.* 1993;23(11):941-8.
137. Landau LI, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. *Pediatr Pulmonol.* 1993;16(1):31-5.
138. Johnston NW, Mandhane PJ, Dai J, Duncan JM, Greene JM, Lambert K et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics.* 2007;120(3):e702-12.
139. Bacharier LB. Management of asthma in preschool children with inhaled corticosteroids and leukotriene receptor antagonists. *Curr Opin Allergy Clin Immunol.* 2008;8(2):158-62.
140. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol.* 1997;145(9):794-803.
141. Lai H-C, Kosorok MR, Laxova A, Makhholm LM, Farrell PM. Delayed diagnosis of US females with cystic fibrosis. *Am J Epidemiol.* 2002;156(2):165-73.
142. Ren CL, Konstan MW, Rosenfeld M, Pasta DJ, Millar SJ, Morgan WJ for the Investigators and coordinators of the epidemiologic study of cystic fibrosis. Early childhood wheezing is associated with lower lung function in cystic fibrosis. *Pediatr Pulmonol.* 2014;49(8):745-50.

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*Correspondence to:*

**Manuela Capozza**

Neonatology and Neonatal Intensive Care Unit  
Department of Biomedical Science and Human Oncology  
'Aldo Moro' University of Bari  
Policlinico Hospital  
Piazza Giulio Cesare 11  
70124 Bari, Italy  
email: manuelacapozza26@gmail.com