

Sex- and Gender-Based Medicine in Pediatrics

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Abstract

The goal of gender medicine is to recognize and analyze the differences between females and males with the aim of ensuring to everyone the best possible diagnostic and therapeutic approach. However, the term gender medicine is not strictly accurate in childhood as in adults, and sex- and gender-based medicine is more appropriate. In the last decade, many studies have been published on gender medicine in adults, but very few data regarding children are available. In this article, an extended summary of the literature will be presented.

Keywords

Pediatrics, gender-based medicine, sex-based medicine.

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Introduction

Sex refers to the genetic and biological status of XX or XY organisms, while gender refers to the social and cultural differences and cultural norms associated with being male or female. The presence of the Y chromosome determines genotypic sex. The expression of the genes in which epigenetics and hormonal processes are important determines phenotypic sex. The term “gender” includes not only the differences in anatomy and physiology, but also the factors related to the environment, society, education, culture and psychology of males and females. Gender is based on the individual’s role in society, his or her self-definitions and expectations from society, manner

of dress and numerous other parameters. Briefly, gender does not depend on biology, but rather upon the social setting. The attributes of gender are fluid; they can change over time or in different regions [1].

The goal of gender medicine is to recognize and analyze the differences between females and males with the ultimate aim of ensuring to everyone the best possible diagnostic and therapeutic approach. However, the term “Gender Medicine” is not strictly accurate in childhood as in adults, and sex- and gender-based medicine is more appropriate.

In the last decade, many studies have been published on gender medicine in adults, but very few data regarding children are available [2-4]. In this article, an extended summary of the literature will be presented.

Child deaths

Sex has a major impact on the outcome of diseases, starting from the beginning of life. Overall, morbidity and mortality rates are higher in males than in females throughout life [5]. During infancy and childhood, increased susceptibility and severity of infectious diseases for males account for this uneven distribution to a large degree [6]. According to the recent UNICEF report, *The State of the World’s Children 2017*, under-5 mortality rates (per thousand) are 43 and 39 in males and females, respectively. These rates 73 and 63 in less developed countries, 84 and 73 in sub-Saharan Africa, but 4 and 4 in Western Europe.

Assessment of gender bias in child mortality is complex, because equality – that is, equal mortality rates for girls – does not imply that there is equity. Under circumstances where there is no discrimination in healthcare, and where girls and boys have the same access to resources and care, higher mortality rates occur among boys due to their greater biological frailty. Some of these differences might be sex-related rather than gender-related [7].

Gender inequality fuels maternal undernutrition and increases the incidence of low birth weight (LBW) babies and of malnutrition of children of both genders. Such malnutrition and associated infectious diseases challenge the survival of children. This pathway is further reinforced by the link between maternal education and child mortality. In 2010, the United Nations Development Programme (UNDP) developed a Gender Inequality Index (GII) which is derived

from five major indicators, including percentage of higher (secondary level and above) education attainment by women, parliamentary representation of women, labour force participation by women, maternal mortality rate, and adolescent fertility rate. GII has a significant positive correlation with neonatal mortality, infant mortality and child mortality rates. Therefore the initiatives to curtail child mortality rates should extend beyond medical interventions, and should prioritize the rights of girls and women [7].

Son preference is widely prevalent in many societies, especially in strongly patriarchal societies, where the cultural and economic value of sons is at a premium which manifests itself in many ways, ranging from differential allocation of household resources, nutrition, medical care and neglect of girl children to female infanticide. Unwanted girls, born to multiparous women without any living sons, have significantly less chance to survive, or they grow up in adverse psychosocial circumstances. Unfortunately, son preference is sanctified by religions [8].

It is clear that the male is more vulnerable from the beginning of life. Caregivers assume that from birth a boy ought always to be tougher than a girl. In addition, in places where males are more highly valued, they get relatively better care [9].

Maternal and fetal disorders

Pregnancies with a male fetus have also been associated with higher rates of complications such as pre-eclampsia, pregnancy-induced hypertension of the mother, intrauterine and early postnatal death and higher risk of fetal distress during labor in males compared with females [10, 11].

In preterms born at < 32 weeks’ gestation, male sex has been associated with increased placental lesions, potentially signifying an aberrant maternal immune response against the male (XY) interstitial trophoblasts [12].

Chorioamnionitis is a major factor resulting in very preterm birth, which may, among others, predispose for early-onset neonatal bacterial infections. A female advantage also could be seen in early-onset neonatal infections with lower rates of mortality observed in girls [13].

The overall prevalence of congenital anomalies is higher among male fetuses, while there are also some subtypes with a higher prevalence among females, including neural tube defects, choanal atresia and cleft palate [14].

Intrauterine growth restriction

Male fetuses are larger in early pregnancies before the onset of intrauterine testosterone secretion. This shows the existence of a significant genetic factor in growth before the onset of hormonal changes [15].

Intrauterine growth restriction (IUGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size. IUGR causes a spectrum of perinatal complications, including fetal morbidity and mortality, iatrogenic prematurity, fetal compromise in labor, need for induction of labor, and cesarean delivery. Fetuses with IUGR who survive the compromised intrauterine environment are at increased risk for neonatal morbidity and mortality. IUGR during fetal development also has a potential to program increased risks for developing a metabolic syndrome later in life, namely obesity, arterial hypertension, hypercholesterolemia, cardiovascular disease, impaired glucose tolerance, or diabetes mellitus type 2 [16]. Fetal sex is not accepted as an independent risk factor for IUGR [17, 18]. On the other hand, boys are more sensitive than girls to intrauterine malnutrition because of their more rapid growth rate.

Uteroplacental insufficiency, the main cause of IUGR, results from impaired placental development that often arises as a consequence of maternal diseases such as preeclampsia, hypertension and metabolic diseases. Inducing uteroplacental insufficiency through bilateral uterine vessel ligation surgery in rats results similar to low birth weight offspring identified in humans, with similar structural changes in both sexes (nephron and β -cell deficits). However, outcomes are highly dependent upon the sex of the offspring, and the programmed disease phenotype (hypertension, glucose intolerance, impaired insulin response) is only evident in male offspring during their adulthood. This suggests that the placentas of males and females respond differentially to adverse events during pregnancy. These sex-specific placental adaptations are often associated with male offspring developing adult diseases, while females are minimally affected [19].

Environmental pollution may also cause IUGR. Prenatal exposure to phthalates widely used as plasticizers is associated with increased risk of IUGR, and male newborns are more sensitive to phthalates than females [20].

There are many reports on the long term effects of exposure to undernutrition during the *in-utero* life by studying adults who were *in utero* during the Dutch Hunger Winter, which was a rapid-onset

and abrupt-end six-month famine that occurred in the Netherlands during the Second World War. Increased body mass index (BMI), waist circumference, adiposity, and a disrupted lipid profile (increased cholesterol and triglycerides) have been observed specifically in females but not males who were exposed to the famine *in utero* [21-23]. Interestingly, famine-exposed males have been shown to have decreased brain volume, suggesting male vulnerability to neurological damage [24].

Maternal obesity

High maternal BMI before and during pregnancy is a predictor of offspring obesity, adiposity, and metabolic syndrome in young adolescents and adults [25]. Among the 2-6-year-old children from obese pregnancies, body fat was found to be increased in boys, but not in girls, compared to children from a normal weight pregnancy [26]. Conversely, in another study, it has been shown that the association between maternal pre-pregnancy BMI and offspring growth pattern from 0 to 7 years of age is stronger in females than males [27]. There is also considerable evidence that females are more susceptible to developmental programming by a diabetic mother or father [25].

The hypothalamus plays a causal role in the development of obesity-associated leptin resistance and disruption of energy homeostasis [28]. A rodent model revealed that male offspring exposure to a high-fat diet during either gestation or lactation displayed decreased leptin sensitivity in the hypothalamus, whereas, in female offspring, decreased leptin sensitivity was caused only by *in-utero* exposure to a high-fat diet, revealing a sexual dimorphism in the timing of programming of leptin sensitivity [29]. A further study investigating the effects of exposure to maternal overnutrition during either gestation or the lactation period has shown female-specific programming of glucose homeostasis also occurs during the *in-utero* period [30]. These animal studies show that females seem particularly susceptible to develop disrupted glucose homeostasis as a result of exposure to *in-utero* undernutrition or high sugar environments, respectively.

Intrauterine testosterone exposure

The testicle begins to secrete testosterone during the 9th week of gestation, and its secretion reaches its peak around the 14th to the 18th week

of gestation, achieving levels close to those of an adult male. Testosterone has various effects on the developing organism, including sex organs, and fetal growth rate. Testosterone also has a significant influence on the differentiation of the brain as male and female brains. Girls with congenital adrenal hyperplasia exposed to increased levels of prenatal androgens prefer masculine toys, such as trucks when playing alone [31]. In addition, gender identity problems in girls with congenital adrenal hyperplasia were not found to be related to the degree of genital virilization or age at which genital reconstructive surgery was done [32]. Women with congenital adrenal hyperplasia have a greater tendency to be sexually attracted to women than do women who were not influenced by overexposure to testosterone during their fetal life [33]. Furthermore, girls exposed to increased levels of testosterone *in utero* exhibit during adolescence a decrease in verbal ability, improved spatial orientation abilities, and heightened aggression as usually seen in males [34]. Women with polycystic ovary syndrome have increased testosterone levels, and when they become pregnant these testosterone levels may affect their female fetuses as more anxiety-like behavior [35].

Mixed-gender twins

Female-female twins have lower early neonatal and infant mortality and decreased risk of respiratory morbidity compared to male-male twins of all gestational ages. In dizygotic twin pairs of opposite sex, male neonates appear protected from respiratory morbidity by having a female co-twin [36]. In dichorionic twin pregnancies, the presence of a female co-twin is associated with higher birth weight, longer duration of pregnancy and higher *in-utero* growth rate, whereas the presence of a male co-twin is associated with increased risk of preterm delivery and prematurity-related morbidity. For female neonates, the presence of a male co-twin is associated with an increased risk of respiratory and neurological morbidity at a similar level to that observed in male twins. Female neonates in male-female twins have also increased risk of intraventricular hemorrhage in comparison with female-female pairs [37].

The findings indicating higher infant mortality and neonatal morbidity in male twins than their female co-twins are supported by a recently published study. According to the US National Center for Health Statistics Linked Birth-Infant

Death Cohort, among the mixed-gender twins, there is no significant difference in fetal mortality between male twins and their female co-twins. However, male twins were at increased odds of neonatal and infant mortality relative to their female co-twins. Congenital abnormalities were identified significantly more frequently in male than female twins. Having low 5-minute Apgar score (< 7), assistant ventilation more than 30 minutes, and respiratory distress syndrome were more common in male twins relative to their female counterparts [38].

Studies on rodents have shown that testosterone from male fetuses transfers to adjacent fetuses via amniotic diffusion [39], and this phenomenon has been proposed to occur also in human twin pregnancies [40]. According to the prenatal testosterone (or twin testosterone transfer) hypothesis, the presence of a male co-twin may have masculinizing effects in women. It is supported by studies on small samples where various aspects of phenotype as BMI [41], tooth crown size [42], the eruption of teeth [43], the second- to fourth-digit ratio [44], leukocyte telomere length [45], and cerebral lateralization [46] are considered. However, its behavioral effects are contradictory [47]. Gender identity disorder (GID) is more common in males than in females. In a small sample with 7 opposite-sex twins, all cases were found to be discordant for GID [48].

Since autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are more prevalent in males than females, it has been suggested that prenatal testosterone exposure of girls increases the risk also for ASD and ADHD [49]. However, it has been reported that girls with a female co-twin had an increased risk of ADHD and slightly elevated autistic traits compared with girls with a male co-twin [50]. Therefore findings of the studies on the prenatal testosterone hypothesis must be evaluated with caution.

Intrauterine stress

Disasters cause an increase in the frequency of spontaneous abortions involving male fetuses among women under major stress (Trivers-Willard effect). According to this theory, males born into a difficult environment should be more robust because the birth of weaker males is blocked by the mechanism of spontaneous abortion that enables the woman to begin a new pregnancy that will lead to the birth of a girl or a more robust boy [51, 52].

Mothers who suffer from increased anxiety and depression during their pregnancies may be more likely to give birth to children with ADHD, particularly in boys [53]. Severe maternal emotional stress during the first trimester of pregnancy, for example in times of war, may increase the risk of schizophrenia in both boys and girls in later life, but this effect is extended into the second trimester in boys only [54, 55]. In another study, it has been found that this risk was four times higher among women than among men [56]. Pregnant rats under emotional stress during their pregnancies gave birth to male rats that exhibited female rather than male sexual behaviour [57].

Prenatal exposures

Boys and girls have mostly similar outcomes when prenatal alcohol exposure is linked to poor physical and neurocognitive development [58]. Nevertheless, sex ratios implicate lower viability and survival of males, and girls have more dysmorphology and neurocognitive impairment than boys [59]. Increased vulnerability in male fetuses to alcohol consumption might be explained by the upsetting of the balance of thyroid hormones in the brain. Thyroid hormone-inactivating enzyme deiodinase-III (Dio3) gene controls how much active thyroid hormone is in the brain. A delicate balance of the thyroid hormone is critically important in the development of the fetal brain. When males inherit a variation of the Dio3 gene from their mother, they do not make enough of this enzyme in their hippocampus to prevent an excess of thyroid hormones. The resulting overdose of the hormones makes the hippocampus vulnerable to damage by even a moderate amount of alcohol [60].

Smoking during pregnancy is associated with long-term consequences on offspring behavior. A higher number of cigarettes per day during pregnancy is significantly associated with higher anxiety/depression and higher attention problems at 3 years, and the associations are stronger for girls compared to boys [61].

Orbitofrontal, middle frontal, and parahippocampal cortical tissues measured using magnetic resonance images are thinner in adolescents exposed *in utero* to maternal smoking, as compared with non-exposed ones, and these differences are more pronounced in female adolescents. In exposed females, the thickness of the orbitofrontal cortex correlates negatively with a self-rated assessment

of caring, one of the components of a model of positive youth development [62].

Intrauterine exposure to cannabis is associated with an increased risk for aggressive behavior and attention problems as early as 18 months of age in girls, but not boys [63]. Offspring's use of cigarettes and marijuana were found to be more pronounced for males than females following prenatal exposure to marijuana [64]. The effect of prenatal cocaine exposure on developing language abilities is stronger for girls than for boys [65, 66].

Antenatal steroids

Placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) maintains low cortisol levels in the fetal circulation, which is required for fetal hypothalamic-pituitary-adrenal (HPA) axis maturation and regulation of steroid synthesis [67]. Therefore, preterm infants exhibit very low plasma cortisol levels without apparent ill effect. However, a lack of an adrenal response to physiological stressors may leave them vulnerable in the first days of life [68]. Very low birth weight (< 1,500 g) male neonates have lower blood pressures than females on day 1 of life [69], and extremely preterm males are more likely to require treatment for hypotension within the first week of life [70].

Administration of glucocorticoids to a pregnant woman at risk of preterm birth to decrease the incidence of RDS and intraventricular hemorrhage (IVH) may also cause suppression of fetal HPA axis, and limits the ability of the preterm neonate to mount an adequate stress response and maintain physiological stability following birth. However, maternal glucocorticoids increase significantly placental 11 β HSD2 activity in females, which decreases the suppression on adrenals, and protect the female fetus from excess glucocorticoid exposure, enabling them to mount a more appropriate adrenal response to perinatal stress [71]. Increase in placental 11 β HSD2 is likely to be dependent on the interactions of multiple glucocorticoid receptor isoforms expressed in the placenta, which shows sex differences [72].

Increase in placental glucocorticoid inactivation in females may also protect them from the antenatal glucocorticoid-induced effects on reactive oxygen species (ROS) production, and could contribute to the pathophysiologic processes underlying ROS diseases of the newborn, such as bronchopulmonary dysplasia, periventricular

leukomalacia, and retinopathy of prematurity, conditions known to exhibit a male excess [73]. Therefore sex difference in the expression of 11 β HSD2 following antenatal steroids may partly explain one of the potential mechanisms underlying the observed excess of male morbidity and mortality following preterm birth [71].

Neonatal disorders

Respiratory distress syndrome

Male gender, apart from the degree of prematurity, is one major factor for respiratory distress syndrome (RDS) [74]. Failure of CPAP and need for intubation and mechanical ventilation, and mortality from RDS are also higher in male neonates [75].

Lung development in female fetuses is more advanced compared with males of an identical gestational age. Lecithin/sphingomyelin ratio as an established indicator of biochemical lung maturation between 28 and 40 weeks of gestation reveals a significant difference in the degree of lung maturation by 1.2-2.5 weeks in favor of female neonates [76]. However, in an animal study it has been shown that the greater morbidity and mortality due to respiratory insufficiency in preterm lambs do not appear to be related to differences in lung structure, the composition of major surfactant phospholipids and the expression of surfactant proteins before birth, but may relate to physiological adaptation to air-breathing including inadequate surfactant function at birth [77].

Higher catecholamine levels in female fetuses before and during birth seem to be important in pulmonary adaptation [78]. A surge in catecholamines in vaginal delivery cause rapid clearance of fetal lung fluid mediated by transepithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells, and enhance surfactant secretion into alveoli [79]. Methyl CpG binding protein 2 (MeCP2) and peroxisome proliferator-activated receptor gamma (PPAR- γ) genes, which are regulators of alveolarisation, are significantly increased in female intrauterine growth restricted rats. Thus, even under the aspect of epigenetic regulation, a female advantage seems to be operative in lung development [80].

To explain the gender difference in the development of RDS, sex hormones were postulated to play a permissive role in lung development by up-

regulating several groups of genes controlling the structural and functional lung development. Male sex differentiation leads testosterone secretion by fetal testes, which begins around 8 weeks of pregnancy, and a peak in plasma testosterone level occurs in between 12-18 weeks of pregnancy, several weeks before the surge of surfactant production by type II alveolar cells, which takes place at around 28th-34th weeks of pregnancy. After 24 weeks of pregnancy, testosterone levels are low in both sexes. Therefore, the male lung is exposed to higher levels of testosterone than females during the mid-gestation, whereas both sexes are exposed to increasing levels of estradiol [81].

Estrogen receptors (ERs) are a group of proteins found inside cells. Two classes of ER exist: ER α and ER β . Both receptors are activated by the hormone estrogen (17 β -estradiol), and are widely expressed in different tissue types, but there are some notable differences in their expression patterns. Although ER α is undetectable in the lung, ER β is abundantly expressed and biologically active in the lung. ER β exert a strong effect on lung differentiation, especially during the transition from saccular to alveolar period of lung development, and in the maturation of pulmonary surfactant synthesis. In female ER β knockout mice, but not in male knockout mice, after birth the number of alveoli, and pulmonary surfactant protein A (SP-A) and pro-surfactant protein C (pro-SP-C) densities are reduced [82]. Prenatal exposition to estrogen and progesterone receptor antagonists in pregnant sows causes a reduced number of alveoli in lung tissues, and diminished vascular growth factor (VEGF, a strong regulator of alveolarisation) gene expression in female neonatal piglets [83]. Androgens delay the biochemical lung maturation [84]. A number of genes involved in structural lung development, and surfactant synthesis and metabolism are negatively modulated by androgens [85-87].

However, the fetal lung is not exclusively and passively exposed to circulating sex hormones, but also has the capacity to synthesize and inactivate them. The expression of androgen-metabolizing enzymes in the fetal lung of both sexes suggests a physiological role for androgens in lung development as in early-branching morphogenesis [74].

In addition, androgens interact with estrogens and/or glucocorticoids to modulate various regulatory proteins such as epidermal growth factor (EGF) and transforming growth factor-beta

(TGF- β). Type II pneumocyte maturation is under the regulation of multiple paracrine factors released by fibroblasts. This cell-to-cell communication is accelerated by glucocorticoids, while androgens blocks and delay do not totally inhibit the positive effect of glucocorticoids in the production of paracrine factors [88], which explain the gender-dependent response to prenatal corticosteroids in favour of females in epidemiological studies [89]. Understanding the effects of sex hormones on glucocorticoid metabolism signaling and function may lead to the development of new prophylactic strategies for lung immaturity [74, 81].

Others

Male gender is a significant risk factor in transient tachypnea of the neonate [90], and persistent pulmonary hypertension [91].

Bronchopulmonary dysplasia (BPD) is more (1.5 times) common in infants with birth weights less than 1,500 g [92, 93]. At preschool age, lung function is more impaired in those children suffering from BPD during the neonatal period, with male gender being the main risk factor [94].

Prognosis

Preterm males are more susceptible to brain injury in the perinatal period [95]. Preterm males have a higher incidence and increased severity of brain lesions, such as IVH and periventricular leukomalacia (PVL) [96, 97]. Extremely preterm male infants also have a higher risk of long-term cognitive, behavioural and neurological sequelae in the absence of severe IVH or PVL [98-103], which may be partly explained with an animal study showing males' increased sensitivity to oxidative stress [104].

The Trial of Indomethacin Prophylaxis in Preterms (TIPP) study was a large randomized controlled trial of indomethacin prophylaxis (3 doses of indomethacin administered at 24-hour intervals in the first days of life) in the prevention of IVH in preterm infants weighing between 500 and 999 g [105]. A significant reduction in IVH was found in males only [106].

Treated males had improved outcomes of death and survival with disability [107], and associated with higher verbal scores at 3 to 8 years of age [106], and less functional MRI abnormalities in key areas of the brain responsible for subsequent language development [108].

Cardiac disorders

D-transposition of the great arteries, left-sided obstructions, and double-outlet right ventricle have a strong male predominance, whereas more girls present with patent ductus arteriosus (PDA), secundum atrial septal defect, and Ebstein anomaly of the tricuspid valve. Other lesions, such as ventricular septal defect and truncus, seem to be equally distributed between sexes [109]. Gender differences are also seen in the treatment of these malformations. Female sex is a risk factor for mortality among children undergoing cardiac surgery [110]. Increased risk of death by a factor of 5.4 is reported in female patients with congenital cardiac disease who required postoperative extracorporeal membrane oxygenation support [111].

Female sex is associated with poor response to indomethacin in small preterm infants with PDA [112, 113]. These gender-based differential responses to indomethacin would be explained by a sexual developmental difference in the prostaglandin responsiveness of the ductal tissue that may prevent spontaneous closure of the ductus in females; or a gender difference in the degree of inhibition of prostaglandin by COX inhibitors [112].

Male-to-female ratio is 2.7:1 in perinatal supraventricular tachycardia [114], 1:1.9 in congenital third-degree atrioventricular block [115]. In a study of complete heart block after viral infections, all patients were female [116]. Although adult women with long QT syndrome are more prone than men to the development of torsades de pointes, there is no gender disparity at birth [117].

Lung disorders

Asthma

Genetic predisposition is known in asthma, but heritability is more pronounced in male offspring. Atopy is a risk factor for asthma. Allergic rhinitis and atopic dermatitis are more common in girls with asthma; however, allergy to grass and dust mites has been more frequent in male patients with asthma. Environmental pollution might be a triggering factor in females. Maternal smoking and child obesity are risk factors in male patients. Low gestational age, as a predisposing factor for asthma, is more prevalent in males [118]. At young adult

age, however, women had a higher risk of asthma than men with a history of very preterm birth [119].

Between the age of 4 and 14 years, asthma is more prevalent in boys compared to girls. However, after puberty, asthma becomes more prevalent and severe in women. Women seem to experience an aggravation of asthma symptoms during the premenstrual or menstrual phases of their cycle. Increased inflammatory response coinciding with hormonal fluctuations could trigger asthma exacerbations in some women [120].

Female patients suffer from more symptoms than males when compared to males with the same baseline pulmonary function tests, and in females the prevalence and severity of the disease increase with age. On the other hand, in children under the age of 12, hospitalization of boys is higher than that of girls, while after the age of 12 the reverse is true [118].

Bronchiectasis and cystic fibrosis

While data are sparse in bronchiectasis children, male to female ratio is 2:1 in patients aged less than 18 years; however, females generally have a worse clinical outcome, more severe infections, and mortality. This gender difference may be explained by sex hormones [121]. Estrogen augments mucin (a key component of mucus) production by regulating MUC58 gene expression [122], and progesterone inhibits airway cilia beat frequency and function, and affects mucociliary clearance [123]. In addition, estrogens dehydrate the airway-surface liquid [124]. These two effects increase susceptibility to microbial colonization and infection. The nature of respiratory pathogens predominant in patients with cystic fibrosis (CF) and non-CF bronchiectasis is gender-specific [125, 126]. Females have higher risks of *P. aeruginosa* colonisation and mucoid conversion in both CF and non-CF bronchiectasis [127].

CF transmembrane conductance regulator (CFTR) is an ion channel protein that conducts chloride ions across epithelial cell membranes. Mutations of the CFTR gene lead to dysregulation of epithelial fluid transport in the lung, pancreas and other organs, resulting in CF. Testosterone, and estrogen (but not progesterone) increase CFTR epithelial expression [128, 129]. Estrogen suppresses the protective acute inflammatory reactions necessary to clear bacterial (including *Pseudomonas spp.*) infection [130], and estrogen promotes the conversion of *P. aeruginosa* from

a non-mucoid to a more pathogenic mucoid phenotype in CF [131].

Gastrointestinal diseases

Coeliac disease

Coeliac disease is more common in females. The gender seems to have an important influence in the manifestations and severity of the disease. In women over 14 years old, a lower percentage of silent pathology and iron-deficient anemia seems to prevail, whereas males seem to have a greater risk of malnutrition and lower bone density [132]. Females show greater levels of autoantibodies [133], and more frequently encoding alleles for DQ2 or DQ8 [134]. On the other hand, patients with coeliac disease have a substantial risk of developing intestinal T cell lymphoma, which is more common in males [135].

Crohn's disease

Crohn's disease has a greater incidence in males during childhood, whereas in females in adulthood [136]. However, the disease is more severe in females [136, 137]. In children with Crohn's disease, in females the body fat levels are significantly lower than in males [138].

One of the theories that explain the greater incidence of Crohn's disease in males during childhood is related to the interleukin-6 gene promoter polymorphism, which is negatively regulated by estrogens [139]. On the other hand, a variant of the DLG5 gene, which is required to maintain intestinal integrity, has a protective effect on susceptibility in females of pediatric age [140].

Others

In children less than 15 years of age who underwent appendectomy, females have more numerous postoperative complications, while males often have intestinal perforations [141]. In children with chronic constipation, the presence of nerve fibers containing substance P in intestinal biopsies, which is associated with slow colonic transit, in females is lower than in males [142].

Hematologic disorders

Hemoglobin levels are similar in male and female infants and gradually rise at the same rate

during childhood. Gender-specific differences in hemoglobin levels begin to emerge in adolescence. In females, the hemoglobin level reaches a plateau during early puberty, while in males the hemoglobin level continues to rise through puberty to higher levels due to androgen secretion. Iron deficiency anemia is more common in adolescent girls because of beginning menstrual blood loss [143].

Sickle cell anemia affects males and females equally but morbidity is higher in males. After the age of 15 years, males have a greater rate of pain attacks due to veno-occlusive crisis [144]. Since nitric oxide is important in maintaining vasomotor tone in addition to its inhibiting effect on platelet aggregation, the basis for the differences could be related to the reduced nitric oxide bioavailability and responsiveness in males [145]. Estrogens facilitate nitric oxide production and limit its consumption, and may increase fetal hemoglobin [146].

Oncologic disorders

Childhood cancer is more frequent in males than in females, with exceptions. There is a striking male preponderance for non-Hodgkin's lymphomas (male:female ratio 3.2 for Burkitt's lymphoma and 1.7 for other non-Hodgkin's lymphomas). However, thyroid cancer is 5 times more frequent in females than in males. Wilms' tumour is slightly more frequent in females than males with the male:female ratio 0.92:1 for unilateral tumors, and 0.60:1 for bilateral cases [143]. In lymphoid leukemia and acute myeloid leukemia, male:female ratio is 1.3. However, some subtypes are more common in females than males, as t(1:19) in acute lymphoblastic leukemia (ALL) and del(5q) in myelodysplastic syndrome [147].

Gender-specific differences are also seen in the outcomes of cancer patients. Girls with acute lymphoblastic leukemia have a better outcome concerning early induction chemotherapy and overall survival when compared to male patients. Boys also have an additional risk of relapse in the testicles [148]. However, in a subgroup of pediatric patients with acute myeloid leukemia, male gender is a positive prognostic factor for survival [149]. On the other hand, females are almost twice as likely as males to develop a second cancer (especially breast cancer) after treatment for Hodgkin's lymphoma in childhood [150].

In children and adolescent patients, the impact of gender seems to vary between the

different histological subtypes of non-Hodgkin's lymphomas. In lymphoblastic T-cell lymphoma and diffuse large B-cell lymphoma, male patients have a better outcome than female patients; other subtypes do not show gender difference [151].

Some differences in response to drugs exist. Females treated for acute lymphoblastic leukemia have more severe long-term side effects than males [152]. Toxic effects of chemotherapy as in doxorubicin-induced cardiomyopathy are higher in girls than boys [153]. Intellectual performance problems following chemotherapy for ALL [154], neurocognitive deficits following radiotherapy plus chemotherapy for medulloblastoma are more frequent in girls than boys [155]. Cranial irradiation in combination with chemotherapy, especially before 4 years of age, can severely compromise developing language and verbal abilities in girls but not in boys [156].

Nephrologic disorders

Kidney diseases

In patients with chronic renal diseases, the prevalence of end-stage renal disease is higher in males than in females. Among children with chronic kidney disease, non-glomerular diseases are more common. In addition, time for development and progression to chronic disease is shorter in males. There is no such gender difference in glomerular disease [157].

During infancy and early childhood, renal failure due to congenital urologic anomalies is predominantly seen in boys. Minimal-change glomerulonephritis is slightly higher in boys than in girls. Girls with steroid-sensitive nephrotic syndrome show a trend towards less frequent post-pubertal recurrences than males [158]. Autosomal recessive polycystic kidney disease is more common in males [159].

Female patients with polycystic kidney diseases, membranous glomerulonephritis, focal-segmental glomerulosclerosis and nephropathies of unknown etiology have a favorable renal outcome compared to males. Renal involvement in several systemic diseases also shows distinct gender-dependent features. For example, renal involvement occurs more frequently and more severely in males with systemic lupus erythematosus. Outcome and survival of renal grafts are much better in female than in male recipients [158].

Urolithiasis

In the first decade of age, kidney stone disease is more prevalent among boys than among girls. In the second decade, girls are affected more often than boys. Overall, however, girls in the pediatric population are more commonly affected by stones than were boys [160]. Calcium containing calculi are the most common in each gender [161].

Endocrine disorders

Obesity

Girls have both greater fat mass and distinct pattern of fat distribution compared with boys from the neonatal period to adulthood. Newborn girls have more fat than male neonates, and exhibit greater subcutaneous fat in the truncal region than do boys, which causes gender-specific reference values for abdominal circumference despite having similar body weights [162, 163].

While maternal weight is positively related to macrosomia in both sexes, and negatively with IUGR in male fetuses, gestational diabetes mellitus is associated with macrosomia in males [164]. Prepubertal girls also have more subcutaneous and visceral fat stores. When puberty begins, however, boys develop a greater waist circumference than do girls, and girls develop greater extremity and hip deposits than boys [165].

Childhood obesity is one of the most serious public health problems of the 21st century without any gender difference [166, 167]. The different incidence of obesity in boys and girls seems to be also the consequence of genetics. In Korean children, it has been recently reported that variations in Sirtuin 1 (a longevity-associated gene) genotypes (GG, GA, and AA) are associated with pediatric obesity. BMI and waist circumference were higher in the GA + AA group than in the GG group in both males and females; the reductions in total cholesterol and low-density lipoprotein cholesterol levels were greater in the GG group in boys; the reductions in insulin resistance levels were greater in the GA + AA group in girls [168].

Obesity leads to early appearance of pubertal signs in girls. In addition, obese girls are also at increased risk of hyperandrogenism. In boys, obesity has been associated with advanced puberty in some studies, whereas others have reported a delay in pubertal onset [169].

In a South African cohort, it has been shown that among females who became obese from the 1-2 years to 13-15 years periods, obesity was persistent, or present during 16-18 years, in 36.1%, while in 16.9% cases in males [170]. The therapeutic-behavioral approach to overweight and obesity should be different between males and females. The reduction of the hours spent in front of the television is an effective weight-loss method in males, while in females it is more useful to promote physical exercise [171]. Asthma and obstructive sleep apnea prevalence or severity is more prominent in obese boys [172, 173].

Type 1 diabetes mellitus

The onset age has two peaks, the first between the age of 5 and 7 and the second during puberty. Between the ages of 5 and 7, the F:M ratio is 1:1.1, while in puberty the ratio is 1:1.7. In the adult age, the ratio is 1:1.5 [174].

In adults, obese males frequently have impaired fasting blood glucose, while obese females have more often insulin resistance syndrome. This difference is not present among children under 12 years of age, which may be related to pubertal changes [175]. Blood C-peptide levels are significantly higher in females than in males, especially during puberty [176].

Among children who are neither overweight nor obese, girls as young as 5 years are more insulin insensitive than boys are before puberty, and it has been speculated that this gender difference may contribute to the female preponderance of type 2 diabetes mellitus in childhood [177, 178]. Puberty is associated with a transient decrease in insulin sensitivity in young men and women; however, this effect is more pronounced in girls. By the completion of pubertal development, both boys and girls restore their insulin sensitivity to what it is before pubertal onset [179]. This transient decrease for both sex could not be explained by sex steroid hormones and BMI [180]. High leptin levels in females may be related to insulin resistance in children and adolescents [181].

Leptin levels are high in females from the newborn period to puberty [182-184], which may be related to the relative insensitivity to leptin compared with males. This theory may be supported by lower soluble leptin receptor levels that enhance leptin action in girls compared with boys [184].

The 1858T allele of the PTPN22 (protein tyrosine phosphatase N22) gene, which is found

in the 1p13 chromosome, encodes a lymphocyte-specific alkaline phosphatase expressed in both the T and B lymphocytes acting as an inhibitor of the pathway of antigen-specific activation of the T lymphocytes. It has been found to be associated with type 1 diabetes pathogenesis in females. The sex hormones may play a role in the expression of PTPN22 gene [185].

Response to hormone therapy

Females have a higher risk of developing congenital hypothyroidism [186]; however, girls with congenital hypothyroidism require lower doses of hormone therapy [187]. Therapy with growth hormone analogs is more effective in males than in females in patients with GH deficiency [188].

Boys aged < 8 years have higher salivary cortisol levels compared to girls, and this pattern is reversed after the age of 8 years. However, there are no gender differences in serum cortisol of boys and girls < 8 years or 8-18 years [189]. However, in patients with congenital adrenal hyperplasia, the needed dosage of hydrocortisone at puberty is significantly higher in males compared to females [190].

Neurological disorders

Male sex is a risk factor for cerebral palsy [191]. In infants born at < 27 weeks gestation who underwent magnetic resonance imaging (MRI) at term equivalent age, myelination was found compromised more frequently in boys, whereas cerebellar abnormalities were more common in girls. These sex-related differences observed on neonatal MRI were found to be correlated with developmental scores at both global and regional levels [192].

Males are more susceptible than females to develop neurological damage from heavy metals such as cadmium, manganese, arsenic and mercury [193]. Prenatal exposure to PCB (polychlorinated biphenyl)-contaminated cooking oil compromise spatial reasoning abilities in boys, but not girls [194].

Psychiatric disorders

Autistic disorders

The prevalence of ASDs is 15 times higher in males than in females. The clinical manifestations

are also different. Males generally have a later onset, and a more severe cognitive impairment, whereas females have fewer problems in communication and language development, but they have social anxiety disorders [195, 196] and a lower intellectual quotient [197].

ADHD is more frequent in males, whereas epilepsy is more frequent in females [193]. Within psychogenic nonepileptic seizures disorders, female children have more frequently atonic falls and long-term crises, while males have tonic-clonic limb movements [198]. In males, crises are frequently associated with school failure and the diagnosis of ADHD, while females frequently have a diagnosis of major depressive disorder [199].

Eating disorders

Although it is known that eating disorders are more frequent in women, recent studies show that the sub-clinical forms of eating disorder, such as occasional binge eating, the use of laxatives, prolonged fasting, are as frequent in males as in females [200], and have higher mortality in males [201], with greater risk to develop co-morbidities such as depression, substance abuse and anxiety [202].

Emotions and pain

The expression of emotions shows gender differences. Females express more frequently internalizing emotions (sadness, anxiety), while males show more externalizing emotions like anger [203].

In pre-pubertal girls and boys, migraine has the same prevalence, but its prevalence changes to 18% for females and 6% for males after puberty. Moreover, the prevalence of one or more common pain complaints is similar among girls and boys before puberty but increased in girls after puberty, which may be related to the higher pain perception in females but not in males [204].

Migraine begins earlier in males than in females, with peak onset between the ages of 5 and 10 years and 12 and 17 years, respectively. Prevalence of non-migraine headache seems to be similar for school-age girls and boys with increasing prevalence for girls after puberty. Moreover, girls seem to have recurrent headaches more than boys [205].

Girls are more than twice as likely as boys to suffer from headaches and abdominal pain, and

they have greater pre-treatment pain severity, and higher depression and anxiety at pre-treatment than boys. Psychological treatment in children with non-headache pain conditions was significantly more effective in females than in males [206].

Skin disorders

In newborns, no gender differences in the development of eczema have been found. However, in the first 6 months of life, the frequency of eczema is higher in boys than girls. In contrast, there is a higher prevalence of eczema in girls than in boys in the preschool ages. Eczema without concomitant respiratory allergies may be more common in girls than in boys, whereas males more commonly have eczema with concomitant respiratory allergies. These findings suggest that girls have atopic eczema less frequently than do boys; however, non-atopic eczema has been noted to occur more commonly in girls [207].

Orthopedic disorders

Female sex is an important risk factor for congenital dysplasia of the hip [208]. Legg-Calvé-Perthes disease (osteonecrosis of the hip) is 4 to 5 times more common in boys than in girls [209]; however, female sex is a poor prognostic factor [210].

Juvenile idiopathic scoliosis is more frequent in females, especially during puberty. Estrogens play a fundamental role in the progression of the spine deformation with pro-osteoclastogenic and counter-osteoclastic effects. The lack of estrogens could, therefore, lead to an increase in bone turnover [211].

Infectious diseases

The prevalence, severity and complications of infectious diseases are generally higher in males, with exceptions [212]. Females display increased innate and adaptive immune responses to most viral infections compared to males [213]. HIV infection in pregnancy can lead to perinatal transmission of HIV *in utero*, intrapartum, or through breastfeeding postpartum. More females are born with HIV infection, because males more often died during pregnancy. On the other hand, males with HIV infection are more frequently malnourished than females [214].

Upper respiratory tract bacterial infections, such as sinusitis and tonsillitis, are found more

frequently in females, whereas lower respiratory tract bacterial infections are more common and more severe in males, with exceptions [212, 215]. As an example, group A streptococcal pharyngitis has a slightly higher incidence in boys [216], and rheumatic fever after streptococcal infection is also observed at higher rates in boys than in girls [217]. Pertussis has higher incidence, severity and mortality rates in females [218, 219]. Male patients less than 2 years have invasive pneumococcal disease rates 1.5-2 times higher than females [220]. Atypical pneumonia due to *M. pneumoniae* shows a clear predominance in females [221]. Tuberculosis incidence is similar in males and females during childhood [222]. Expression of bacterial inflammatory markers such as C-reactive protein, neutrophil count and erythrocyte sedimentation rate seems to be higher in females compared to males [223].

Vaccination

Childhood or adult vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox and dengue viruses, protective antibody responses can be twice as high in females compared to males of all ages [224]. Female children also have higher antibody responses than do males to diphtheria, pertussis, pneumococcal, human papilloma virus, and rubella vaccines [225-227].

On vaccination, as with most vaccines, females show higher measles, mumps and rubella (MMR) antibody titers that persist longer [228]. The prevalence of serum IgG antibodies against measles, mumps and rubella over 15 years of age is significantly higher in girls than in boys after vaccination at 12-15 months [229, 230].

Vaccination against both BCG and measles reduces mortality due to causes other than tuberculosis and measles, respectively [231, 232]. Measles vaccine reduces the non-measles mortality, especially in girls [233]. BCG vaccine also improves overall survival and reduces susceptibility to respiratory infections more in girls than boys [234, 235]. However, the nonspecific effects of the diphtheria-tetanus-pertussis vaccine, in contrast to those of the live vaccines, are to increase mortality after administration in girls [236].

Higher inflammatory responses to vaccines in females result in increased adverse events following vaccination in females compared with

males. In the late 1980s, a high-titer measles vaccine was introduced into high-measles-endemic settings due to its ability to induce robust antibody responses in the presence of maternal antibody. This vaccination caused an approximately 50% increase in mortality in females, but not in males [237]. In subsequent years, it has been reported that females develop more often and severe adverse reactions, including fever, pain and inflammation to vaccines [227, 238]. Adverse reactions, including fever, parotitis and joint and limb pain, are higher in females than in males (6-13 years of age) up to 14 weeks after the second immunization with the MMR vaccine [239, 240]. However, among children < 5 years old, males have greater rates of immune thrombocytopenic purpura to MMR vaccine than females [241]. All these reports show that the design of vaccines and vaccine strategies should be sex-specific, to reduce adverse reactions in females and increase immunogenicity in males [242].

Autoimmunity

More vigorous innate, cell-mediated, and humoral immune responses to antigens in females may lead to a consequent increase in immune-related [243], auto-immune [244, 245] and inflammatory diseases (e.g. chronic lung and inflammatory bowel diseases) [246, 247].

The twice higher risk of severe congenital CMV disease leading to brain damage in females [248] is thought to be induced by immune-inflammatory responses [249, 250]. Gender difference is also seen in measles complications being males more likely affected by subacute sclerosing panencephalitis (SSPE), while females show longer latency periods and milder SSPE symptoms [251]. Reactivation of varicella-zoster virus as shingles occurs more often in women [252].

In the adult population, autoimmune diseases are far more common in women, while for some diseases the male gender is a risk factor for a more severe course. This sex dimorphism is less common in childhood diseases, probably because, at this age, the hormonal milieu differences between males and females are negligible. Juvenile idiopathic arthritis (JIA) shows a strong predilection for girls (F:M = 3-6.6:1). Chronic anterior uveitis associated with JIA is also more common in girls, but boys tend to have a more severe course. Systemic lupus erythematosus predominantly affects girls and women (F:M =

3-5:1 in children, F:M = 10-15:1 in adults). At the diagnosis, males rarely have alopecia, malar rash and arthralgia, but these signs are more frequent in females [253].

In Hashimoto's thyroiditis, a female prevalence is reported in both children and adults [254]. Behçet's disease has been reported to be more prevalent in adult males (F:M = 1:1-4); in children, there are no differences. The sex ratio is equal in children and adults for Henoch-Schönlein purpura (F:M = 1:1). A higher male-to-female ratio exists for Kawasaki disease (F:M = 1:1.1-1.6 in children, F:M = 1:1.5 in adults). Juvenile dermatomyositis (F:M = 2-5:1), systemic sclerosis (F:M = 4:1 in children, F:M = 6:1 in adults), and Takayasu arteritis (F:M = 2:1 in children, F:M = 7-9:1 in adults) are more common in girls and women than in boys and men. There is no gender bias for acute rheumatic fever in children, while in adults the F:M ratio is 2:1 [255].

Pharmacogenomics

Sex differences play a crucial role in the pharmacological response, and the frequency and severity of adverse drug reactions are higher in females. The mechanisms causing these differences in drug response are still not very well known. Genes, transcriptional gene regulation due to sex-specific epigenetic modifications, post-transcriptional modifications, the effects of sex hormones are all effective [256].

Sex differences have been undervalued in medical studies. Men are accepted to be more convenient research subjects, because they do not have menstrual periods and do not get pregnant. In two-thirds of the studies published in the leading medical journals, women are not included in the studies, or the results are not analyzed according to sex and gender [257]. Furthermore, even in studies of diseases whose incidence is much higher in women, male animals are primarily used [258].

Epilogue

In adults, the difference in the incidence of several diseases may be explained for the most part by the hormonal differences between the two sexes, even if the exact mechanism on which this difference is based is not totally known [259]. Sex hormones act as important modulators of immune responses, being their receptors expressed in various immune cells. Androgens are general

immunosuppressive. Estrogen tends to shift adaptive immune responses in favor of type 2 (humoral) immune responses. Therefore females produce more elevated circulating levels of antibodies than males. Androgens exert opposing effects on B cells and inhibit antibody. However, the effects of sex hormones are not similar magnitude in type 1 and type 2 associated adaptive immune responses; the difference in the strength of immune responses between females and males is larger for type 2 associated immune responses than for type 1 associated immune responses [260-266]. However, before puberty, these hormonal differences may explain only marginally the diversity of incidence between males and females, and it can therefore be assumed that there are other mechanisms at the basis of these differences in children [267]. Among the other mechanisms involved, an important role is probably to be attributed to genetic differences.

Genetics

In humans, the Y chromosome contains only 78 genes, which are mostly involved in male development. However, the X chromosome contains nearly 1,000 genes, including the largest number of immune-related genes in the human genome. Any damaging mutations or polymorphisms to X-linked genes are more likely to have an immune consequence in males XY compared to females XX [268]. To prevent excessive gene activity in X-linked genes, one of the X chromosomes is inactivated in females with global methylation. However, at least 15% of X-linked genes completely escape inactivation. As a result, females have higher gene expression of some X-linked genes, which may modify their immune response, reducing the risk against infections but increasing the risk for autoimmune disorders [269]. In addition, autoimmune phenomena are observed in X-linked primary immunodeficiencies. Thus it is likely that genes on the X chromosome may also play a role in autoimmunity [270]. Nevertheless, some genes in the non-recombinant Y chromosome region could play an important role in regulating the immune response [271]. There is evidence that among the subjects with Klinefelter syndrome (47, XXY) have an increased risk of developing autoimmune diseases while, among the subjects with the Turner syndrome (45, X), males have a greater risk of developing these pathologies [272, 273].

Epigenetics

Epigenetic mechanisms are also responsible for gender differences in diseases. These mechanisms can act like a switch to change, activate, or deactivate the operation of the genes. Epigenetic changes occur through one or more of three processes: histone modification, micro RNA changes, and DNA methylation. Non-coding microRNAs (miRNAs) are major regulators in post-transcriptional gene expression, by either repressing mRNA translation or triggering mRNA degradation. The majority of mRNAs are targeted by one or more miRNAs, and a single miRNA may regulate the expression of hundreds of different genes. The X chromosome contains 10% of the approximate 800 miRNAs in the genome, whereas the Y chromosome contains only 2 miRNAs [274]. Accordingly, the prevalence of miRNAs on the X chromosome that includes a large number of immune-related genes inevitably influences sex-based differences in immune responses [269]. Sometimes females may express more miRNAs due to incomplete X inactivation, further contributing to sex differences in immune responses. In addition, miRNA expression can be under sex hormone control. Differential expression of microRNAs between the sexes may be an important underlying mechanism for gender-based disease outcome [275].

Epigenetic changes in the placenta that change gene expression will affect fetal development. The observation in mice of increased DNA methylation of female placentas may partly explain why females have better protection from exogenous insults than male fetuses. For example, if the leptin receptors in the placenta are epigenetically silenced by DNA methylation, male babies are born more lethargic and hypotonic, whereas female newborns are not affected [276].

Genetically modified females

Sex chromosomes originate from autosomes, and have evolved independently. The early proto-Y chromosome was originally the same size as and genetically identical to its partner, the X chromosome. However, unlike the other chromosomes, Y chromosomes are only ever present as a single copy, passed from fathers to their sons. Because of that, genes on the Y chromosome cannot undergo genetic recombination, which helps to eliminate damaging gene mutations. Deprived of the benefits of recombination, genes on the Y

chromosome degenerate over time. Lacking an effective repair mechanism, the Y chromosome began to deteriorate and has lost two-thirds of its size and 90% of its genetic content. In other words, the Y chromosome is a degraded X chromosome [277]. The female X chromosome carries approximately 1,000 genes, while the male Y chromosome carries only around 80 genes. Most of the genes on the Y chromosome are unnecessary (e.g. genes for growth of nose and ear hair in aging men), and are the only chromosomes not necessary for life. Nevertheless, the Y chromosome carries SRY (sex-determining region Y) that determines the sex of the embryo [277, 278].

Gender in danger

The estimated number of genes on the ancestral Y chromosome was about 1,700. If we assume a linear rate of loss, it is predicted that the Y chromosome will disappear in 4.6 million years [277], and are eventually lost from the genome. However, an alternative way of sex determination must have evolved before the complete elimination of the Y chromosome, and genes required for male function must have been translocated to other chromosomes, or new sex-determining genes and chromosomes maybe lead to the evolution of new hominid species [278].

It has been shown that a male mouse without any Y chromosome genes but with only two transgenically activated Y chromosome genes – Sox9 (downstream target of SRY) and spermatogonial proliferation factor (Eif2s3x) – can generate haploid gametes and male offspring with the help of assisted fertilization [279].

In addition to chromosomal instability of the Y chromosome, many studies have suggested that sperm counts have been decreasing over the past several decades in different countries throughout the world. A 50-60% decline among men has been reported in western countries between the years 1973-2011 [280]. Although etiology of this decrease is unclear, exposure to chronic and low dose dietary supplements, drug use, and the environmental pollution (PCBs, phthalates, pesticides, etc.) are being found to have a dramatic impact on sperm production [281].

Grandmothers

Evolution makes men the stronger sex physically, but makes them the weaker sex over a lifetime. The

survival advantage of women has fundamental biological underpinnings and is supported by the fact that, under very harsh conditions, females survive better than males even at infant ages when behavioral and social differences may be minimal or favor males [282]. Although women live longer than men, they bear the burden of more years of unhealthy life [283]. Furthermore, compared to men, women are affected more frequently and more heavily by the side effects of therapies [256]. This is called “woman’s paradox”.

Female fertility ends at similar ages in humans and great apes. Ape females become frail in their thirties and usually die during the menstrual cycling years. However, in humans, even among hunter-gatherers, women past the childbearing years make up substantial fractions of human populations. According to the “grandmother hypothesis”, the advantage of the post-fertile stage is that grandmothers enhance the survival of their grandchildren, by helping her fertile daughter by caring and feeding the infants [284].

Grandmothers could also help in the training of their grandchildren, by transferring skills, knowledge, and social abilities. The skills and knowledge attained during childhood can increase the survival rate and fecundity for the whole adult life of the grandchildren. All these hypotheses are aimed at explaining the evolutionary advantage of the long post-fertile life period of *Homo sapiens*. So we have to support and respect the grandmothers, as indicated in the Fourth Commandment (Exodus, 20:12) [285]: “*Honor your father and your mother*”.

Declaration of interest

The Author declares that there is no conflict of interest.

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