TURNER SYNDROME, SEXOLOGY, QUALITY OF LIFE, DEPRESSION, ANXIETY AND MEDICINAL TREATMENT – UNTANGLING THE INTRICACIES

Claus H. Gravholt[1,2]

[1] Molekylær Medicinsk Afdeling, Aarhus Universitets Hospital

[2] Diabetes og Hormonsygdomme, Aarhus Universitets Hospital

Studienummer: 20171035

"Masterafhandling ved Masteruddannelsen i Sexologi, Aalborg Universitet"

Vejledere:
Professor Christian Graugaard, Aalborg Universitet
Professor Anna-Maria Giraldi, København Universitet

Letter count (without references): 77726

Problem

Is there at all a problem in relation to sexuality in Turner syndrome? I have been dealing with females with Turner syndrome of all ages during my entire time working as a physician. I have been treating them for all kinds of diseases, both relatively innocuous conditions such as Hashimoto thyroiditis, hypertension and short stature (treated with growth hormone), but also life-threatening conditions, such as aortic dissection and acute myocardial infarction. Most consultations with females with Turner syndrome will sooner or later also include a discussion of infertility. Among adults with Turner syndrome, infertility is judged as the most important health issue and many women with Turner syndrome go to great length to achieve pregnancy, often through oocyte donation or adoption. Gonadal dysgenesis and subsequent hypergonadotropic hypogonadism is the forerunner of infertility. Discussing infertility with young females with Turner syndrome also often introduces the concept of sexuality and problems related to that. However, when discussing sexuality, other issues such as quality of life, the way a woman with Turner syndrome views her body (body image), treatment with estrogens for hypogonadism, additional morbidity and treatment thereof, intimacy and how deal with a partner, often pops up. One could say that although sexuality is not always easy or straightforward among many people, it is almost always quite complicated and complex in Turner syndrome, because in addition to medical problems, short stature, altered body image, neurocognitive problems adds to the picture. But having encountered different patients with Turner syndrome with specific problems does not necessarily paint a full picture of sexuality in this group of patients. Sexuality has been dealt with scientifically by others, but most often only in small groups and as an adjunct to other questions concerning for instance quality of life. Therefore, I thought it timely and

appropriate to start a holistic study aimed at covering all relevant aspects of life with Turner syndrome in order to answer questions related to sexuality. Because there are so many variables, conditions, and specific factors that might influence sexuality among women with Turner syndrome, I aimed at including all these factors in a questionnaire study covering as many women with Turner syndrome in Denmark. I therefore forged an alliance with the Danish Association for Turner syndrome, which was interested in this study and have agreed to forward this questionnaire to all members above 18 years of age.

Introduction

Turner syndrome is a rare, but familiar, sex chromosome abnormality syndrome in which there is complete or partial absence, or a structural abnormality, of the second sex chromosome (Gravholt et al., 2017). One of the first lessons and memorable images learned by students of pediatrics, genetics, endocrinology, and cardiology is that of an infant or young girl with Turner syndrome, sometimes described using "45,XO" instead of the current 45,X. The external features of short stature, short neck with webbing, characteristic facial appearance (down-slanting palpebral fissures, ptosis, prominent pinnae), infertility with hypergonadotropic hypogonadism and lymphedema comprised the sole composite phenotype for many years, sometimes portrayed in unflattering photos. However, the external appearance, internal anomalies, and neuropsychologic performance of individuals with Turner syndrome varies greatly. Table 1 provides a list with tentative frequencies of some the characteristics that one can encounter in Turner syndrome (compiled from different sources and reviewed in (Gravholt et al., 2017)). No longer a disorder familiar only to pediatricians and pediatric specialists, as well as adult endocrinologists and cardiologists, Turner syndrome is now more widely encountered by primary care providers (family physicians, nurse practitioner, physician assistants) and other internal medical specialists who therefore need to be well informed of their medical needs. There is a powerful need to collect and share longitudinal information demonstrated by similar reviews about other rare syndromes Klinefelter syndrome (Gravholt et al., 2018), another syndrome with sex chromosome aneuploidy (47,XXY), but affecting males. Here we recently sought to integrate knowledge of sexuality in a holistic manner, with information concerning quality of life, symptoms of depression, anxiety, exercise and medicinal treatment (Skakkebaek et al., 2018).

Although Turner syndrome is considered to be a rare syndrome (usually defined as less than 50 cases per 100,000 individuals), this may not be the case when considering Turner syndrome during intrauterine life. In order to discuss the occurrence of Turner syndrome in adolescents and adult women, it is necessary to review the foundation of considerable epidemiologic data from fetal and neonatal life. Since up to 99% of Turner syndrome fetuses are spontaneously miscarried during the first trimester (with intrauterine mortality peaking between weeks 11-13), the prenatal prevalence of Turner Syndrome exceeds the postnatal (birth) prevalence several-fold (Gravholt et al., 1996; Hook et al., 1983). Nevertheless, ascertainment is incomplete, and in Denmark, prenatal screening for Down syndrome also captures up to 40% of fetuses with Turner syndrome (Viuff et al., 2015). Remarkably, there was no difference between the capture rate for 45,X cases compared with all other Turner syndrome karyotypes. Early epidemiological studies estimated the prevalence from prospective chromosome surveys of newborns (Nielsen et al., 1990). The prevalence of 50 per 100,000 newborn girls was later confirmed by two large Danish registry studies (Gravholt et al., 1996; Stochholm et al., 2006). The diagnosis of Turner syndrome is often thought of as a childhood event and late diagnosis and non-diagnosis is widespread which influences research methods and analysis. This results in a median age at diagnosis of 15 years with three distinct diagnostic peaks in infancy, adolescence, and adulthood. About half of women with Turner syndrome are not diagnosed until adulthood, or go through life without a diagnosis (Schoemaker et al., 2008; Stochholm et al., 2006). In light of this, vigilance should be high among physicians taking care of adolescents and adults with short stature, reduced fertility, bicuspid aortic valves, and endocrine disorders.

A recent study characterized the prevalence of X chromosome aneuploidy in a population of 244,848 women from the UK Biobank using SNP array data (Tuke et al., 2018).

The prevalence was almost 4 times higher than expected, although the majority had a 45,X/46,XX mosaic karyotype. Most of these individuals were not aware of their condition. The prevalence of 45,X karyotype was only half of the expected (12 per 100,000), perhaps explained by the tendency for healthy individuals to participate more often in a biobank and that childhood morbidity was not included.

Although sexuality can encompass a range of topics, including intimacy, sexual activity, and sexual orientation, the discussion here will focus primarily on sexual activity as it relates to Turner syndrome. Sexuality among women with Turner syndrome has been addressed as a specific topic in an increasing number of articles over time (Carel et al., 2006; Naess et al., 2010; Rolstad et al., 2007; Ros et al., 2013), although intimacy is usually included in reviews of quality of life, fertility, and hormone therapy. A lack of data in this area of care was acknowledged in the recent international guidelines on Turner syndrome (Gravholt et al., 2017). In addition to the medical literature, a compelling personal plea from the Turner syndrome community urged providers and patients to talk about sex more openly (Clifton, 2013). Concerns included a feeling that the subject of sex was "almost taboo", a request for physicians to be "bold and delve a bit deeper", and the insight that not all women with Turner syndrome would share the same viewpoints on sex and sexuality.

Among women with Turner syndrome, it is reasonable to consider that medical factors may contribute to reduced sexual activity, although there has been no systematic study interrelating multiple factors known to affect sexuality. An observational study of 26 adults with Turner syndrome followed in an endocrinologic gynecology clinic in Barcelona reported that only 50% of Turner syndrome had been sexually active and that they had poorer arousal outcome when studied with the Female Sexual Function Index (FSFI) questionnaire compared to a normal control group treated with oral contraception and a

second control group of females with congenital hypogonadism by other causes (Ros et al., 2013). Comparison of these two clinical groups noted differences between women with Turner syndrome and those with congenital hypogonadism. Women with congenital hypogonadism had even lower scores (i.e., less sexual desire), although not statistically significant, than the Turner syndrome group (Ros et al., 2013), perhaps indicating that hypogonadism alone cannot account for poorer sexual function among women with Turner syndrome.

Studies of European and North American women with Turner syndrome have noted that compared to the general population, they move away from their parents and have a sexual debut at a later age, if at all (Amundson et al., 2010; Carel et al., 2006; Naess et al., 2010; Rolstad et al., 2007). In a Norwegian study, only 48 of 80 (60%) women with Turner syndrome responded to a questionnaire, but approximately 50% of both women with Turner syndrome and age-matched controls were satisfied with their sexual life. Compared to controls, women with Turner syndrome had less confidence as a sexual partner, had fewer partners, and the late induction of puberty with exogenous estrogen was coupled with late sexual debut (Naess et al., 2010). A follow-up study within the same cohort of 56 women showed similar findings. Women with Turner syndrome still reported fewer partners and felt less confident as a sexual partner (Fjermestad et al., 2016). Similarly, in a large French study of 566 young adult women with Turner syndrome (mean age = 22.6 years) who had been treated with GH, only 38% had intercourse (age of 20 years), while 63% had no sexual experience at all (Carel et al., 2006). A study from the National Institute of Health in the US, with acknowledged referral bias, noted that many fewer individuals with Turner syndrome were or had been married (48% vs 78%), which indirectly was viewed as a surrogate indicator of sexual activity (Gould et al., 2013). While reduced sexual activity may partly

relate to the medical factors discussed above, greater difficulty establishing intimate relationships may also reflect broader difficulties with social communication, discussed elsewhere in this review.

In my clinical experience, and as noted previously (Sybert & McCauley, 2004), most individuals with Turner syndrome identify as women and heterosexual, but experience considerable anxiety and/or ambivalence about initiating romantic relationships. It is possible that due to social and cultural factors within Turner syndrome communities, there may be expectations regarding sexual orientation, gender identity and/or gender expression. For the adolescent with Turner syndrome, the initial discussion about intimacy and sexuality should take place with a parent or trusted adult, at an appropriate time. Ideally, information should be provided no later than at transition (when the girl is transferred from pediatric to adult care), and by the physician who has a sustained relationship with the young woman. Later in adulthood, ongoing discussion and care could be provided by a gynecologist or endocrinologist experienced in caring for women with ovarian insufficiency, with an awareness that women with Turner syndrome who are sexually active may not express a desire to change sexual function. Appreciating an individual's social abilities or weaknesses e.g. whether she is extremely shy, unable to interact with partners and date, etc., Turner syndrome providers should counsel women who are not sexually active when they express an interest. Topical estrogen *per vaginum* or systemic androgen supplements may be beneficial, but currently, little information on their use in women with Turner syndrome (Trolle et al., 2012a; Zuckerman-Levin et al., 2009).

However, most females with Turner syndrome will need estradiol supplementation from very early on in life when puberty has to be induced. Later on a gestagen component will have to added in order to establish a normal menstrual period. Women with Turner

syndrome, like women with a 46,XX karyotype, are endowed with a finite number of germ cells, most of which undergo atresia. They attain the same peak germ cell mass at 20 weeks of intrauterine life (approximately 6-7 million), accompanied by an accelerated loss of germ cells (one million at birth and 400,000 by puberty). The decline is clinically imperceptible in childhood, as the hypothalamic-pituitary axis that controls the ovarian cycle is quiescent, but is activated at puberty when the hormonal events of the ovarian cycle ensue. By menopause germ cells are essentially depleted. In a minority of women with Turner syndrome, puberty and menarche occur spontaneously (Negreiros et al., 2014; Tanaka et al., 2015). In a cohort from Italy, 32% had spontaneous puberty and menarche occurred in 16%, mainly in those with mosaic karyotype containing a 46,XX cell line (Pasquino et al., 1997). Even when spontaneous menarche is achieved, most of these young women develop irregular menses and early menopause (Negreiros et al., 2014). Thus, the majority of girls and women with Turner syndrome experience ovarian failure represented by hypergonadotropic hypogonadism, low AMH (Lunding et al., 2015) as well as undetectable inhibin B (Gravholt et al., 2002; Hagen et al., 2010) and require induction of puberty and hormone replacement therapy (HRT). The induction of puberty in Turner syndrome is reviewed in order to appreciate the use of hormone replacement therapy in adolescents in transition, and ultimately as adult women briefly. The international guidelines recommend confirming ovarian dysfunction, and starting estrogen replacement therapy between 11 and 12 years of age in order to promote normal growth and psychosocial development (Gravholt et al., 2017). Low doses of estradiol are initiated and titrated to promote secondary sexual characteristics and uterine growth without early closure of the growth plates , ensure a normal tempo of bone mineralization (Cleemann et al., 2011), normalize cognitive maturation (Ross et al., 1998; Ross et al., 2000), body composition (Cleemann et al., 2017),

reduce lipids (Gravholt et al., 2000) and liver enzymes (Koulouri et al., 2008) and reduce cardiovascular risk in the long term (Gravholt et al., 1998; Ostberg et al., 2007) and perhaps even increase longevity (Figure 1). Transdermal estradiol is the preferred method for estrogen administration (Gravholt et al., 2017; Klein et al., 2018), but oral estradiol can also be used. Estrogen replacement strategies for pubertal induction in girls with Turner syndrome (Gravholt et al., 2017) recommend increasing the dose by 25 to 100% every 6 months to attain adult dosing over the span of 2-3 years. Routine measurement of gonadotropins is not recommended (Gravholt et al., 2017); instead, careful monitoring of Tanner staging, bone age and growth rates, uterine volume via pelvic ultrasound, and bone mineral accrual via bone mineral density is more useful in guiding estrogen titration. Progesterone therapy, which is discussed in detail in the following section, is initiated once breakthrough bleeding occurs or after 2 years of estrogen therapy.

In most young women with Turner syndrome, HRT is the cornerstone of long-term medical treatment. After puberty induction, HRT must be continued at least until the age of natural menopause (approximately 50 years or later), depending on an individual assessment of risks and benefits. In adolescents with Turner syndrome who undergo natural puberty and menstruate on their own, the patient and her physician must be vigilant of her menstrual history as early menopause or ovarian failure is inevitable. In such cases, HRT can be initiated when menses occur less frequently or cease for a few months. At this time hormonal evaluation will show high FSH and low AMH concentrations. HRT has multiple benefits including a sense of well-being and feminization, bone health (Hogler et al., 2004), improvement in vascular function (Ostberg et al., 2007), improvement in lipids and blood pressure (Gravholt et al., 1998). In addition, HRT is important for appropriate development of uterine volume if future in vitro fertilization is required. The impact of karyotype (45,X vs.

mosaicism) on uterine volumes varies (Bakalov et al., 2007; Doerr et al., 2005), although the duration of treatment and dose of estrogen are likely to influence uterine size.

The estrogen compounds used for replacement in Turner syndrome include 17β-estradiol (E2), conjugated equine estrogens (CEE), and ethinyl estradiol (EE). 17β-estradiol is the natural estrogen secreted in the ovaries. Conjugated equine estrogens consist of >100 forms of estrogens of different receptor affinity and potency. Ethinyl estradiol, used in most oral contraceptive pills, is a potent synthetic E2 analog that is not metabolized to E2 (Klein et al., 2018). Oral contraceptive use for HRT is generally not recommended in young women with Turner syndrome; EE is the least physiologic and potential adverse effects include higher blood pressure, insulin resistance and it may not be the most appropriate estrogen for bone health (Herrmann et al., 2010). Exceptionally, young women with Turner syndrome mosaicism who have spontaneous cycles and desire contraception, may wish to use oral contraceptives containing EE. Similarly, while previously more popular, CEE is currently less favored as HRT.

As can be appreciated estrogen replacement options for adult women with Turner syndrome are manifold (Gravholt et al., 2017). The preferred estrogen for hormone replacement in Turner syndrome is E2, which is available in oral, transdermal, and gel forms. All are used in Turner syndrome and are effective in achieving the desired goal of providing estrogen replacement, however, transdermal E2 is favored over oral therapy. Doses of transdermal E2 may range from 25 to 200 μg daily, usually 50 μg or higher. However, some patients may be allergic to the adhesive in patches and E2 gels may be more expensive in some countries (or less desirable to patients); under such circumstances oral E2 may be appropriate. Doses of oral estradiol have ranged from 1-4 mg daily (Cleemann et al., 2017). The goal of treatment is achievement of adequate concentrations of estradiol for the

individual woman commensurate with those in normally cycling women. A recent randomized study using oral conventional (2 mg/day) or higher dose (4 mg/day) of estradiol for 5 years, showed that the high dose group had a greater increase in muscle mass during treatment, while bone mineral density was similar in the two groups. This may be important knowing that females with Turner syndrome have a skewed body composition with higher fat mass and lower muscle mass than control women. It may also be relevant to metabolic syndrome or type 2 diabetes seen in Turner syndrome (Cleemann et al., 2017). These E2 formulations are available in many countries. Depot E2 may be available to some practitioners but it is generally not used.

Progestins must be given, along with estrogen, to avoid endometrial hyperplasia and protect the uterus in Turner syndrome after puberty induction. The three most commonly used progestins for endometrial protection are micronized progesterone, norethisteroneacetate and medroxyprogesterone. These can be given cyclically, to mimic the normal ovarian cycle with menses after progestin withdrawal, or daily to avoid menses. Micronized progesterone is prescribed as 100 mg daily or 200 mg for 12 days each month and medroxyprogesterone acetate as 2.5 mg daily or 10 mg given for 10 days each month. Norethisteroneacetate (1 mg) is typically added in sequential combination pills with E2 and used for 10 days each month. Cyclic therapy is generally preferred in Turner syndrome, to mimic normal ovarian cyclicity. Some women with Turner syndrome may wish to avoid menses and continuous therapy, as above, may be appropriate. Combination patches containing E2 and a progestin are available in many countries and depending on the preparation, the patient applies one patch weekly or one patch twice weekly. Combination oral formulations containing E2 and a progestin (norethindrone or drospirenone) are available in the USA but the 1 mg E2 dose may be low for some women with Turner

syndrome. In Europe, several 2 mg containing E2 formulations are also available (Klein et al., 2018), combined with a progestin. The woman should be advised that with continuous treatment erratic episodes of bleeding may occur in the first six months; if they persist evaluation may be required. Alternatively, protection of the endometrium may be afforded with the use of an intrauterine contraceptive device releasing the progestin levonorgestrel.

Interestingly, none of all these hormonal replacement options have ever been examined in the context of sexuality in Turner syndrome. And in other conditions of premature ovarian insufficiency the knowledge gap is also considerable, as is described in recent review (see figure on this page from this review, aimed at describing the interactions that may be present in premature ovarian failure) (Nappi et al., 2019). All the conditions mentioned in this review and presented in this figure are present in Turner syndrome to a greater or lesser degree. All the described biomedical condition described here are also present among females with Turner syndrome, as are to a large extent the cultural issues mentioned, although these have not been clearly documented in Turner syndrome, except for quality of life. As mentioned below, many of the intrapersonal and interpersonal issues presented in the figure, are also

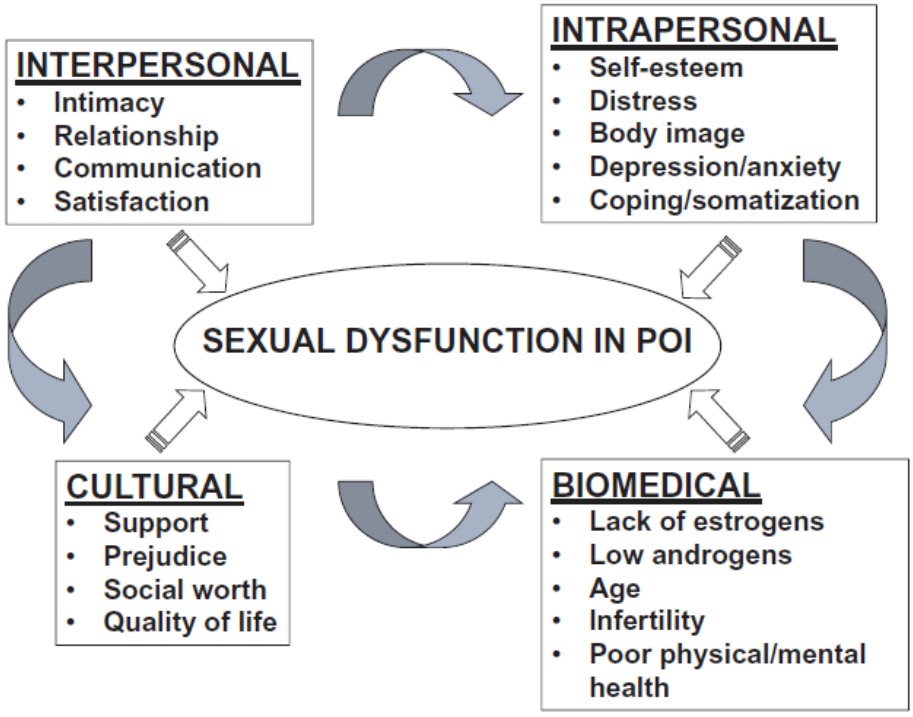


Figure 1. Multitude of biomedical and psychosocial variables contributing to sexual dysfunction in women with premature ovarian insufficiency (POI).

present in Turner syndrome. In short, although it is difficult and not appropriate to directly compare other conditions of premature ovarian failure with Turner syndrome, there are clearly overlapping themes.

It is interesting and a lapse in knowledge that the most optimal hormone replacement therapy has not described, given the fact that most women with Turner syndrome have the prospect of receiving these estrogenic compounds for at least 40 years (from around 11-12 years until the normal natural menopause years around 53 years of age) during what should be their reproductive years. To add to this shortage of knowledge, androgen concentrations are also decreased in women with Turner syndrome. Normally, androgens in women are produced from the adrenals (about 50%) and the ovaries (about 50%), but in Turner syndrome, the ovarian component is missing because of the gonadal dysgenesis, which means that the circulating amount of testosterone and other androgenic compounds is reduced by about 50% (Gravholt et al., 1999). A randomized controlled trial in 14 women with Turner syndrome showed improvements in lipid profile, bone mineral density, body composition, neurocognition, quality of life and sexual desire when methyl-testosterone was added to HRT versus placebo (Zuckerman-Levin et al., 2009). Additional research is dearly needed in this area before androgen supplementation can be considered as a necessary adjunct to therapy. Given the fact that sexuality seems to be impaired in Turner syndrome (see below), it is obvious that supplementation of also testosterone could seem relevant in Turner syndrome.

Despite recommendations promoting the benefits of HRT, Turner syndrome clinicians are well aware that many adolescents and adults are not using HRT. In the experience of the author, this may approximate 15% in Denmark, although formal trend analysis through the lifespan is not yet available (manuscript under analysis). Failure or reluctance to use HRT

is multifactorial, variably related to lack of education, financial resources or access to caregivers. Early on there can be a deliberate rejection of medication which causes menses. Clearly, education of the individual patient, outreach toward the Turner syndrome community, and research should be a priority because lack of HRT may be associated with increased morbidity from bone loss and other signs of increased aging.

Clinically, quality of life measures are often used as a general indicator of psychosocial health. In Turner syndrome, quality of life has been investigated in cross-sectional studies (Boman et al., 2001; Boman et al., 2004; Lasaite et al., 2010; Nadeem et al., 2014), in four cohort studies (Carel et al., 2005; Carel et al., 2006; Fjermestad et al., 2016; Naess et al., 2010), in randomized clinical trials (Bannink et al., 2006; Freriks et al., 2015; Taback et al., 2011; Zuckerman-Levin et al., 2009), and in a case–control study (Amundson et al., 2010). Most of these studies used the Short Form Health Survey (SF-36) questionnaire, but other questionnaires have been used, including the Psychological General Well-Being index, General Health Questionnaire, part of the Nottingham Health Profile, and adapted versions of the World Health Organization Quality of Life (WHOQOL) Assessment, making generalization difficult. Some studies comparing Turner syndrome with a normal sample form the population concluded that quality of life was normal in females with Turner syndrome (Bannink et al., 2006; Carel et al., 2005; Taback et al., 2011), while others reported that their quality of life was reduced (Boman et al., 2001; Fjermestad et al., 2016; Lasaite et al., 2010; Nadeem et al., 2014; Naess et al., 2010). A recent review concluded that it is necessary to develop Turner syndrome specific tools in order to fully appreciate the intricacies of their quality of life (Reis et al., 2018). Quality of life is likely influenced by multiple factors including age, height, pubertal development, infertility, sexuality, use of growth

hormone, age at diagnosis, physical aspects, socio-economic status, education, reduced hearing, and the burden of morbidity.

Body image is a multidimensional construct that includes self-perceptions and attitudes with relation to one's own body, and involves many related components, such as how appearance is evaluated by oneself. This develops from early in life and is based on shared experiences and interactions with parents, peers, social media, and society. Negative body image has been linked to a number of conditions, such as eating disorders, negative affect, social anxiety, and social inhibition (Avalos et al., 2005). Body image has only been sparingly examined in Turner syndrome. Bodily attitude scale has been rated similarly among women with Turner syndrome and an appropriate control group (Lagrou et al., 2006); furthermore, a less favorable body image may contribute to their lack of sexual intimacy and desire (Sutton et al., 2005). Some women with Turner syndrome also cited feeling less desirable due to short stature and/or infertility or lack of similar pubertal development to peers.

Most of the current studies on sexuality and quality of life in women with Turner syndrome are small in size and tend to have studied sexuality and quality of life as an adjunct to other questions related to general health, instead of as a primary topic. It is clear that sexuality and quality of life should be viewed holistically with regard to body image, medications like hormonal replacement therapy, and assorted medical conditions. A bio-psycho-social framework should be used with consideration of social communication skills, emotional functioning, level of anxiety, socioeconomic status, and educational attainment. The importance of an integrated analysis of variables is illustrated by a recent study of sexuality and quality of life in Klinefelter syndrome (47,XXY) at Aarhus University Hospital. Using questionnaires to study health issues, socioeconomic indicators, sexuality, and

treatment (especially testosterone replacement, and also other medications), (Skakkebaek et al., 2018) this study noted that sexuality of individuals with Klinefelter syndrome was affected by a number of co-variates such as socioeconomic status, medicinal use, physical activity, and BMI (Skakkebaek et al., 2018). Additionally, the Turner Syndrome Research Registry created by the Turner Syndrome Society of the United States (TSSUS) includes a module on sexuality with the intent of capturing more comprehensive, patient-driven research in this area (Prakash et al., 2019). This data will further enrich the scientific community's understanding of sexuality in Turner syndrome in the coming years.

It is possible that as the treatment of young women with Turner syndrome is optimized from a medical and psychosocial point of view, then sexuality and quality of life may improve. Currently, the young women with Turner syndrome who reach normal height due to growth hormone treatment, which may add up to 15-18 cm to final height, and have age-appropriate pubertal development report normal health-related quality of life. Satisfaction with breast development (and height) also have a positive influence on several health-related quality of life scales (Bannink et al., 2006). Therefore, it seems that induced puberty at a physiologically appropriate age optimizes self-esteem, social adjustment, and initiation of the patient's sex life (Carel et al., 2006; Naess et al., 2010), although one study showed that both estrogen use and age of puberty did not influence sexual function in individuals with Turner syndrome (Sheaffer et al., 2008).

In addition to ongoing efforts to conduct research to obtain more data, providers should be reminded to include sexuality with current counseling about fertility and parenting. If a primary care physician, geneticist, or endocrinologist is not comfortable with discussing the necessary details, e.g., lubrication, then referral to a gynecologist or endocrinologist should be made. Options may vary among different healthcare models

worldwide. Importantly, when discussing sexuality with the adolescent or with an individual whose cognitive function or development is delayed, prior review with the parent or guardian is necessary. Some individuals may wish to include their partner if delivery of information by a physician would be more comfortable.

In addition to the abovementioned complicating factors for a normal sexual life, females with Turner syndrome demonstrate an increased frequency of neurocognitive challenges, which will be shortly reviewed here. Although women with Turner syndrome often demonstrate overall intellectual functioning within age-based expectations, with only 5-10% in the range of intellectual disability, often associated with a ring X karyotype (Kubota et al., 2002). However, overall measures of intellectual functioning may not accurately predict global functioning given the well-defined pattern of significant variability that often characterizes the neuropsychological profiles of women with Turner syndrome (Knickmeyer et al., 2019). This pattern appears to be largely stable over the course of the lifespan and impacts daily functioning, likely contributing to increased risk of mental health concerns, reduced quality of life, and health outcomes, although as mentioned above, most studies of quality of life actually finds this to be comparable to controls. Thus, formal neuropsychological evaluation and mental health care are critical components of psychosocial care for women with Turner syndrome.

The neuropsychological profile that is often observed in women with Turner syndrome is characterized by age-appropriate verbal abilities with core deficits in visuospatial skills, quantitative/math reasoning skills, social communication, executive

functions, and fine motor skills and coordination (El-Mansoury et al., 2009; Knickmeyer et al., 2019).

From a neurological perspective, the discrepancy between verbal and spatial skills (verbal greater than spatial) that frequently characterizes the neuropsychological profile of women with Turner syndrome was initially interpreted as indicative of right hemisphere dysfunction. Functional imaging studies have revealed atypical activation patterns in the parieto-occipital, frontoparietal, and sensorimotor regions (Hart et al., 2006; Knickmeyer et al., 2019). These structural and functional differences may reflect the differential impact of multiple factors on brain development, including genetic vulnerabilities and gonadal steroid insufficiency due to loss of ovarian function, as well as the long-term systemic influence of chronic medical conditions and estrogen replacement therapy (Knickmeyer et al., 2011; Knickmeyer et al., 2019). From a clinical perspective, MRI of the brain is not part of the standard surveillance for women with Turner syndrome in the absence of focal changes, seizures, or memory changes, but neuroimaging research clearly indicates that interpretation of the typical neuropsychological profile as solely indicative of focal right hemisphere dysfunction would be oversimplified.

As might be expected in a condition affecting typical development, there are learning and behavioral difficulties that are typically identified in early childhood which can persist, but not always does so, throughout the lifespan (Rovet, 2004). In structured conversations, these difficulties may not be immediately apparent to others, as women with Turner syndrome often have relative strengths in vocabulary and factual knowledge, as well as receptive language skills and auditory comprehension. Women may show a strong interest in performing arts, music, and language arts. Difficulties with visuospatial skills are more likely to manifest as trouble with driving and spatial navigation, as well as with

mathematics (Hong et al., 2011). Many women with Turner syndrome have a history of math disability which may require specialized instruction throughout their formal education, including receipt of academic accomodations through college (Hong et al., 2011), although others with Turner syndrome are actually very proficient at math and even obtain degrees in math. Ongoing assistance with financial management can be needed, especially for those who have lower intellectual functioning. Importantly, not all women with Turner syndrome are challenged by all forms of math. It is a clinical experience, that computational and biostatistics can be areas of academic and career success.

There may also be associated weaknesses in attentional regulation and aspects of executive function. Beginning in adolescence, women with Turner syndrome are more likely to be diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) with approximately 25% meeting diagnostic criteria (McCauley et al., 2001; Russell et al., 2006). In clinical experience with adult women, this is most likely to be the inattentive subtype of ADHD, although higher rates of hyperactivity have been reported in children and adolescents with Turner syndrome (Green et al., 2015). There are usually difficulties initiating tasks that are perceived to be challenging and disengagement on tasks that are uninteresting or overstimulating. Processing speed, or the rate at which one can integrate and act upon new information, is also often reduced. As task complexity increases, there are also often difficulties with organization.

Despite these neurocognitive risk factors, women with Turner syndrome often achieve educational goals at a similar or increased level compared to the general population (Gravholt et al., 2017; Naess et al., 2010). Research suggests that women with Turner syndrome may have lower occupational status than expected based on academic achievement and report less positive working experiences (Downey et al., 1991; Fjermestad

et al., 2016). Clinically, it is observed that women with Turner syndrome are most successful in vocational environments that provide routine expectations, clear organizational hierarchies, supportive social interactions, and other accommodations (e.g., typing instead of handwriting). Career choices are broad. Women Turner syndrome have doctorates in computational math and biostatistics, and advanced degrees in psychology. There are, for example, several physicians with Turner syndrome in Denmark (a mark of excellence?).

Social communication challenges are often observed in women who have Turner syndrome, to the degree that often warrants diagnosis with a Social (Pragmatic) Communication Disorder. There may be reduced attention to nonverbal communication cues (e.g., eye contact, facial expression) but also difficulties interpreting ambiguous or non-literal language, especially in a fast-paced or novel environment (Lesniak-Karpiak et al., 2003). Women with Turner syndrome are often most comfortable interacting with familiar individuals in structured situations where social roles are clear or explicit. To care for the adolescent and adult with Turner syndrome, it should be appreciated that beginning in childhood, there may be difficulties initiating or sustaining peer relationships which can lead to social isolation in adulthood, when opportunities to interact with non-family members are often more limited and less structured.

The prevalence of psychiatric diagnoses is probably increased. The combination of learning and social communication challenges often leads to a prolonged transition and/or more limited functioning in adulthood, as well as emotional difficulties. Approximately half (52%) of women with Turner syndrome develop clinically significant anxiety or depression at some point in their lifetime (Cardoso et al., 2004; Schmidt et al., 2006), with later diagnosis (adolescence) possibly conferring a higher risk of depression (Reimann et al., 2018). Rates of anxiety and depression may increase at the transition from

adolescence to adulthood. Women with Turner syndrome may experience acute distress about finding and maintaining success in a vocational pursuit, as well as establishing intimate relationships. These concerns are often superimposed upon the responsibility of managing their chronic medical conditions. Adult women with Turner syndrome often have some awareness of their challenges, resulting in lower body image, self-esteem, and perceptions of social competence (Boman et al., 2001; Lagrou et al., 2006), which can contribute to the emergence of social anxiety, generalized anxiety, and depression. There may also be psychiatric disorders that are not necessarily secondary to psychosocial stressors.

Materials and Methods

Design

The study I propose is a quantitative questionnaire study, which should include as many women above the age of 18 years with Turner syndrome as possible. Currently, there are about 1100 diagnosed females with Turner syndrome in Denmark (Berglund et al., 2019). About 800 of these females will be above 18 years of age and thus eligible to be invited to participation in this study. For each female with Turner syndrome, we will match 5 control women from the general population. Matching will be on age, postal code and socio-economic status. The random process of finding the controls is done by Statistics Denmark. From previous questionnaire studies, I expect a participation rate at least above 50%.

Procedure

Women with Turner syndrome have been identified from endocrine, and genetics departments throughout Denmark. So far we have identified at least 286 women above the age of 18 years. The Turner syndrome association in Denmark has also been contacted and all members has been invited to participate in the study. At present, we do not a complete picture of how many additional females with Turner syndrome this will add to the patient population. All will be karyotypically verified with Turner syndrome. For each of the women with Turner syndrome, Statistics Denmark will identify five non-Turner syndrome control women and match on age, zip code and education level from the general population. All participants will receive an electronic link to all the questionnaires assembled in one grand set (Appendix 1). Answering the combined set of questionnaires will take approximately one hour, and it is possible to leave the questionnaires and return at a later stage. One reminder will be send to non-responders.

Measures

Demographics

In addition to age, demographic measures include height and weight, from which body mass indices (BMIs) will be calculated. Participants are asked if and when they have left their parents' home, whether they live alone (rather than with a partner), and whether they have any children.

Socioeconomic status

Participants are invited to indicate their level of education (primary school, high school, some college, completed college, or vocational training), employment status (employed, unemployed, or retired), hours worked per week, as well as when they worked (i.e., during

the day or night), and income. This will enable us to establish an assessment of socio-economic status among both participants with Turner syndrome and controls.

Health behaviors

Participants' health-related behaviors include alcohol use (number of drinks per week), cigarette smoking (daily, sometimes, former smoker, or never smoked), and daily medicine intake (yes or no). Here focus will be on hormone replacement therapy, but also include additional medicinal treatment, which can be seen as a surrogate for morbidity burden.

Physical activity

Participants' physical activity is ascertained by the IPAQ4 questionnaire (Hagstromer et al., 2006). We know from previous studies that physical activity, and thus resultantly exercise capacity, among many women with Turner syndrome is below what is normally recommended (Gravholt et al., 2006).

Psychological strain

For each of 15 important stages of life (e.g., starting school, or working in a job etc.), participants are asked to indicate the level of strain they experienced (none, some, high, or not relevant) during that period. This gives us an index of their resilience.

Health related problems

Participants are asked to indicate whether they currently suffer from any of a number of the most significant health problems among Turner syndrome females (e.g., hypogonadism, diabetes, broad neck, low hairline, use of hearing aid, scoliosis, congenital

heart malformations etc). This will enable summation of Turner syndrome specific traits. It is known that the number of Turner syndrome specific stigmata can be seen as an indirect measure of severity of the syndrome (El-Mansoury et al., 2007).

Medical follow-up

Participants with Turner syndrome are asked to indicate whether they had received any medical follow-up for their Turner syndrome-related health problems. Those who do are asked to indicated whether their follow-up care come from a general practitioner, fertility clinic, endocrinologist, or other doctor. Participants with Turner syndrome are also asked use a five-point Likert scale from 1 ("not at all") to 5 ("very much") to indicate how satisfied they were with their follow-up care.

Sexual function

Sexual function is assessed using the Female Sexual Functioning Inventory (FSFI) (Rosen et al., 2000), which assesses female sexual function. In addition, a female sexual function distress scale will be used. This latter scale can be used to assess females that do not have an active sexual life or perhaps never have had that. Questions concerning gender identity and social relations are included stemming from the Projekt SEXUS' examination of Danes sexuality (https://www.projektsexus.dk/).

Quality of Life (QoL)

To maximize the content validity of this study's primary outcome concerning sexuality, QoL will be assessed using two of the most prominent and well-validated QoL instruments: the brief version of the World Health Organization's Quality of Life Assessment (WHOQOL-

BREF)(1998) and the RAND Corporation's Short Form Health Survey (SF-36)(Bjorner et al., 1998). The WHOQOL-BREF is a 26-item assessment of individuals' perceived QoL during the preceding 2 weeks. Twentyfour of these items are divided across four domains: "physical health" (seven items), "psychological health" (six items), "social relationships" (three items), and "environmental health" (eight items). The final two domains—general health and overall QoL—are composed of one item each. Each item is rated on a Likert scale from 1 ("very poor") to 5 ("very good"). The SF-36 comprises eight domains: "physical functioning" (ten items), "role physical" (four items), "bodily pain" (two items), "general health" (five items), "vitality" (four items), "social functioning" (two items), "role emotional" (three items), and "mental health" (five items). Two standardized summary scores—the physical component summary and the mental component summary—will be calculated based on the subscales. The physical component summary score will be calculated using the four subscales in the physical domain (physical functioning, role physical, bodily pain, and general health), and the mental component summary score will be calculated from the four subscales in the mental domain (mental health, vitality, social functioning, and role emotional).

Perceived stress

Perceived stress will be assessed with a stress scale.

The Center for Epidemiologic Studies Depression Scale (CES-D)

Depressive symptoms will be assessed with the CES-D questionnaire, which is a commonly used freely available self-report measure of depressive symptoms(Carleton et al., 2013).

Adult ADHD Self-Report Scale

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist will be used to asses for ADHD symptoms. The reasoning behind testing for ADHD symptoms is that such symptoms are more frequently seen among both children and adults with Turner syndrome (Hutaff-Lee et al., 2019).

Body image

Body image is a multidimensional construct which includes self-perceptions and attitudes that relates to the body. Body image involves related components, such as how appearance is evaluated, how the body is esteemed by the individual, and how accurate ones body size is perceived. Body image will be assessed with a short questionnaire (Avalos et al., 2005). Body image has been linked a number of conditions, such as eating disorders, negative affect, social anxiety and inhibition, and is also related to sexuality (Avalos et al., 2005). Body image has only been sparingly examined in TS. One study concluded that the bodily attitude scale was rated similarly among TS females and an appropriate control group (Lagrou et al., 2006). Here, we want to add this concept of body image in order to ascertain whether it affect sexuality.

Statistical analysis

Descriptive statistics and bivariate correlations will be computed. Then separate group comparisons will be conducted between Turner syndrome participants and controls for each of the study variables. Females with Turner syndrome receiving hormonal replacement therapy will be compared with those who do not receive this treatment. Structural equation modelling will be used to identify independent predictors of physical

and mental quality of life (PQoL and MQoL, respectively)—both within and between women with Turner syndrome and controls. This will be done in order to determine how these factors combine to predict both quality of life outcomes. Subsequently, path analyses will be performed and used to identify direct and indirect links between being Turner syndrome or control, quality of life, sexuality, body image and other variables. Since data is entered directly in RedCap by the participants, there will be no need for us having to enter data manually.

Ethical perspectives

This is a questionnaire study without any kind of intervention, other than asking participants to answer questions as indicated above. Participants will be anonymous and not known to us, and it will not be possible to identify participants. Permission from the science ethics committee is therefore not necessary in accordance with Danish law and collection of informed consent will not be performed. Nevertheless, we will inform each participant concerning the theme and scope of this questionnaire study (see appendix 1 - front page).

Results

The results from this study is presently pending, as we are awaiting answers from the participants. Presently, prospective participants with Turner syndrome are being contacted. When we know who are being contacted, we will contact Statistics Denmark, who will then help us with the matching of controls.

Discussion

Sexuality in Turner syndrome is likely a complex construct that at this point in time is not fully understood. Based on the available literature it seems that there is a lack of knowledge concerning sexuality in Turner syndrome and how interactions are present with physical stigma, such as short stature and sometimes simply "looking different", i.e. having a syndrome which other people will often, but not always, be able to spot, presence of morbidity, the psychological impact of infertility and the need for taking medication as a very young person. Other variables that will likely impact sexuality are socio-economic status, physical appearance (BMI, height), quality of life, and exercise capacity – variables that was shown to interact in Klinefelter syndrome is complex ways (Skakkebaek et al., 2018). In addition, it is likely that the specific neurocognitive phenotype and the often encountered social communication challenges may further complicate matters. As mentioned above, no studies have examined the impact female hormonal replacement therapy in Turner syndrome on sexuality, and even in the broader context of premature ovarian failure, this subject is virtually unstudied (Nappi et al., 2019). And given the multitude of ways that hormonal replacement therapy can be devised in Turner syndrome (Gravholt et al., 2017; Klein et al., 2018), it is clearly unsatisfactory not to be able to present females with Turner syndrome with an evidence-based therapy that will create an optimal starting point for the development of a healthy sexuality with in a sound biopsychosocial framework.

In another endocrine condition with altered levels of sex hormones, congenital adrenal hyperplasia, there have been scant investigations of sexuality. Both males and females with congenital adrenal hyperplasia have a disordered secretion of especially adrenal androgens. Among females with congenital adrenal hyperplasia, many will have

an elevated secretion of androgens, necessitating treatment with cortisol (Hydrocortisone) and aldosterone (Florinef), in order to normalize levels. However, during intra-uterine life the elevated production and secretion of androgens will have been unchecked and often one can see internal and external genitalia that have been masculinized and sometimes this will necessitate genital operations. Furthermore, the brain may also have been partly masculinized which may lead to gender dysphoria (a contentious term, that not all may adher to)(Speiser et al., 2018). During adult life several studies have documented that sexuality among females with congenital adrenal hyperplasia can be troublesome (Meyer-Bahlburg et al., 2008), and quality of life decreased in comparison with controls (Johannsen et al., 2006). Others have found that sexuality is rated almost similarly as among controls, despite having been subjected to genital operations (Lesma et al., 2014).

Beyond the familiar medical problems of childhood, adult women with Turner syndrome must be monitored for both common medical problems (e.g., hypertension) and Turner syndrome specific disorders (e.g., aortic dilatation and dissection). In addition to treating the medical issues, the management of an adult woman with Turner syndrome benefits from deliberate care coordination (Freriks et al., 2011; Trolle et al., 2012b). This requires a team leader which in Denmark would be within a Turner syndrome clinic which serves as coach to a large team, or as the coordinator at the center of spokes on a wheel. For patients and providers, the recent international guidelines (Gravholt et al., 2017) were created to bring consistency to care, but should not be viewed as rigid rules or self-enacting.

Becoming an independent woman with Turner syndrome with a fulfilling sexual life in addition to coping with an often significant physical and mental morbidity, is a continuation of the transitional period into the third decade and beyond. Many young women with Turner syndrome follow familiar educational and social milestones from high

school, often progressing to university or other kinds of education, and occasionally to advanced degrees. Ideally, women of all ages will be motivated to seek and obtain employment. For many women with Turner syndrome there may be barriers to independence related to neuropsychologic challenges, mental health problems and in addition a less than fulfilling sexual life, which may delay or prevent independence. Reliance on parents for financial and healthcare support may be prolonged. Professional life and career "coaches" can be invaluable to provide direction and enhance confidence.

It is not uncommon for Turner syndrome specialists to hear that an adolescent or adult patient has never met another individual with Turner syndrome. With the explosion of information on the Internet, a simple query using any major search engine produces a profusion of photographs, videos, and educational figures. Not all are accurate or representative, but they do provide easy access to the subject matter. For some women, curiosity is tempered with hesitation and a wish to preserve their privacy. Those who are very shy or dealing with social interaction challenges common in Turner syndrome may be reluctant to meet others and discuss issues related to sexuality. Because of the wide spectrum of appearance and function associated with mosaicism, some individuals may not identify with Turner syndrome as a diagnostic category or label. Those who seek a more realistic opportunity for socializing and education are usually delighted to become members of the support groups for individuals, families, and friends of Turner syndrome. In particular, the national association plays an important role in creating a social milieu, with education and access to research through its website, as well as through local and annual national meetings. In turn, Turner syndrome clinicians and bench scientists can meet girls and women in a more relaxed atmosphere than the typical clinic visit. In Denmark, the national Turner syndrome association has taken initiatives to put issues concerning sexuality on the agenda,

and such initiatives are no doubt of enormous importance, because it shows individual women with Turner syndrome that also for them, sexuality is not taboo and can and should be addressed.

Table 1. Symptoms associated with Turner syndrome and their approximate prevalence.

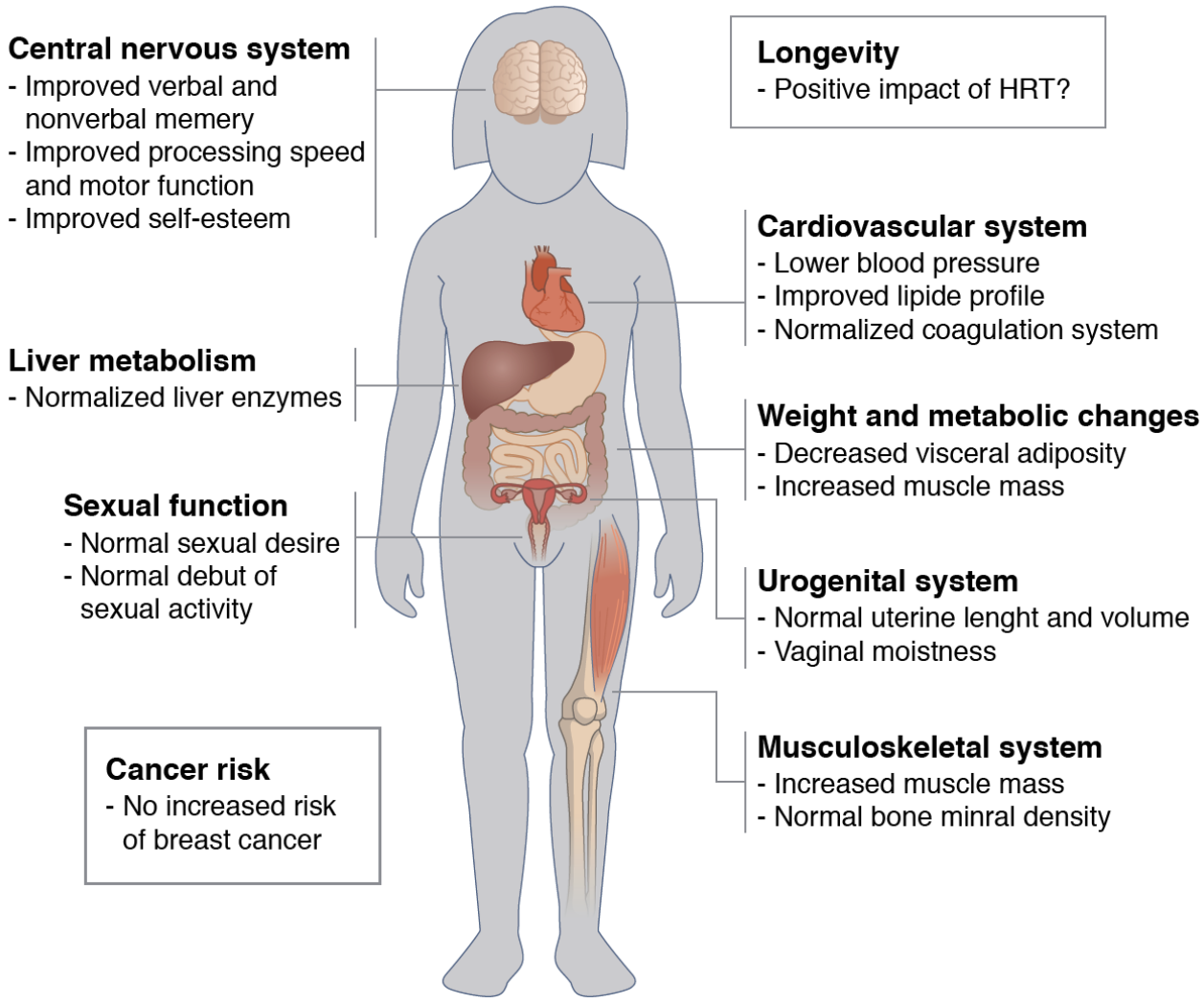
Feature	Frequency (%)[a]
Endocrine disorders	
Growth failure and reduced adult height	95–100
Hypergonadotropic hypogonadism	90–95
Glucose intolerance	15–50
Type 1 diabetes mellitus	Unknown
Type 2 diabetes mellitus	10
Thyreoiditis and hypothyreosis	15–30
Android body composition	Unknown
Autoimmune diseases	Increased risk of all autoimmune conditions
Gastrointestinal and hepatic disorders	
Elevated hepatic enzymes	50–80
Coeliac disease	8
Inflammatory bowel disease	2–3
Phenotypic characteristics: eyes	
Epicanthus	20
Nearsightedness	20
Strabismus	15
Ptosis	10
Phenotypic characteristics: ears	
Infections of the middle ear	60
Hearing defects	30
Deformity of external ear	15
Phenotypic characteristics: mouth	
Micrognathia (small mandibular bone)	60
High-arched palate	35
Abnormal dental development	Unknown
Phenotypic characteristics: neck	
Low posterior hairline	40
Broad short-appearing neck	40
Pterygium colli (webbed neck)	25

Phenotypic characteristics: thorax	
Broad chest (shield chest)	30
Inverted nipples	5
Phenotypic characteristics: skin, nails and hair	
Increased skin ridge count	30
Lymphedema of hands and feet	25
Multiple pigmented naevi	25
Nail hypoplasia/dystrophy	10
Vitiligo	5
Alopecia	5
Phenotypic characteristics: skeleton	
Bone age delay	85
Decreased bone mineral content[b]	50–80
Cubitus valgus	50
Short fourth metacarpal	35
Genu valgum	35
Congenital hip luxation	20
Scoliosis	10
Madelung deformity	5
Phenotypic characteristics: heart	
Bicuspid aortic valve	14–34
Coarctatio aorta	7–14
Aortic dilation/aneurysm	3–42
Hypertension	50
Phenotypic characteristics: kidneys	
Horseshoe kidney	10
Abnormal positioning or duplication of renal pelvis, ureters or vessels	15
Renal aplasia	3
Neurocognitive and psychosocial issues[c]	
Emotional immaturity	~40
Specific (nonverbal) learning disorder	~40
Psychological and behavioral problems	~25
Failure to thrive during first year of life	50

[a]Please note that the approximate prevalence may differ between different karyotypic groups and in general females with the 45,X karyotype is more affected than other karyotypic groups.[b]In the absence of appropriate hormonal substitution therapy. [c]The data are inconsistent, and the given percentages should be viewed with caution.

Figure 1. **The beneficial effects of hormone substitution therapy in TS.**

The figure depicts putative beneficial effects of appropriate female sex hormone substitution therapy in TS. Not all these effects have been thoroughly proven in TS.



Reference List

(1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med* 28:551-558.

Amundson, E., Boman, U.W., Barrenas, M.L., Bryman, I., Landin-Wilhelmsen, K. (2010). Impact of growth hormone therapy on quality of life in adults with turner syndrome. *J Clin Endocrinol Metab* 95:1355-1359.

Avalos, L., Tylka, T.L., Wood-Barcalow, N. (2005). The Body Appreciation Scale: development and psychometric evaluation. *Body Image* 2:285-297.

Bakalov, V.K., Shawker, T., Ceniceros, I., Bondy, C.A. (2007). Uterine development in Turner syndrome. *J Pediatr* 151:528-531.

Bannink, E.M., Raat, H., Mulder, P.G., de Muinck Keizer-Schrama SM. (2006). Quality of life after growth hormone therapy and induced puberty in women with Turner syndrome. *J Pediatr* 148:95-101.

Berglund, A., Viuff, M.H., Skakkebaek, A., Chang, S., Stochholm, K., Gravholt, C.H. (2019). Changes in the cohort composition of Turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet J Rare Dis* 14:16-0976.

Bjorner, J.B., Thunedborg, K., Kristensen, T.S., Modvig, J., Bech, P. (1998). The Danish SF-36 Health Survey: translation and preliminary validity studies. *J Clin Epidemiol* 51:991-999.

Boman, U.W., Bryman, I., Halling, K., Moller, A. (2001). Women with Turner syndrome: psychological well-being, self-rated health and social life. *J Psychosom Obstet Gynaecol* 22:113-122.

Boman, U.W., Bryman, I., Moller, A. (2004). Psychological well-being in women with Turner syndrome: somatic and social correlates. *J Psychosom Obstet Gynaecol* 25:211-219.

Cardoso, G., Daly, R., Haq, N.A., Hanton, L., Rubinow, D.R., Bondy, C.A., Schmidt, P. (2004). Current and lifetime psychiatric illness in women with Turner syndrome. *Gynecol Endocrinol* 19:313-319.

Carel, J.C., Ecosse, E., Bastie-Sigeac, I., Cabrol, S., Tauber, M., Leger, J., Nicolino, M., Brauner, R., Chaussain, J.L., Coste, J. (2005). Quality of life determinants in young women with turner's syndrome after growth hormone treatment: results of the StaTur population-based cohort study. *J Clin Endocrinol Metab* 90:1992-1997.

Carel, J.C., Elie, C., Ecosse, E., Tauber, M., Leger, J., Cabrol, S., Nicolino, M., Brauner, R., Chaussain, J.L., Coste, J. (2006). Self-esteem and social adjustment in young women with Turner syndrome--influence of pubertal management and sexuality: population-based cohort study. *J Clin Endocrinol Metab* 91:2972-2979.

Carleton, R.N., Thibodeau, M.A., Teale, M.J., Welch, P.G., Abrams, M.P., Robinson, T., Asmundson, G.J. (2013). The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure. *PLoS One* 8:e58067-

Cleemann, L., Holm, K., Kobbernagel, H., Kristensen, B., Skouby, S.O., Jensen, A.K., Gravholt, C.H. (2017). Dosage of estradiol, bone and body composition in Turner syndrome: a 5-year randomized controlled clinical trial. *Eur J Endocrinol* 176:233-242.

Cleemann, L., Holm, K., Kobbernagel, H., Skouby, S.O., Kristensen, B., Smedegaard, H., Andersson, A.M., Cohen, A., Gravholt, C.H. (2011). Normal tempo of bone formation in Turner syndrome despite signs of accelerated bone resorption. *Horm Res Paediatr* 76:193-201.

Clifton, D. (2013) Let's talk about sex. In, Standing tall with Turner syndrome. Essays by women with Turner syndrome. Editor, Beit-Aharon, C. Nanomir Press, Newton, MA, 35-41.

Doerr, H.G., Bettendorf, M., Hauffa, B.P., Mehls, O., Partsch, C.J., Said, E., Sander, S., Schwarz, H.P., Stahnke, N., Steinkamp, H., Ranke, M.B. (2005). Uterine size in women with Turner syndrome after induction of puberty with estrogens and long-term growth hormone therapy: results of the German IGLU Follow-up Study 2001. *Hum Reprod* 20:1418-1421.

Downey, J., Elkin, E.J., Ehrhardt, A.A., Meyer, B.H.F., Bell, J.J., Morishima, A. (1991). Cognitive ability and everyday functioning in women with Turner syndrome. *J Learn Disabil* 24:32-39.

El-Mansoury, M., Barrenas, M.L., Bryman, I., Hanson, C., Landin-Wilhelmsen, K. (2009). Impaired body balance, fine motor function and hearing in women with Turner syndrome. *Clin Endocrinol (Oxf)* 71:273-278.

El-Mansoury, M., Barrenas, M.L., Bryman, I., Hanson, C., Larsson, C., Wilhelmsen, L., Landin-Wilhelmsen, K. (2007). Chromosomal mosaicism mitigates stigmata and cardiovascular risk factors in Turner syndrome. *Clin Endocrinol (Oxf)* 66:744-751.

Fjermestad, K.W., Naess, E.E., Bahr, D., Gravholt, C.H. (2016). A 6-year Follow-up survey of health status in middle-aged women with Turner syndrome. *Clin Endocrinol (Oxf)* 85:423-429.

Freriks, K., Timmermans, J., Beerendonk, C.C., Verhaak, C.M., Netea-Maier, R.T., Otten, B.J., Braat, D.D., Smeets, D.F., Kunst, D.H., Hermus, A.R., Timmers, H.J. (2011). Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab* 96:E1517-E1526.

Freriks, K., Verhaak, C.M., Sas, T.C., Menke, L.A., Wit, J.M., Otten, B.J., de Muinck Keizer-Schrama SM, Smeets, D.F., Netea-Maier, R.T., Hermus, A.R., Kessels, R.P., Timmers, H.J. (2015). Long-term effects of oxandrolone treatment in childhood on neurocognition, quality of life and social-emotional functioning in young adults with Turner syndrome. *Horm Behav* 69:59-67.

Gould, H.N., Bakalov, V.K., Tankersley, C., Bondy, C.A. (2013). High levels of education and employment among women with turner syndrome. *J Womens Health (Larchmt)* 22:230-235.

Gravholt, C.H., Andersen, N.H., Conway, G.S., Dekkers, O.M., Geffner, M.E., Klein, K.O., Lin, A.E., Mauras, N., Quigley, C.A., Rubin, K., Sandberg, D.E., Sas, T.C.J., Silberbach, M., Soderstrom-Anttila, V., Stochholm, K., van Alfen-van derVelden JA, Woelfle, J., Backeljauw, P.F. (2017). Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol* 177:G1-G70.

Gravholt, C.H., Chang, S., Wallentin, M., Fedder, J., Moore, P., Skakkebaek, A. (2018). Klinefelter Syndrome: Integrating Genetics, Neuropsychology, and Endocrinology. *Endocr Rev* 39:389-423.

Gravholt, C.H., Hjerrild, B.E., Mosekilde, L., Hansen, T.K., Rasmussen, L.M., Frystyk, J., Flyvbjerg, A., Christiansen, J.S. (2006). Body composition is distinctly altered in Turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. *Eur J Endocrinol* 155:583-592.

Gravholt, C.H., Juul, S., Naeraa, R.W., Hansen, J. (1996). Prenatal and postnatal prevalence of Turner's syndrome: a registry study. *BMJ* 312:16-21.

Gravholt, C.H., Klausen, I.C., Weeke, J., Christiansen, J.S. (2000). Lp(a) and lipids in adult Turner's syndrome: impact of treatment with 17beta-estradiol and norethisterone. *Atherosclerosis* 150:201-208.

Gravholt, C.H., Naeraa, R.W., Andersson, A.M., Christiansen, J.S., Skakkebaek, N.E. (2002). Inhibin A and B in adolescents and young adults with Turner's syndrome and no sign of spontaneous puberty. *Hum Reprod* 17:2049-2053.

Gravholt, C.H., Naeraa, R.W., Nyholm, B., Gerdes, L.U., Christiansen, E., Schmitz, O., Christiansen, J.S. (1998). Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. *Diabetes Care* 21:1062-1070.

Gravholt, C.H., Svenstrup, B., Bennett, P., Christiansen, J.S. (1999). Reduced androgen levels in adult Turner syndrome: influence of female sex hormones and growth hormone status. *Clin Endocrinol Oxf* 50:791-800.

Green, T., Bade, S.S., Chromik, L.C., Rutledge, K., Pennington, B.F., Hong, D.S., Reiss, A.L. (2015). Elucidating X chromosome influences on Attention Deficit Hyperactivity Disorder and executive function. *J Psychiatr Res* 68:217-25. doi: 10.1016/j.jpsychires.2015.06.021. Epub@2015 Jul 2.:217-225.

Hagen, C.P., Aksglaede, L., Sorensen, K., Main, K.M., Boas, M., Cleemann, L., Holm, K., Gravholt, C.H., Andersson, A.M., Pedersen, A.T., Petersen, J.H., Linneberg, A., Kjaergaard, S., Juul, A. (2010). Serum levels of anti-mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. *J Clin Endocrinol Metab* 95:5003-5010.

Hagstromer, M., Oja, P., Sjostrom, M. (2006). The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutr* 9:755-762.

Hart, S.J., Davenport, M.L., Hooper, S.R., Belger, A. (2006). Visuospatial executive function in Turner syndrome: functional MRI and neurocognitive findings. *Brain* 129:1125-1136.

Herrmann, M. ,Seibel, M.J. (2010). The effects of hormonal contraceptives on bone turnover markers and bone health. *Clin Endocrinol (Oxf)* 72:571-583.

Hogler, W., Briody, J., Moore, B., Garnett, S., Lu, P.W., Cowell, C.T. (2004). Importance of estrogen on bone health in turner syndrome: a cross-sectional and longitudinal study using dual-energy x-ray absorptiometry. *J Clin Endocrinol Metab* 89:193-199.

Hong, D.S., Dunkin, B., Reiss, A.L. (2011). Psychosocial functioning and social cognitive processing in girls with Turner syndrome. *J Dev Behav Pediatr* 32:512-520.

Hook, E.B. ,Warburton, D. (1983). The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Hum Genet* 64:24-27.

Hutaff-Lee, C., Bennett, E., Howell, S., Tartaglia, N. (2019). Clinical developmental, neuropsychological, and social-emotional features of Turner syndrome. *Am J Med Genet C Semin Med Genet* 181:126-134.

Johannsen, T.H., Ripa, C.P., Mortensen, E.L., Main, K.M. (2006). Quality of life in 70 women with disorders of sex development. *Eur J Endocrinol* 155:877-885.

Klein, K.O., Rosenfield, R.L., Santen, R.J., Gawlik, A.M., Backeljauw, P.F., Gravholt, C.H., Sas, T.C.J., Mauras, N. (2018). Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations. *J Clin Endocrinol Metab* 103:1790-1803.

Knickmeyer, R.C. ,Davenport, M. (2011). Turner syndrome and sexual differentiation of the brain: implications for understanding male-biased neurodevelopmental disorders. *J Neurodev Disord* 3:293-306.

Knickmeyer, R.C. ,Hooper, S.R. (2019). The deep biology of cognition: Moving toward a comprehensive neurodevelopmental model of Turner syndrome. *Am J Med Genet C Semin Med Genet* 181:91-99.

Koulouri, O., Ostberg, J., Conway, G.S. (2008). Liver dysfunction in Turner's syndrome: prevalence, natural history and effect of exogenous oestrogen. *Clin Endocrinol (Oxf)* 69:306-310.

Kubota, T., Wakui, K., Nakamura, T., Ohashi, H., Watanabe, Y., Yoshino, M., Kida, T., Okamoto, N., Matsumura, M., Muroya, K., Ogata, T., Goto, Y., Fukushima, Y. (2002). The proportion of cells with functional X disomy is associated with the severity of mental retardation in mosaic ring X Turner syndrome females. *Cytogenet Genome Res* 99:276-284.

Lagrou, K., Froidecoeur, C., Verlinde, F., Craen, M., De Schepper, J., Francois, I., Massa, G. (2006). Psychosocial Functioning, Self-Perception and Body Image and their Auxologic Correlates in Growth Hormone and Oestrogen Treated Young Adult Women with Turner Syndrome. *Horm Res* 66:277-284.

Lasaite, L., Lasiene, D., Lasas, L. (2010). Cognition, emotions and quality of life in Lithuanian girls with Turner syndrome after growth hormone therapy discontinuation. *J Pediatr Endocrinol Metab* 23:443-450.

Lesma, A., Bocciardi, A., Corti, S., Chiumello, G., Rigatti, P., Montorsi, F. (2014). Sexual function in adult life following Passerini-Glazel feminizing genitoplasty in patients with congenital adrenal hyperplasia. *J Urol* 191:206-211.

Lesniak-Karpiak, K., Mazzocco, M.M., Ross, J.L. (2003). Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *J Autism Dev Disord* 33:55-67.

Lunding, S.A., Aksglaede, L., Anderson, R.A., Main, K.M., Juul, A., Hagen, C.P., Pedersen, A.T. (2015). AMH as Predictor of Premature Ovarian Insufficiency: A Longitudinal Study of 120 Turner Syndrome Patients. *J Clin Endocrinol Metab* 100:E1030-E1038.

McCauley, E., Feuillan, P., Kushner, H., Ross, J.L. (2001). Psychosocial development in adolescents with Turner syndrome. *J Dev Behav Pediatr* 22:360-365.

Meyer-Bahlburg, H.F., Dolezal, C., Baker, S.W., New, M.I. (2008). Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. *Arch Sex Behav* 37:85-99.

Nadeem, M. ,Roche, E.F. (2014). Health-related quality of life in Turner syndrome and the influence of key features. *J Pediatr Endocrinol Metab* 27:283-289.

Naess, E.E., Bahr, D., Gravholt, C.H. (2010). Health status in women with Turner syndrome: a questionnaire study on health status, education, work participation and aspects of sexual functioning. *Clin Endocrinol (Oxf)* 72:678-684.

Nappi, R.E., Cucinella, L., Martini, E., Rossi, M., Tiranini, L., Martella, S., Bosoni, D., Cassani, C. (2019). Sexuality in premature ovarian insufficiency. *Climacteric* 22:289-295.

Negreiros, L.P., Bolina, E.R., Guimaraes, M.M. (2014). Pubertal development profile in patients with Turner syndrome. *J Pediatr Endocrinol Metab* 27:845-849.

Nielsen, J. ,Wohlert, M. (1990). Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Birth Defects Orig Artic Ser* 26:209-223.

Ostberg, J.E., Storry, C., Donald, A.E., Attar, M.J., Halcox, J.P., Conway, G.S. (2007). A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. *Clin Endocrinol (Oxf)* 66:557-564.

Pasquino, A.M., Passeri, F., Pucarelli, I., Segni, M., Municchi, G. (1997). Spontaneous pubertal development in Turner's syndrome. Italian Study Group for Turner's Syndrome. *J Clin Endocrinol Metab* 82:1810-1813.

Prakash, S.K., Lugo-Ruiz, S., Rivera-Davila, M., Rubio, N., Jr., Shah, A.N., Knickmeyer, R.C., Scurlock, C., Crenshaw, M., Davis, S.M., Lorigan, G.A., Dorfman, A.T., Rubin, K., Maslen, C., Bamba, V., Kruszka, P., Silberbach, M. (2019). The Turner syndrome research registry: Creating equipoise between investigators and participants. *Am J Med Genet C Semin Med Genet* 181:135-140.

Reimann, G.E., Bernad Perman, M.M., Ho, P.S., Parks, R.A., Comis, L.E. (2018). Psychosocial Characteristics of Women with a Delayed Diagnosis of Turner Syndrome. *J Pediatr* 199:206-211. doi: 10.1016/j.jpeds.2018.03.058. Epub@2018 May 9.:206-211.

Reis, C.T., de Assumpcao, M.S., Guerra-Junior, G., de Lemos-Marini, S.H.V. (2018). Systematic review of quality of life in Turner syndrome. *Qual Life Res* 10-1810.

Rolstad, S.G., Moller, A., Bryman, I., Boman, U.W. (2007). Sexual functioning and partner relationships in women with turner syndrome: some empirical data and theoretical considerations regarding sexual desire. *J Sex Marital Ther* 33:231-247.

Ros, C., Alobid, I., Balasch, J., Mullol, J., Castelo-Branco, C. (2013). Turner's syndrome and other forms of congenital hypogonadism impair quality of life and sexual function. *Am J Obstet Gynecol* 208:484-486.

Rosen, R., Brown, C., Heiman, J., Leiblum, S., Meston, C., Shabsigh, R., Ferguson, D., D'Agostino, R., Jr. (2000). The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 26:191-208.

Ross, J.L., Roeltgen, D., Feuillan, P., Kushner, H., Cutler, G.B., Jr. (2000). Use of estrogen in young girls with Turner syndrome: effects on memory. *Neurology* 54:164-170.

Ross, J.L., Roeltgen, D., Feuillan, P., Kushner, H., Cutler-GB, J. (1998). Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab* 83:3198-3204.

Rovet, J. (2004). Turner syndrome: a review of genetic and hormonal influences on neuropsychological functioning. *Child Neuropsychol* 10:262-279.

Russell, H.F., Wallis, D., Mazzocco, M.M., Moshang, T., Zackai, E., Zinn, A.R., Ross, J.L., Muenke, M. (2006). Increased prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. *J Pediatr Psychol* 31:945-955.

Schmidt, P.J., Cardoso, G.M., Ross, J.L., Haq, N., Rubinow, D.R., Bondy, C.A. (2006). Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *JAMA* 295:1374-1376.

Schoemaker, M.J., Swerdlow, A.J., Higgins, C.D., Wright, A.F., Jacobs, P.A. (2008). Mortality in women with Turner syndrome in Great Britain: a national cohort study. *J Clin Endocrinol Metab* 93:4735-4742.

Sheaffer, A.T., Lange, E., Bondy, C.A. (2008). Sexual function in women with turner syndrome. *J Womens Health (Larchmt)* 17:27-33.

Skakkebaek, A., Moore, P.J., Chang, S., Fedder, J., Gravholt, C.H. (2018). Quality of life in men with Klinefelter syndrome: the impact of genotype, health, socioeconomics, and sexual function. *Genet Med* 20:214-222.

Speiser, P.W., Arlt, W., Auchus, R.J., Baskin, L.S., Conway, G.S., Merke, D.P., Meyer-Bahlburg, H.F.L., Miller, W.L., Murad, M.H., Oberfield, S.E., White, P.C. (2018). Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 103:4043-4088.

Stochholm, K., Juul, S., Juel, K., Naeraa R.W., Gravholt, C.H. (2006). Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab* 91:3897-3902.

Sutton, E.J., McInerney-Leo, A., Bondy, C.A., Gollust, S.E., King, D., Biesecker, B. (2005). Turner syndrome: four challenges across the lifespan. *Am J Med Genet A* 139A:57-66.

Taback, S.P. ,Van, V.G. (2011). Health-related quality of life of young adults with Turner syndrome following a long-term randomized controlled trial of recombinant human growth hormone. *BMC Pediatr* 11:49-

Tanaka, T., Igarashi, Y., Ozono, K., Ohyama, K., Ogawa, M., Osada, H., Onigata, K., Kanzaki, S., Kohno, H., Seino, Y., Takahashi, H., Tajima, T., Tachibana, K., Tanaka, H., Nishi, Y., Hasegawa, T., Fujita, K., Yorifuji, T., Horikawa, R., Yokoya, S. (2015). Frequencies of spontaneous breast development and spontaneous menarche in Turner syndrome in Japan. *Clin Pediatr Endocrinol* 24:167-173.

Trolle, C., Hjerrild, B., Cleemann, L., Mortensen, K.H., Gravholt, C.H. (2012a). Sex hormone replacement in Turner syndrome. *Endocrine* 41:200-219.

Trolle, C., Mortensen, K.H., Hjerrild, B.E., Cleemann, L., Gravholt, C.H. (2012b). Clinical care of adult Turner syndrome--new aspects. *Pediatr Endocrinol Rev* 9 Suppl 2:739-49.:739-749.

Tuke, M.A., Ruth, K.S., Wood, A.R., Beaumont, R.N., Tyrrell, J., Jones, S.E., Yaghootkar, H., Turner, C.L.S., Donohoe, M.E., Brooke, A.M., Collinson, M.N., Freathy, R.M., Weedon, M.N., Frayling, T.M., Murray, A. (2018). Mosaic Turner syndrome shows reduced penetrance in an adult population study. *Genet Med* 10-0271.

Viuff, M.H., Stochholm, K., Uldbjerg, N., Nielsen, B.B., the Danish Fetal Medicine Study Group, Gravholt, C.H. (2015). Only a minority of sex chromosome abnormalities are detected by the Danish national prenatal screening program for Down syndrome. *Hum Reprod* 30:2419-2426.

Zuckerman-Levin, N., Frolova-Bishara, T., Militianu, D., Levin, M., Aharon-Peretz, J., Hochberg, Z. (2009). Androgen replacement therapy in Turner syndrome: a pilot study. *J Clin Endocrinol Metab* 94:4820-4827.