Sex Chromosome Aneuploidies and Fertility: 47 XXY, 47XYY, 47XXX, and 45X/47XXX

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ABSTRACT

The overall incidence of sex chromosome aneuploidies is approximately 1 per 500 live-born infants, but far more common at conception. I shall review the fertility aspects of the sex chromosome trisomies, XXY, XYY, XXX, with special reference to the karyotype 45,X/47,XXX. Each has a “specific” (but variable) phenotype, but may be modified by mosaicism. Although the alterations in the hypothalamic-pituitary-gonadal axis are important (and discussed), the emphasis here is on potential fertility and if one might predict that at various epochs within an individual’s life span: fetal, “mini”-puberty, childhood, puberty and adulthood.

The reproductive axis is often affected in females with the 47,XXX karyotype with diminished ovarian reserve and accelerated loss of ovarian function. Fewer than 5 % of females with the Turner syndrome have the 45,X/47,XXX karyotype. They have taller stature and less severe fertility issues compared to females with the 45,X or other forms of Turner syndrome mosaicism. For the 47,XXY karyotype non-obstructive azoospermia is almost universal with sperm retrieval by micro-testicular sperm extraction possible in slightly fewer than half of the men. Men with the 47,XYY karyotype have normal to large testes and much less testicular dysfunction than those with the 47,XXY karyotype. They do have a slight increase in infertility compared to the reference population, but not nearly so severe as those with 47,XXY karyotype. Assisted reproductive technology, especially micro-TESE has an important role, especially for those with 47,XXY; however, more recent data show promising techniques for the in vitro maturation of spermatogonial stem cells and 3-D organoids in culture. Assisted reproductive
technology is more complex for the female, but vitrification of oocytes has shown promising advances.

INTRODUCTION

Overall the incidence of sex chromosome aneuploidy is quite common, approximately 1 per 500 live births, but far more common at conception. Held and colleagues [1] estimated that less than 1% of conceptions with the 45,X karyotype were live born. In fact, the 45,X karyotype is the single most common chromosomal aneuploidy noted for fetal loss [2].

The purpose of this review is to explore the fertility aspects of the sex chromosome trisomies XXY, XYY, XXX, with specific reference to the mosaic karyotype 45,X/47,XXX. All have distinct phenotypes with altered hypothalamic-pituitary-gonadal (HPG) axis, as recently reviewed [3]. However, these phenotypes and states of the HPG axis are modified by mosaicism often expressed differently among the many tissues and organs of the individual. This report is specifically crafted to be included as part of a single issue of Endocrine Connections that gathered papers from The 3rd International Workshop on Klinefelter Syndrome, Trisomy X, and XYY that was held in Leiden, the Netherlands, on September 12-14, 2022. It is derived from one of the keynote presentations: *Sex Chromosome Aneuploidies and Fertility: 47,XXY, 47,XYY, 47,XXX, and 45,X/47,XXX*. The purpose of the review is to explore the fertility aspects of the above noted trisomies with special attention to women with 45,X/47,XXX. The endocrine aspects have been previously reviewed [3]. A summary table (Table 1) has been added in which the trisomy sex chromosome aneuploidies are compared and contrasted with reference to the phenotype, karyotype, hypothalamic-pituitary gonadal (HPG) axis hormonal levels, and fertility
preservation options. The data set includes: the specific karyotype, with the caveat re: determined or occult mosaicism, circulating levels of the hormones of the HPG axis and antral follicle content when available, and finally methods of oocyte), ovarian tissue or embryo cryopreservation (including vitrification) [4]. Additional data on the cardiovascular contraindications to fertility preservation are noted in summary [5].

It should be noted that the greatest amount of data is available for men with the Klinefelter syndrome and women with the Turner syndrome. Many fewer are available for the other trisomies, consisting of case reports and reviews of other case reports. The Turner syndrome is not a sex chromosome trisomy, but is relevant to the trisomies because of the 45,X/47,XXX mosaic karyotype. Early primary ovarian failure is common in many girls with the Turner syndrome; however, up to one-third will have some degree of spontaneous pubertal maturation, but a much smaller percentage complete puberty spontaneously and even fewer have a spontaneous pregnancy [6, 7]. If fertility can be preserved, either spontaneous or through oocyte, ovarian tissue or embryo cryopreservation (including oocyte vitrification), then one must be concerned that the resulting pregnancy will be high risk with mortality from aortic dissection and morbidity from cardiac (hypertensive) and other associated medical conditions [8, 9]. The risk of mortality from aortic dissection may be as high as 150-fold above the general population [10]. Those factors more favorable to spontaneous fertility or the greater probability of retrieving oocytes include: a karyotype with a 2nd or 3rd cell line, a cell line with more than one X chromosome and spontaneous menarche [11] or low FSH and high AMH levels to go along with spontaneous puberty and menarche [6-9]. Those with a lymphocyte (and some other tissues) karyotype, 45,X and spontaneous puberty or fertility are likely to carry cryptic mosaicism in the ovary [12]. By contrast, Goldstein and co-investigators reported a girl who phenotypically had
multiple stigmata of the Turner syndrome and the biochemical signature of hypergonadotropic hypogonadism, but multiple tissues with a 46,XX karyotype. The only tissue that had a 45,X karyotype was in the streak gonad [13].

The emphasis here will be on fertility and how one might predict that at various epochs within an individual’s lifespan: fetal, “mini”-puberty, childhood, puberty, adulthood and aging (summarized in Table 1).

PHYSIOLOGY

Fetal

Masculinization of the fetus is a very time-sensitive process depending on androgen action at specific time windows during fetal development. The masculinization programming window (late first to early second trimester) [14] depends on earlier in gestation androgen action [15, 16]. It involves the GnRH neurons developing and moving from their origin (epithelial tissue of the olfactory placode) migrating along nerve fibers through the cribriform plate to the preoptic area of the medial basal hypothalamus [17]. These neurons become active to permit the pituitary to secrete LH and FSH at approximately 9 week’s gestation in both sexes; however, due to sex hormone negative feedback the gonadotropin levels decline until birth.

Fetal Leydig cells produce testosterone (T) and the Sertoli cells secrete anti-Müllerian hormone (AMH) that leads to the regression of the Müllerian structures [18]. The fetal T fosters the development of the male urogenital system. The levels of circulating T are high and it is assumed that the levels of intra-testicular T are (much) higher. However, there will be no spermatogenesis (capacity for reproduction), just as there is none at “mini”-puberty because the expression of the androgen receptor on the Sertoli cells remains very low until early childhood [19].
anogenital distance may be useful as a marker of intrauterine androgen action [20]. The Leydig cell also produces insulin-like factor 3, an important component acting in concert with T to promote testicular descent [21].

The female fetus lacks AMH, permitting the Müllerian structures to remain and lacks the T to stimulate the male ducts. The development of primordial follicles precedes the 13th week of gestation, but the bulk of follicular development occurs after the 14th and 15th weeks with a peak approximating 7 x 10^6 germ cells by the fifth month of gestation [22, 23]. During the third trimester the pool of oocytes is being established. Then begins a physiological decline until menopause. It should be noted that follicular growth and atresia occur during all stages of development—fetal to menopause. At birth there are somewhat fewer than 1 x 10^6 immature follicles, each with an oocyte arrested in prophase of the first meiotic division [24].

**Mini-puberty**

After birth the newborn is no longer susceptible to the gonadotropin inhibiting effects of placental estrogens. The HPG axis becomes progressively more active, but with different kinetics in boys and girls (reviewed in [3]). The LH levels are higher in boys than girls and the opposite true for FSH. LH levels peak within the first 10 weeks in boys resulting in the T peak. The LH levels then decline to prepubertal levels by the sixth month to remain low until the onset of puberty. The FSH levels remain elevated for up to 4 years in girls, although the LH levels decrease by the sixth month.

Normal mini-puberty is likely important, perhaps critical, for future fertility, as there are increases in the numbers of Sertoli cells [25] and germ cells [26]. Despite low adult normal
values for T with perhaps much higher levels of intra-testicular T, there is no spermatogenesis, since the Sertoli cells do not have active androgen receptors [19].

During mini-puberty there is augmented linear growth and less fat accumulation in boys compared to girls as well as increased penile growth in the boys [27]. Testosterone treatment within the first 4 months of life of boys with Klinefelter syndrome increased body mass, especially the fat-free component as well as increased body length and stretched penile length [28]. For those with gonadotropin deficiency, it may be prudent to treat with gonadotropins rather than T to induce mini-puberty, for that should stimulate the Leydig cell (endogenous T) and Sertoli cell (eventual spermatogenesis) functions [29].

There is greater gain in fat mass and lesser gain in fat free mass in the girls during the first six months of life [27] with a greater increase in length in the boys during this time frame, likely due to the effects of testosterone. There appears to be no difference in the length velocity of boys and girls beyond 6 months [30].

The re-activated HPG axis also affects follicular development in mini-puberty and beyond. After approximately 4 months the gonadotropin and estradiol concentrations decline reaching their nadir (childhood levels) at 1-2 years and remain very low until mid-to-late childhood (see below)

**Childhood**

Following mini-puberty one notes relative gonadal quiescence determined by a centrally active suppression of the gonadal axis. This occurs whether the child had primary hypogonadism or is eugonadal and has been studied in girls with the Turner syndrome [31] and boys with the testicular regression (vanishing testis) syndrome [32]. One is aware of some very low level follicular activity during the pre-pubertal hiatus between mini-puberty and pubertal maturation.
because the levels of estradiol are significantly higher in girls than boys when estradiol is measured by an appropriately sensitive assay [33].

**Puberty**

Clinically, puberty is heralded by breast development in girls and testicular enlargement in boys. However, there is evidence for HPG activity and pulsatile release of LH, albeit at very low levels, well before the external signs of pubertal maturation. Pulsatile secretion of LH begins at night and is virtually at low basal levels as the morning begins. Gonadal steroid secretion remains low and then begins to appear early in the morning after the nighttime pulses of LH. As puberty unfolds the secretion of LH continues further into the day, although still showing a nighttime predominance, especially at mid-puberty. Steroid hormone secretion become greater and lasts for a greater period of the day before demonstrating the adult pattern very late in pubertal maturation [34-37].

In boys intra-testicular concentrations of T up to 100 times those in the circulation and FSH stimulation of the Sertoli cells drive spermatogenesis, since the Sertoli cells now have functional androgen receptors [38]. In a similar manner the early stages of follicular development are mainly caused by local factors, but both gonadotropins are necessary for further follicular maturation [39]. However, the AMH levels remain rather constant and are an indication of follicular maturation at least through the pre-antral stage.

**Table 1 (near here)**

**Karyotype 47, XXX**

Trisomy X syndrome occurs in approximately 1 per thousand live-born females; however, it is estimated that only approximately 10 % of these females are ever diagnosed correctly [40]. Girls
with this syndrome have a wide variety of medical and psychological challenges, most commonly tall stature, hypotonia in infancy, clinodactyly, epicanthal folds and constipation [41-43]. Multiple psychological difficulties including speech and language deficits, learning disabilities and attention deficit disorder are common. An unbiased sample of 244,000 women from the UK biobank noted a lower prevalence than previously reported, 45/100,000 [44]. The reproductive axis is often affected, but with a normal age at menarche, diminished ovarian reserve and an accelerated loss of ovarian function (premature ovarian insufficiency) prominent. Menopause occurs approximately 5 years earlier [44]. Although infertility has been described previously, the UK biobank study noted a similar number of pregnancies and no additional pregnancy loss than 46,XX controls [44]. Others have found diminished fertility by approximately 1/3, based on the Danish Cytogenetic Central Registry [45]. Osteoporosis and psychological distress are common in women with the 47, XXX karyotype, as are a series of hospitalization-based organ system diagnoses. Those with the mosaic karyotype 46,XX/47,XXX were intermediate between those 47,XXX and those 46,XX [46]. Baronchelli and colleagues evaluated a 269 women with premature ovarian failure and noted a 5-fold increase of those with 47,XXX karyotype compared to those with 46,XX [47]. A similar percentage was noted in a series of 531 Chinese women with premature ovarian failure (~0.6%) [48]. In a smaller series of 52 women with premature ovarian failure, 2 were noted to have the 47,XXX karyotype along with autoimmune thyroid disease [49].

Davis and colleagues measured anti-Müllerian hormone (AMH) levels, a marker of ovarian reserve for it reflects the primordial follicle pool [43]. It is produced by the granulosa cells of the maturing follicles and thus is an index of the remaining number of follicles. The median level for the subjects with trisomy X was significantly below that of control females and all those with the
47, XXX karyotype had serum AMH concentrations below the median level of control subjects with most below the 2.5\textsuperscript{th} percentile. All subjects in both groups had normal levels of gonadotropins and estradiol. Twelve of thirteen girls with the 47,XXX karyotype above the age of 10 years had spontaneous menarche. It is likely in this population that the low AMH level will indicate diminished ovarian reserve and subsequent infertility. Given that the female with trisomy X syndrome is at higher risk for premature ovarian insufficiency, it may be prudent to periodically measure the AMH level and to consider fertility preservation options as young adults or as the levels of AMH decrease.

Assisted reproductive technology (ART) for women is more complex than that for men (see below). For women the steps include ovulatory stimulation, collection of gametes, \textit{in vitro} fertilization including intra-cytoplasmic sperm insertion (ICSI), \textit{in vitro} embryo culture, cryopreservation, embryo transfer and perhaps trophoblast or blastocyst biopsy [50]. More recently oocyte vitrification or fast freezing has replaced the slower method. The oocyte is rapidly supercooled and converted to a glass-like, amorphous solid to specifically prevent ice crystal formation [51]. Other applications of this technique include its use on sperm, ovarian tissue, and embryos. There are concerns from animal studies for disordered imprinting of specific genes, but this phenomenon is less well studied in the human [51]. Assisted reproductive technology is not often required for women with the 47,XXX karyotype or 45,X/47,XXX (just below).

\textbf{Karyotype 45,X/47, XXX}
Special consideration has been given to this variant of Turner syndrome. This chromosomal mosaic karyotype occurs in less than 5% of females with Turner syndrome [41]. Girls with this karyotype have few if any of the common stigmata of Turner syndrome (e.g., cardiovascular and renal anomalies). Short stature may be the only manifestation of a 45, X cell line. Ovarian function in women with the 45,X/47, XXX karyotype ranges from normal to virtually absent with normal ovarian anatomy to streak ovaries, likely depending on the tissue distribution of the two cell lines [52, 53]. Follicle number may be low with its attendant premature ovarian insufficiency, but spontaneous (natural) pregnancy is more common than the very low rate in those with 45, X karyotype [52]. There are multiple case reports, many with “a review of the literature” as part of the title. Tang and associates and Lim and associates have described single patients and perhaps have the most robust series of reported cases and case series [54, 55]. One might summarize that those with the 45,X/47,XXX mosaic karyotype in general have a mild Turner syndrome phenotype, most, but not all, with short stature, spontaneous pubertal maturation and menarche without structural abnormalities. Spontaneous pregnancies are far more common in these women than in those with other karyotypes; however, one must consider publication bias making it likely that the actual pregnancy rate is lower than commonly considered [52, 54]. The women are however prone to premature ovarian insufficiency, often by age 30 y. That should enter into family planning as an important part of care for those with this mosaic karyotype, encouraging them to start thinking about their fertility at an earlier age.

Although oocyte preservation is not so often required compared to women with a 45,X karyotype (noted in the introduction), one should periodically evaluate ovarian reserve and plan for assisted reproduction, if indicated.
Karyotype 47, XYY

The typical man with a 47,XYY karyotype has tall stature (approximately +1 SD) and normal sized-to-larger testes, as opposed to the small firm testes of the man with Klinefelter syndrome [56, 57]; however, some men do have smaller than normal testicular volume. Although there are limited data, pubertal maturation may be within normal limits and on time [57, 58]. For that reason, the genetic diagnosis may be delayed, with a median age of 17.1 years noted by a Danish registry study [59]; however, there are many more likely causes of delayed puberty in mid-to-late adolescent males, including the normal variant constitutional delay of growth and puberty and a large number of systemic diseases causing functional hypogonadotropic hypogonadism. Some may be identified in childhood with learning problems and delayed speech and language development, but most are not identified until much later. There are a series of comorbidities that accompany men with the 47,XYY karyotype: a 2.4 fold increase in hospital-based diagnoses, especially those based on congenital malformations, genetic disorders and disorders of multiple organ systems, compared to a proper control group [60]. There was also a 25 % increase in prescription of medications [60].

There is an increased percentage of men with 47, XYY over the general population presenting to infertility clinics [61]. Although only approximately 18 % of men with the XYY karyotype are eventually diagnosed, most are relatively young (median age at diagnosis is 15.1 years). That is well before issues of infertility present. Diagnosis is often based on the behavioral and learning disabilities with mild delays in language and motor development and higher rates of ADHD and autism spectrum disorder [62].
Most published series of diagnosed patients have a bias toward those infertile. The men have an increased incidence of sperm mosaicism and aneuploidy. In addition, sperm maturation may arrest at an immature state [61, 63]. Sperm counts may range from within normal limits to frank azoospermia and a low count can contribute to the increased incidence of infertility and require the use of in vitro fertilization or intracytoplasmic sperm injection (ICSI) to achieve biological pregnancy [64]. Men with the 47,XYY karyotype have a high rate of gonosomal aneuploidy in sperm and pre-implantation embryos [65].

**Karyotype 47,XXY**

Klinefelter syndrome is the leading genetic cause of testicular failure. Its incidence is approximately 1/650 males [66] with an expanded phenotype from the original description by HF Klinefelter in 1942 [67] of tall stature, gynecomastia and small testes and failure of spermatogenesis. The expanded phenotype now includes prepubertal and pubertal boys as well as behavioral and psychological factors [68, 69]. Pubertal maturation usually begins on time, but only progresses part way. The height increase may not begin until mid-childhood. The testes may increase to 6-8 mL as expected in an early pubertal male, but then stop growing and even regress to 4 to 6 mL [70] Testicular maturation starts on time, but by mid puberty there is often a marked rise in FSH concentration and a lesser rise in LH level [70]. Testosterone levels are often in the lower range of normal for stage of maturation, but may decrease further as destruction of the testis occurs. As the men age the expanded phenotype includes a higher prevalence of type 2
diabetes mellitus, dyslipidemia, fatty liver disease, hypercoagulability, osteopenia and osteoporosis [71].

Histologic evaluation shows near absence of germ cells in the late adolescent/emerging adult [72-74]. It should be noted that when evaluated by the micro-testicular sperm extraction technique, most men will have some spermatic tubules with sperm [72]. The process of tubule cell failure begins at the onset of puberty and then rapidly escalates. Nearly all have spermatogonia on testis biopsy before age 10 years [73, 74]. The transition to an emerging adult decreases that number to about 50% [72-74]. However, the external genitalia mature normally [70]. By mid-puberty there is often evidence for androgen deficiency. Gynecomastia rarely begins before puberty and is likely due to low androgen concentration, but increased estrogen levels due to a high level of the aromatase enzyme [75-76]. Early neurodevelopmental, behavioral and language difficulties are often presenting signs in childhood and may be the factor that sets the diagnostic odyssey in motion [77].

**Assisted Reproductive Technology (ART) for Men**

Assisted reproductive technology had permitted many men with Klinefelter syndrome (and other causes of male infertility) to father biological children. The various techniques available have been reviewed by Bernie and co-workers [78], but the most relevant to men with Klinefelter syndrome has been micro testicular sperm extraction (microTESE) [79] (see also a review of this technique with specific reference to men with Klinefelter syndrome, [80]). At present it is not possible to use the hormonal signature (LH, FSH, testosterone and Inhibin B) to predict in whom micro TESE will be helpful for either predicting who might have the possibility of sperm
extraction or the presence of spermatogonial stem cells (SSC). The closest to that are that the FSH levels are higher in those whose micro TESE harvesting has been unsuccessful compared to those successful; however, the median level of FSH is distinctly elevated in both groups [81].

**Spermatogonial Stem Cells (SSC) and the Future of Assisted Reproduction**

A new and exciting field in assisted reproductive technology is the use of SSC and the possibility of expanding and differentiating them to more mature sperm [81]. Functional SSCs from the seminiferous tubules may either self-renew or mature to become differentiating spermatogonia and then sperm. These SSCs are key to interventions to restore fertility: by transplantation, testicular tissue grafting, and *in vitro* or *ex vivo* spermatogenesis.

Deebel and colleagues have shown that SSC exist in men with Klinefelter syndrome, even those in whom microTESE was unsuccessful, but as noted above in diminishing numbers as the adolescent and emerging adults mature [81]. The seminiferous tubules of the prepubertal male seemingly have more SSC’s and may be appropriate for biopsy and extraction; however, all the attempts at extraction and proliferation are considered experimental and no clear protocol exists in man, although there is almost 30 years’ experience in the rodent [82]. Various “adjunctive” therapies have been tried, including stopping exogenous T therapy a few months before planned sperm extraction, adding therapy with hCG, and selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) with the goal to attain a proper T to E ratio to support spermatogenesis. Others have used intra-nasal T to attempt to preserve some gonadotropin function that will also support spermatogenesis.

Galdon and co-workers successfully propagated immature human SSC for almost 30 weeks with an approximate 10-fold increase in cell number after 11 days of culture [83]. They cultured
isolated testicular cells and their numbers markedly expanded. XXY spermatogonia were present at the start of the culture, but at the end there were not only XXY, but also XX and XY spermatogonia. However, the difficult step of in vitro spermatogenesis had not been accomplished at the time of that report, but it has been in some murine models [84].

Since germ cell loss accelerates in boys with the Klinefelter syndrome as they enter and progress through pubertal maturation, one might consider retrieving viable spermatogonia from peri-pubertal boys with KS. Testicular biopsies could be stored before expanding their cell numbers in in vitro culture. As a proof of concept Galdon and colleagues isolated testicular cells from 3 biopsies from adolescents with KS. A heterogeneous mix of spermatogonial stem cells, and somatic cells was cultured [85]. After a few days qPCR analysis revealed characteristic gene expression from undifferentiated spermatogonia, Leydig, Sertoli and peritubular cells with at least 1 X 10^6 fold increase in cell number. As time in culture increased in addition to XXY cells XY and XX cells were identified. The investigators considered such expansion could potentially enable spermatogonial stem cell transplantation [85]. To date there is no specific technique to return the cultured cells to the recipient, although in animals direct microinjection to the seminiferous tubules or the rete testis has been accomplished [82]. The small, often sclerosed testis of the man with Klinefelter syndrome would present an additional barrier compared to one who survived childhood malignancy [86].

A technologically advanced technique is to use three-dimentional testicular organoids to study human spermatogenesis (and perhaps gonadotoxicity) in vitro. Pendergraft and colleagues made such preparations and noted the formation and histology that indicated the three primary cell types, SSC, and Sertoli and Leydig cells [87]. They produced testosterone with or without added hCG, and had the appropriate cell-specific gene expression over time as well as somatic cell
functional markers. A proportion of the SSC’s did demonstrated spermatogenic differentiation. Although many hurdles remain, for example, spatio-temporal micro-environment and essential regulators of the process, optimization of the system and the ability to culture organoids from men with sex chromosomal aneuploidies to produce sperm \textit{in vitro} with this system may not be too many years into the future.

\textit{Ex vivo} spermatogenesis has its own set of challenges including the proper micro- and macro-environment for the culture of testicular fragments (not cells). To date the systems that have been tried are quite inefficient and not translated to primate testicular tissue [88].

The mico TESE technique is successful in perhaps half of the men who undergo that procedure. But what about the other half? Here is where the technique of propagating undifferentiated spermatogonia may be employed. Thus, there is hope that this \textit{in vitro} system may be translated to the infertile men with Klinefelter syndrome, especially those in whom no sperm were extracted on micro TESE. One of course would have to consider much younger patients with Klinefelter syndrome because as noted above there would be near universal availability of spermatogonial stem cells in those below 10 years with continuing loss as emerging adulthood is achieved. This would be another reason to make the diagnosis of Klinefelter syndrome earlier than at present.

\textbf{Summary and Conclusions}

Men and women who have the sex-chromosome aneuploidies have a number of alterations in their HPG axes (reviewed in [3]) and bio-behavioral development (reviewed in [77]). In addition to relatively wide variation among children and adults with the trisomies (XXX, XXY, XYY)
there is the added variability in mosaicism, tissue-by tissue. The focus here has been the natural and assisted fertility procedures that may be offered to these patients. Testicular sperm extraction and micro TESE have led to a marked rise in possible paternity for men, especially those with the Klinefelter syndrome. Newer methods of cryopreservation have made fertility possible for men with the trisomies and other conditions that lead to infertility. In addition cryopreservation (including oocyte vitrification) of follicles or ovarian tissue has changed the fertility landscape for those with mosaic Turner syndrome, perhaps most importantly those with the 45,X/47,XXX mosaic karyotype.

On the horizon are more sophisticated in vitro techniques to mature sperm, including co-culture with additional testicular tissue to the point of being able to devise and maintain 3-dimensional organoids capable of supporting germ cell differentiation.

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### Table 1 Phenotype and HPG Axis Function in Sex Chromosome Trisomies (details and original references in reference [3])

<table>
<thead>
<tr>
<th>Sex Chromosome Aneuploidy (trisomies)</th>
<th>Cardinal Manifestations</th>
<th>HPG axis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>45,X/47, XXX</strong></td>
<td>spontaneous puberty (all &gt;10 y) Menarche (all &gt;12 y) Pelvic ultrasound- most with normal ovaries <em>n.b.</em> some with premature ovarian failure increased incidence of autoimmunity</td>
<td>Basal FSH wnl or slight ↑ rest of HPG axis mainly wnl</td>
</tr>
<tr>
<td><strong>47,XXX</strong></td>
<td>tall stature hypotonia spontaneous puberty and menarche (on time) fertility is <em>likely</em> increased incidence of autoimmunity</td>
<td>FSH, LH slightly ↑ compared to controls ↑LH, FSH to GnRH stimulation E₂ INH B, ovarian volume ↓ (all indicative of dysregulated HPG axis at level of ovary)</td>
</tr>
<tr>
<td><strong>47,XXY</strong></td>
<td>tall stature (onset may be in mid-childhood) Accelerated germ cell loss at puberty Small testes (onset mid-adolescence) Speech and behavioral problems</td>
<td>mini-puberty-contradictory results Childhood-↑INH B; ↑AMH Adolescent usually nl T, but ↑ FSH, LH Adult primary hypogonadism</td>
</tr>
<tr>
<td><strong>47,XYY</strong></td>
<td>tall stature nl or large testes puberty usually wnl (limited data)</td>
<td>FSH ↑ but not to levels in XXY LH ↑ but less than FSH testosterone near bottom of normal range</td>
</tr>
</tbody>
</table>

(abbreviations: HPG hypothalamic, pituitary, gonadal; wnl within normal limits)