The natural history of endocrine function and spermatogenesis in Klinefelter syndrome: what the data show

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Once thought to be a chromosomal aberration associated with absolute sterility, Klinefelter syndrome may now be potentially treatable by testicular sperm retrieval coupled with intracytoplasmic sperm injection. With these therapeutic advances, azoospermic 47,XXY men now may have an opportunity for biological paternity. However, our knowledge of the basic mechanisms underlying germ cell loss and Leydig cell compromise is lagging, and is just now beginning to evolve and provide answers to some of the field's most vexing questions: how to maximize and preserve fertility in Klinefelter males many years or even decades before they wish to actively pursue fatherhood. This article reviews the development of the androgenic and spermatogenic compartments of the Klinefelter testis through puberty, and recommends that it is only with a clear understanding of the basic facts that a rational, considered approach to fertility optimization and preservation can be determined. (Fertil Steril® 2012;98:266–73. ©2012 by American Society for Reproductive Medicine.)

Key Words: Klinefelter syndrome, azoospermia, fertility preservation

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Klinefelter syndrome, the most common chromosomal abnormality found in the infertile male population (15% of azoospermic males), occurs at a frequency of 1/600 newborn males, as reviewed by Ghorbel et al. (1). There is some thought that the incidence may actually be increasing: a prevalence rise from 1.09 to 1.72 per 1,000 male births (2). Advancing paternal age may, in part, be causative (3, 4). In an adult male who presents with infertility and is found to have a 47,XXY Klinefelter karyotype, the chances of finding sperm during testis tissue extraction are approximately 50% (5–7). There do not seem to be many useful preoperative predictors of successful sperm recovery (8). There is a suggestion that age may be a factor (9), but this possibility should not necessarily be extrapolated to young men or serve as a reason to perform testicular sperm extraction (TESE) with cryopreservation before that boy or man is ready for parenthood, as some investigators have suggested (10). Usually, only a few individual seminiferous tubules are found sprinkled throughout large areas devoid of tubules and replaced by fibrosis and Leydig cell hyperplasia. This ability to treat and help Klinefelter men become fathers has stimulated a resurgence in interest, knowledge, and speculation about all aspects of this chromosomopathy.

Diagnosis may be made in several ways: as an unexpected outcome of amniocentesis, during childhood on a workup for existing learning difficulties, at the time of puberty for lack of virilization, during the teenage years after the finding of small testes on physical examination, or during adulthood during the workup of infertility (11). Many men with Klinefelter syndrome, when not diagnosed in childhood, grow and mature to lead healthy, productive lives (12). The wide and varied clinical spectrum is well reviewed by Aksglaede et al. (13) in 166 boys, adolescents, and adults with Klinefelter syndrome and by Abdel-Razic et al. (14) in 198 adult Klinefelter males with infertility.

It is unknown why a certain male will present on one end of the phenotypic spectrum with failure to

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virilize while another may actually be quite well androgenized with severe oligospermia. However, research and workshops are under way in an effort to find that answer, whether it be genetic, epigenetic, or a combination, as we still have so much to learn and so many questions to answer (15). For example, Bojesen et al. (16) reported that height, arm span, and bone mineral density at the spine and hip were positively correlated with androgen receptor polymorphism in the CAG_n repeat, a novel discovery that refuted the thought that these features were all the direct result of simply low levels of testosterone. Efforts are under way to try to increase identification of Klinefelter males as soon as possible to allow intervention at an earlier stage, although it is unknown whether that will necessarily change the course of the disorder. Although this may certainly turn out to be important for the learning difficulties that are part of the Klinefelter phenotype, it is unclear at this time whether early therapeutic involvement in terms of androgen replacement or fertility is helpful or hurtful to the individual. This article briefly summarizes what is understood about testicular function and anatomy in Klinefelter syndrome as regards both the androgenic and spermatogenic compartments.

WHAT IS KNOWN ABOUT THE EMBRYONIC, FETAL, AND INFANT 47,XXY TESTIS IN TERMS OF ANDROGENIC AND SPERMATOGENIC FUNCTION?

At approximately 5 to 6 weeks after fertilization, primitive bipotential germ cells, having originated in the yolk sac, migrate along the dorsal mesentery to the urogenital ridge, guided directionally by chemotactic signals (17, 18). A few weeks later, mesenchymal cells (nascent Leydig cells), interspersed between developing sex cords, begin to secrete testosterone and insulin-like factor 3 (INSL3) while the evolving cohort of Sertoli cells elaborate antimüllerian hormone (AMH). Locally secreted testosterone stimulates morphogenesis of the reproductive ductal division of the ipsilateral mesonephric duct (distal two thirds of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct) while AMH triggers regression of the ipsilateral paramesonephric duct. At a much later stage of embryogenesis and fetal growth, peripheral conversion of testosterone (T) to dihydrotestosterone via 5α-reductase initiates male external genital differentiation and development while INSL3 is required for proper testicular descent (19).

Is germ cell migration and testis development normal in the early 47,XXY embryo? The brief answer is that the exodus of 47,XXY gonocytes from the yolk sac and their voyage to the urogenital ridge probably follow a natural path, both temporally and spatially, but this is certainly not known definitively. As reviewed by Lue et al. (20), the XXY mouse model may provide information in this regard. The investigators cited the data of Hunt et al. (21) who elegantly demonstrated that the number of germ cells that arrive at the genital ridge are typical but that the mitotic proliferation and expansion of their numbers is reduced as the testis develops. This may be due to reactivation of the additional X chromosome when the germ cells reach their destination, but they also concluded that this reduction was related to a defect in Sertoli cell–germ cell communication (21). In a very tangential way, this thought is supported by Lue et al. (22), who transplanted XY germ cells into 41,XXY murine testes and showed that some of those donor cells could complete spermatogenesis, suggesting that both the XXY germ cell and the XXY environment contribute to impaired spermatogenesis.

Parenthetically, even though the nontesticular aspects are not the subject of this review, the mouse model developed by Lue et al. (20) "suggest[s] that the common genes that escape the X inactivation between the XXY mouse and men may be responsible for the clinical manifestations in men with Klinefelter syndrome." This amazing and valuable 41,XXY mouse model is reviewed nicely by Swerdloff et al. (23). It may be the key to future therapeutic strategies to preserve and/or enhance, if possible, future fertility in the 47,XXY human. Finally, testicular histology (light microscopy) at this stage would be helpful to clarify this issue, but cases of 47,XXY fetal testis examination are extremely limited. Two reports suggest a decrease in germ cell numbers, and two suggest a normal quantitative population (24–27).

Is the androgenic function of the testis normal in the 47,XXY fetus in the later stages of pregnancy? During fetal development, as the testis grows and descends, prenatal levels of testosterone, as measured in amniotic fluid samples at 16 to 20 weeks of gestation, are indeed normal in the 47,XXY fetus as compared with the 46,XY fetus, demonstrating that, at the very least, the androgenic function and output of the fetal 47,XXY testis is adequate (28). At birth, however, many studies show an increased incidence of cryptorchidism (4.5% to 6.3%) and/or microphallus (1% to 4.5%) (29, 30), perhaps an indication that there is individual variation and a wide range in fetal testosterone secretion, but the true reasons for these increased rates are not yet known. Lahou et al. (31) and Lee et al. (32) point out that the overall rate of genital anomalies in infants with Klinefelter syndrome is low and that androgen receptor insensitivity is unlikely to be causative. It is interesting that Zinn et al. (33) reported an inverse correlation between the androgen receptor CAG_n repeat length and penile length, but that the parental origin of the extra X chromosome, imprinting, and skewed X inactivation did not influence the other clinical variables that were assessed. Zeger et al. (34) also noted reduced penile length in both prepubertal and postpubertal boys.

After birth, is the minipuberty normal in the 47,XXY infant? Minipuberty is the term used to describe the neonatal surge of pituitary gonadotropins leading to a temporary rise of testosterone secretion and an increase in absolute Sertoli cell number along with transformation and expansion of the gonocyte pool into Ad spermatogonia (35). The exact timing of the peak of this process has not been agreed upon: 2 months (36, 37) or 3 to 4 months (38). As reviewed by Hadziselimovic et al. (39), dysfunction of any of the components of the minipuberty may underlie the lowered eventual sperm counts in boys with hypogonadotropic hypogonadism by decreasing the number of spermatogonia produced for the future. Therefore, it is of importance to understand whether the minipuberty is normal in its timing