

Klinefelter syndrome: fertility considerations and gaps in knowledge

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To the Editor:

We would like to thank Drs. Rogol and Skakkebaek for their timely and insightful commentary about medical and ethical issues with regard to sperm retrieval in adolescents with Klinefelter syndrome (KS) (1); the authors present key points discussed at the recent International Workshop on Klinefelter syndrome, in addition to summarizing our pilot clinical trial investigating sperm retrieval rates in adolescents and young adults with KS published in *The Journal of Pediatrics* (2,3). As was acknowledged in the original manuscript, Drs. Rogol and Skakkebaek emphasize potential selection bias in the study, as the sample size was small and many of the eligible subjects declined to participate due to "lack of psychological readiness to focus on fertility"; additionally, none of the patients had been treated with testosterone, indicating a "milder" end of the spectrum (1,2). The potential impact of prior testosterone therapy and other agents on sperm retrieval in this population was identified as a necessary issue for investigation (1,4).

Prospective studies in this area have been limited due to the rarity of making the KS diagnosis early in life, in addition to challenges associated with recruiting adolescents and young adults with KS for fertility related research. According to a 2011 study by Maiburg *et al.*, adults with KS were interested in fathering children and were willing to undergo testicular sperm extraction (TESE) (5). Recent research, however, demonstrates a discrepancy between attitudes of parents and physicians versus those of younger individuals with KS; while most parents of children with KS and pediatricians favored pursuing TESE in a pubertal minor, adolescents with KS reported a lack of interest in fertility and required at least three medical consultations

prior to becoming involved in fertility preservation (6,7). Thus, in order to successfully complete prospective studies to investigate predictors of successful TESE and the impact of exogenous testosterone or other treatments on sperm retrieval, reproductive priorities and potential barriers to acceptance of fertility preservation procedures need to be better understood in this particular population.

Most of the pediatric literature with regard to fertility has been done in oncology, where many males are able to produce an ejaculate for sperm cryopreservation. It is notable that this is generally not an option for individuals with KS, which is in itself, a potential barrier. Additionally, neurocognitive dysfunction is common in KS, and studies have shown lower quality of life and self-esteem, all of which could impact attitudes about reproductive health and willingness to participate in research studies (8). Thus, validated surveys and qualitative methodology should be implemented to further explore key factors such as reproductive concerns, romantic relationships, sexual function, and psychosocial well-being among adolescents and young adults with KS at different ages/developmental stages.

Based on current literature, the recommended age range to consider sperm retrieval among individuals with KS is 15–30 years (3,9,10). Medical professionals who care for individuals with KS have a responsibility to become educated on this topic and offer referrals to fertility specialists to (I) provide comprehensive counseling about the current options along with acknowledging their experimental nature; and (II) consider potential ethical implications in each individual case (6,11). As Drs. Rogol and Skakkebaek point out, many questions remain unanswered, including the viability and quality of sperm

retrieved from this patient population after many years of freezing (1). Opportunities for early diagnosis of KS will likely increase due to increasing use of prenatal testing, and more patients and families may inquire about the potential risks/benefits of cryopreservation of sperm. Thus, longitudinal follow-up to assess utilization of the frozen sperm, pregnancy rates, and outcomes, will be critical for informing future research and clinical care.

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Footnote

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