Klinefelter’s syndrome: From the patient’s and clinician’s perspective

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**Abstract**

Klinefelter’s syndrome, the most common male genetic disorder, is a permanent alteration of the sex chromosomes which affects males, reducing typically male features and possibly increasing female features. Hallmark features include a less-masculinized appearance, hypogonadism and infertility. The condition has many anatomical and physiologic effects, which entail skeletal, multiple endocrinologic, neurocognitive, and psychosocial comorbidities. Long-term and emerging technologies are used to diagnose and treat the disorder and its sequelae. High quality care is most effectively accomplished with an interdisciplinary approach, attentive to the patient and his family’s particularities. Management decision have legal, social, and ethical implications.

*Search terms: Klinefelter’s syndrome, hypogonadism, male infertility*

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**Klinefelter’s Syndrome**

**Case Study**

MG was diagnosed with Klinefelter’s syndrome after a physical for entering foster care. He was in elementary school.

I sat stunned, hearing this from someone with whom I’ve been casually acquainted for several years, someone whose siblings I’ve met. I knew that he was challenged by Klinefelter’s syndrome; I had no idea that family dynamics so compounded matters. I was the interviewer and yet I didn’t know what to say. I felt on the backs of my legs the concrete steps where we sat and talked, and I was suddenly uncomfortable. Luckily, he remained matter-of-fact, and continued.

He was told that something was wrong with his testicular exam, and was referred for genetic testing in Madison, Wisconsin. He remembers being told that he would probably grow breasts, and that he would be infertile. MG doesn’t recall any [articular feelings or reactions to this news. He had medical appointments every six months initially, then once per year, he is not sure of this medical provider’s specialty. His parents, who stayed marginally involved in his life, took him to these appointments, but did not proactively manage his medical care. His mother, who was forty years old at the time of his birth, had and undiagnosed mental health condition, she remained nominally invested, alternating, he reports, between inattentive, overbearing, and physically abusive.

At age 12, he started taking testosterone injections, but stopped at age 15 when he ran away from his foster home. In 1996, as a legal adult at age 18, he was severed from being a ward of the state, and being unable to afford health insurance; he was no longer able to see specialists or get regular medical care. Now, with the Affordable Care Act, it could be different; however, he is still without health insurance, lamenting, “I missed the cutoff to sign up for Obamacare by one day”. MG got a certificate in welding from the local community college; he has never had a job that has offered health insurance and has never seen a primary care provider as an adult.

As a teenager, he noticed difficulty gaining muscle mass, but did gain weight around his hips. His girlfriends were always against him taking testosterone, for fear that he would become overly aggressive or sexual. Infertility never bothered him as a teenager, he considered it an advantage, because, in his mind, it meant that condom use was optional.

As an adult, MG is frequently reminded that he has a “baby face,” which he has never shaved. He feels that he cries more easily than other males and concedes that he probably does have some depression, but “it could be from other things.” He recognize an unhealthy use of alcohol, minimizing potential consequences. MG muses about whether taking testosterone is worthwhile now.

MG has had many broken ribs and a wrist fracture, as well as many muscle problems; some muscle strains have resulted from attempts to compensate for lack of muscle mass. He has never been tested for diabetes;

No one else in MG is known to have Klinefelter’s syndrome or any other sex-chromosome-linked condition. He has one older brother, who actually does not have natural offspring, and two sisters, both of whom have children. His siblings were not placed in foster care. MG’s knowledge of his family history is somewhat limited, leading to gaps in his genogram (see Appendix).

**Risk Factors/ Risk Assessment.**

MG’s father was 47 years old and his mother was 40 when he was born. Advanced maternal age, greater than 35 years old at the time of her child’s birth, is a risk factor for chromosomal anomalies and is an indication for amniocentesis (Danisman, 2013). However, maternal age is a weaker risk factor for Klinefelter’s syndrome than for Down syndrome. Klinefelter’s syndrome is generally considered to be a largely random event (Radicioni, 2010).

**Epidemiology**

Klinefelter’s syndrome is the most common human chromosomal abnormality, with a prevalence of one in 600 live male births (Pacenza et al., 2012). Diagnosis is increasing (Radicioni et al, 2010). Demographic patterns and socioeconomic status of affected families are not described.

Most cases are currently diagnosed in adolescence and childhood, followed by diagnosis in young adulthood, 10% prenatally, and most rarely in middle and elder ages (Pacenza et al., 2012). Patients diagnosed later in life usually have a milder phenotypic expression, which goes undetected for significant portions of time; prenatal diagnosis may precede either mild or severe cases (Girardin & Van Vliet, 2011). Patients who present as children and adolescents may represent more severe phenotypes; the chief finding or presenting concern is usually hypogonadism. Adolescents may present with concern for body composition and masculinity. For men diagnosed in young- and middle-adulthood, infertility is often the presenting concern (Oates, 2011).

Parents of patients diagnosed prenatally have made a conscious decision not to terminate the pregnancy, and are often more involved and supportive of their affected child. This group does not have a higher incidence of repeating a school grade when compared to the general population, in contrast with patients diagnosed as children or adolescents. This suggests that cognitive and psychomotor aspects are amenable to early intervention (Girardin & Van Vliet, 2011).

Historically, however, Klinefelter’s was a diagnosis of adults males of tall stature, with gynecomastia, broad hips, narrow shoulders, sparse body hair, small testes, hypergonadotropic hypogonadism, and azoospermia. Only an estimated 25% of all patients with Klinefelter’s syndrome are diagnosed; diagnosis is often missed in patients with mild and/or atypical presentation and delayed in children; diagnosing prepubertal hypogonadism is often deferred until transience is ruled out (Girardin & Van Vliet, 2011). Approximately 10% of affected prepubertal boys are diagnosed (Weler & Wistuba, 2014).

Of men and boys with Klinefelter’s syndrome, 25-48% have decreased bone mass; six to 15% have osteoporosis. Bone mineral density positively correlates with testosterone levels (Ferlin, Schipilliti, Foresta, 2010).

Cognitively, most Klinefelter’s syndrome patients have IQs 10-15 points lower than their siblings, though still in the normal range. Speech, reading, and social developmental delays are common, often requiring specialist support. A higher prevalence of attention-deficit and autism-spectrum disorders than in the general population exists among patients with Klinefelter’s syndrome, with no difference between prenatally and postnatally diagnosed patients (Girardin & Van Vliet, 2011).

Affected men report lower levels of education, less military service participation, and poorer socioeconomic outcomes than the general population. Fewer live with a partner than unaffected men (Skakkebaek, Wallentin, Gravholt, 2015). Higher rates of homosexuality are popularly thought to exist, but the literature does not bear this out point (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014). Most families indicate that they received incorrect or misleading information at some point.

Overall, sequelae results in a life expectancy, on average, 11.5 years less than the general male population (Nieschlag, 2013).

**Family Effects**

The families of affected males have a complex experience, shaped most strongly in the short-and mid-term by the timing of diagnosis, the quality of contact with clinical staff, and information received. Long-term term experience is strongly shaped by quality of support systems; significant frustration is experienced in the healthcare provider not providing referrals for appropriate specialists and supportive services. Long-term parental concerns include sexuality, masculinity, and fertility of their offspring. Additionally, most families indicate that they received incorrect or misleading information at some point (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014).

Months to years may be spent searching for a diagnosis; however, this process does not inherently confer readiness to receive a chronic, lifelong diagnosis (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014). In children, the family may seek an explanation for hypogonadism, and experience frustration with the clinician deferring final diagnosis until puberty. Children and adolescents who present with social and educational difficulties may not receive adequate physical examination, which would likely trigger the clinician to obtain karyotype testing (Herlihy & McLachlan, 2015).

Upon receiving a Klinefelter’s diagnosis, families report grief reactions similar to others receiving a chronic diagnosis, unique depending on whether the patient and family had identified that something was amiss. In those who intentionally sought an explanation for symptoms, an immediate sense of relief is common (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014).

**Pathophysiology**

Males with Klinefelter’s syndrome have at least one Y chromosome and multiple X chromosomes. The classic manifestation is a 47, XXY karyotype, which exists in 90% of cases; the other 10% of cases are variants containing additional extra X chromosomes; these include

* 47,XXY/46, XY;
* 47,XXY/45, X/46, XY;
* 48,XXXY;
* 49,XXXXY
* 48,XXYY (Pacenza et al., 2012).

Variants, not considered Klinefelter’s syndrome, include Y chromosomal microdeletions, translocations, and structural anomalies (Oates, 2011). The female analogue is Turners syndrome, which classically denotes a XYY karyotype (Pacenza et al., 2012).

These changes are due to an error during the meiotic disjunction (Corona et al, 2010) in which primordial germ cells are presents, but degenerate unusually quickly. This impairs adequate spermatogenesis (Nieschlag). The KDM6A gene, located on the X chromosome, is one of the predominantly overexpressed genes in Klinefelter’s syndrome because it resists the process of X-chromosome inactivation. Additionally it is found in varied congenital anomalies and intellectual impairments (Zitzman, 2015). The mechanism of X-chromosome inactivation escape is described, but phenotypic impacts are not fully known (Valencia & Wutz, 2015).

Affected patients show a specific pattern of elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH), plus reduced testosterone (Corona et al, 2010). However, as many as 40-50% of patients with Klinefelter’s syndrome have normal testosterone levels (Oates, 2011). Normal testosterone levels, however, may not represent actual androgen status; luteinizing hormone (LH) levels may still be elevated. Additionally, objective signs of hypogonadism may still be present. Several studies shave shown that testosterone levels positively correlate with INSL3 levels (Ferlin, Schipilliti, Foresta, 2010). Speculation exists that increased mortality in Klinefelter’s syndrome is due to X-chromosomal factor (Zitzman, 2015). Speculation also exists that clinically significant sequelae result from low testosterone levels the relationships are not entirely clear.

Autism spectrum disorders (ASD) are generally known to be X-chromosome linked; they are much more prevalent in X chromosome-involved conditions, and quite rare in the XYY karyotype. However, this does not explain the prevalence of ASD in males (Margari, Lamanna, Craig, Simone, & Gentile, 2014).

Genes related to the apoptotic cascade, glucose metabolism, and inflammation are located on the X chromosome. Serum concentration of interleukin-6, tumor necrosis factor, high-resolution C-reactive protein, and procoagulatory plasminogen activator inhibitor type 1 are significantly associated with specific differentially expressed genes. Specifically, proinflammatory status may indicate cardiac risk status (Zitzman, 2015). Males with Klinefelter’s syndrome have an increased risk of elevated triglycerides; some studies have shown that this association disappears after controlling for testosterone levels, suggesting that testosterone has a causative effect on hypertriglyceridemia (Gravholt, Jensen, Host, & Bojesen, 2011). However, other studies have shown that testosterone replacement does not correct the lipid metabolism disorder (Pacenza et al, 2011). Insulin resistance, a common comorbidity of dyslipidemia, may lead to further deterioration in testosterone production, and therefore may exacerbate Klinefelter’s syndrome. Type 2 diabetes is a common comorbidity (Gravholt, Jensen, Host, & Bojesen, 2011).

Androgens facilitate bone metabolism, in both trabecular and cortical bone, through promoting periosteal bone formation, primarily in puberty, and reducing bone resorption, mainly in adulthood. Increased periosteal activity stimulates longitudinal and radial growth. Therefore, hypogonadism should raise the index of suspicion for low bone density. Osteoblasts contain androgen receptors (AR), which are located on the X chromosome. Moreover, testosterone aromatizes to estrogens, the level of which is positively correlated with bone mass. Estrogen maintain bone mineral density and facilitate periosteal bone expansion during puberty. Additionally, testosterone acts indirectly on the parathyroid hormone-vitamin D axis. Testosterone levels alone cannot predict bone density; Klinefelter’s syndrome patients who have normal testosterone levels still have decreased bone mass. Other mechanisms may include estradiol levels, vitamin D metabolism, secondary hyperparathyroidism, and unfavorable muscle-to-fat balances. Low insulin-like factor also correlates with impaired trabecular bone mass (Ferlin, Schipilliti, Foresta, 2010).

Androgen deficiency may explain patterns of reduced amygdala size in Klinefelter’s patients. This may play a part in the distinct karyotype of neurocognitive impairment (Corona et al, 2010).

Cryptorchidism is more frequent in Klinefelter’s patients than the general population, and is an indication for referral to a pediatric endocrinologist. One mechanism is impairment of INSL3, which is a protein hormone produced in the Leydig cells of the testes; this impairment indicates Leydig cell undifferentiation, stress, or sparseness (Pacenza et al., 2012).

Affected males may be at increased risk of some autoimmune diseases, particularly those that are predominant in females. Higher incidences of Addison’s disease, type 1 diabetes mellitus, multiple sclerosis, acquired hypothyroidism, rheumatoid arthritis, Sjogren’s syndrome, and systemic lupus erythematosus. The mechanism is not entirely clear; however, it is assumed that these disorders have a sex-chromosome-linked component (Seminog, Yeates, Goldacre, & Seminog, 2015).

**Epigenetic Influences**

Parental origin of the additional X-chromosome contributes significantly to the phenotype (Zitzmann, 2015). Klinefelter’s syndrome is most severe when the origin is maternal, with both of the mother’s X chromosomes affected. Cases are less severe when the origin is maternal, with a single X-chromosome affected, or when the origin is paternal with the only X chromosome affected (Vallabhajosyula & Rajangam, 2015). Phenotypic expression is influenced by X-chromosome escape gene reactivations and Y-chromosome deletions (Heard & Turner, 2011).

Twenty-one genes expressed differently in males with Klinefelter’s syndrome and control subjects exist on the X chromosome. Another 15 are found on the Y chromosome. Variations in gene expression impact the Klinefelter’s syndrome phenotype (Zitzmann, 2015). Males with mosaic patterns of expression are more well-androgenized than non-mosaic case of Klinefelter’s syndrome (Jarvis, 2014) Many influences on expression of these genes is unclear, however.

**Clinical Presentation**

Symptoms are often subtle and often do not appear at the same time (Radicioni et al., 2010), confounding diagnosis.

*Subjective*

Men with Klinefelter’s syndrome report infertility, erectile dysfunction, hypoactive sexual desire, premature ejaculation, and delayed ejaculation; any of these may be a presenting concern. However, when compared with age-matched, tobacco use-matched, and testosterone-matched subjects, the incidences of these events are no longer increased (Corona et al., 2010). Since seminal vesicles create 70% of ejaculate volume and alkalinize the mixture, any male with functional congenital bilateral absence of the vas deferens (CBAVD) will exhibit low fluid amount, acidic pH, plus azoospermia (Oates, 2010). Sexual dysfunction is due to hypogonadism, and is usually solved with testosterone replacement (Corona et al, 2010).

The neurocognitive profile of patients with Klinefelter’s syndrome includes dyslexia, low verbal intelligence quotient, delayed early language development, learning impairment in reading and spelling, syntax production impairment, and impaired word retrieval, phonemic processing, comprehension, and verbal fluency. These challenges may result in poor academic achievement. Mental and behavioral alterations may include depression and poor body image. Impaired social development may manifest as autism spectrum disorders and may result in social isolation (Skakkebaek, Wallentin, Gravholt, 2015). Phobic anxiety has an increased incidence \*(Corona et al, 2010).

*Objective*

Hypergonadotrophic hypogonadism is the classic defining feature. In boys with Klinefelter’s syndrome, puberty onset usually occurs at the expected age. The conventional definition of the onset of puberty, according to Tanner, is testicular volume of 4 ml. However, in Klinefelter’s syndrome, the final volume is typically four to five milliliters. Completion of pubertal changes tends to occur three to four years later than in 46,XY males (Radicioni et al., 2010).

The phenotype includes tall, slim stature; narrow shoulders and broad hips; gynecomastia; small firm testes; possible reduced penile length; sparse facial, axillary and chest hair growth; and female pubic hair patterns (Vallabhajosyula & Rajangam, 2015). Abnormal facies are not present (Radicioni, 2010). Varicose veins may be more prevalent than in the general population (Nieschlag, 2013). Pathologic fractures may be present; reduced bone mass is found in up to 40% of patients with Klinefelter’s syndrome (Pacenza et al., 2012).

Congenital genital malformations visible at birth may include hypospadias, scrotum bifidus, small penis, and cryptorchidism. Other malformations may include fifth finger clinodactyly, cleft palate, and inguinal hernia, and hypotonia. These should be indications for the provider to order karyotype analysis. Klinefelter’s syndrome is the most frequent genetic anomaly associated with cryptorchidism. Varicocele may also be present (Radicioni, 2010). Other causes of delayed puberty are largely endocrinologic, but also include chronic illness

Affected males show increased inflammatory status and procoagulatory status. Thromboses, and epilepsy may be comorbid (Nieschlag, 2013). Patients with Klinefelter’s syndrome have an increased incidence of dyslipidemia and non-alcoholic fatty liver disease, and speculation exists on hypothalamic-pituitary-thyroid dysfunction, which may contribute to unfavorable body composition; both of these contribute to metabolic syndrome and type 2 diabetes (Gravholt, Jensen, Host, & Bojesen, 2011).

Men with Klinefelter’s syndrome show an increased morbidity and mortality from diabetes than the general population. Significantly more patients have elevated fasting plasma insulin and leptin levels, plus decreased insulin sensitivity. These patients have also showed a lipid pattern similar to patients with type 2 diabetes. No difference has been found in blood pressure or overall Body Mass Index, although truncal fat and waist measurements are increased. Reduced testosterone levels are predictive of metabolic syndrome’s increased incidence and decreased insulin sensitivity in patients with Klinefelter’s syndrome, though truncal obesity is the major determinant, even after controlling for altered testosterone levels. In brief, one outcome of metabolic syndrome in patients with Klinefelter’s syndrome is decreased left ventricular function (Gravholt, Jensen, Host, & Bojesen, 2011).

As a population, on electrocardiogram, affected males show a markedly shortened QTC interval. Many fall within the pathologic range. Shortened QTc intervals are related to atrial fibrillation, ventricular fibrillation, and, recently reported, sudden cardiac death. Additionally, erectile dysfunction may have a chronotropic incompetence component in some patients (Zitzmann et al., 2015).

**Differential Diagnosis**

Differential diagnosis includes Fragile X syndrome, Marfan syndrome, Kallman syndrome, and idiopathic hypogonadism. For males in whom infertility is the presenting concern, differential diagnoses include sexually transmitted infections, sperm morphology or motility problems, other causes of oligospermia or azoospermia, genital tract obstruction, and problems originating with the female partner. Other causes of erectile dysfunction include trauma, fibrosis, urethritis, sexually transmission, tumors, and congenital curvature, and psychosocial alterations such as anxiety. Other sexual dysfunction may be functional or organic (Johnson, Thomas, & Porter, 2011). When a patient presents with delayed puberty, the differential diagnosis is largely endocrinologic, but also includes chronic illness (Whittemore, Smaldone, &Steiner, 2012)

Differential diagnosis for osteoporosis in men includes trauma, neoplasm, osteomalacia, osteogenesis imperfect, hyperparathyroidism, and hyperthyroidism (Johnson, Thomas, & Porter, 2011). The differential diagnosis of gynecomastia include the pubertal process itself, drug-induced, cirrhosis, malnutrition, and testicular failure. Differential diagnosis of low libido include drug-induced, psychiatric, and other endocrinologic causes. The causes of lipid disorders, inflammatory disorders, and cardiovascular and clotting disorders are numerous and multisystem.

Klinefelter’s syndrome should be considered as part of the differential diagnosis for individuals with mental retardation (Vallabhajosyula & Rajangam, 2015), as well as autism spectrum disorders (Margari, Lamanna, Craig, Simone, & Gentile, 2014). Differential diagnosis for neurocognitive impairment is broad and includes medication and other foreign substance poisoning, neurological disorders, and hepatic disorder. Neurologic dysfunction is comorbid when the epilepsy occurs.

**Diagnostic Testing**

Postpubertally, Klinefelter’s syndrome is diagnosed by phenotype confirmation on physical exam, plus confirmation of reduced testicular volume, reduced ejaculate volume, acidified sperm, and azoospermia. Normal postpubertal testicular volume will total five milliliters or less (Radicioni et al., 2010). Normal semen analysis reveals a volume of two to five ml, with a population of greater than 20 x106, and a pH of 7.12-7.8. Additionally, seminal vesicles are dysplastic, aplastic, or atrophic (Oates, 2011). Ultrasound is typically used for scrotal imaging (Pagana & Pagana, 2014). Final diagnosis is typically deferred until at least Tanner stage three, to confirm that hypogonadism is not transient.

Additional blood testing reveals reduced testosterone level, elevation of serum FSH with functional Leydig cells, elevated LH, elevated prolactin and estradiol (Pacenza et al., 2012). Normal values:

|  |  |  |
| --- | --- | --- |
| Hormone | Normal Serum Level in Adult male | Alteration in Kleinfelter’s |
| Free testosterone | 1.6-2.9% | reduced |
| FSH | 1.42-15.4 I/L | elevated |
| LH | 1.24-7.8 IU/L | elevated |
| Prolactin | 3-27 ng/ml | elevated |
| Estradiol | 10-50pg/ml | elevated |

(Pagana & Pagana, 2014).

The medical provider may conduct genetic testing prenatally. Advanced maternal age is an indication for amniocentesis (Danisman, 2013); other diagnostic procedures capable of diagnosing Klinefelter’s syndrome include chorionic villus sampling and cordocentesis. All are invasive, and therefore carry risks. The expectant parents should be aware that amniocentesis can not only uncover Down syndrome, but also sex chromosome aneuploidy. These abnormalities are not visible on fetal ultrasound. Sex chromosome aneuploidy occurs in almost 0.5% of amniocenteses (Girardin & Van Vliet, 2011). Rates of subsequent pregnancy termination vary widely. No specific ultrasound or serum markers for Klinefelter’s syndrome have been found; only karyotype analysis through the aforementioned invasive procedures is known to be effective (Radicioni, 2010). No known systematic neonatal screening programs exists, though some advocate that the utility of early intervention justifies creating such programs.

Origin of the additional X chromosome as maternal or paternal may be confirmed through blood cell RNA (Zitzmann et al., 2015). A novel method of detecting X-chromosome inactivation escape is the methylation-specific real time PCR test; this test reveals methylation variances of the X-chromosome inactive-specific transcript gene (XIST), which is only present when multiple X-chromosomes are present. This test is highly sensitive, and promises improvements in detecting subtle karyotype mosaic variations (Werler & Wistbuba, 2014). Other new highly reliable tests are the multiple ligation-dependent probe amplification (MLPA) and quantitative polymerase chain reaction (Werler & Wistuba, 2014).

Mammography distinguishes true gynecomastia from pseudogynecomastia (Johnson, Thomas, & Porter, 2011). For patients found to have congenital bilateral absence of the vas deferens (CBAVD), the provider should obtain cystic fibrosis mutation analysis.

When pathologic fracture is suspected, simple radiography is used. Bone density testing identifies osteopenia and osteoporosis using T-score and Z-score calculations. Serum testing is used for suspected autoimmune antibodies; endocrinologic comorbidities such as diabetes mellitus, thyroid dysfunction, and adrenal dysfunction; cardiovascular markers such as the lipid panel; and inflammatory markers such as C-reactive protein (Pagana & Pagana, 2014). Imaging may be performed for suspected organ dysfunction related to comorbidities; for example, more extensive thyroid or cardiac testing.

**Management**

The ICD-9 code is 758.7. Upon conferring diagnosis, the provider should utilize protocols for breaking bad news (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014).

Testosterone supplementation has helped middle-ages men with abdominal obesity and without Klinefelter’s syndrome to reduce abdominal obesity and improve insulin sensitivity. Testosterone supplementation may also mitigate typically feminine body composition (Gravholt, Jensen, Host, & Bojesen, 2011). Surgical correction of hypospadias or cryptorchidism may be necessary.

Spermatogonial stem cell banking may occur in prepubertal patients. Otherwise, for patients with Klinefelter’s syndrome desiring conception, microsurgical testis sperm extraction recovers spermatozoa with about a 50% success rate. No known events of repeating the Kleinfelter’s aneuploidy in resulting offspring have occurred; however, slightly higher rates of alterations in autosomes 18, known as Edward’s syndrome, and 21, known as Down syndrome are noted. This indicates a need for preimplantation genetic screening (Oates, 2011). Extraction of viable sperm is most successful when attempted in early puberty, before excessive destruction of the seminiferous tubules. Intracytoplasmic sperm injection occurs at the time parenthood is desired. (Aksglaede, 2013).

Osteoporosis may originate in youth. Bone mineral density (BMD) is measured using dual-energy X-ray absorptiometry (DEXA); BMD-defined definitions have been validated for white postmenopausal women only; no consensus BMD-based criteria exist for osteoporosis in men. Clinically relevant fracture is indicative; however, thresholds for increased fracture risk are unknown. To compound diagnostic complexity of these Klinefelter’s syndrome sequela, many apparently healthy children suffer fractures and site-specific bone weaknesses can be found. When testosterone replacement starts after pubertal bone development, this supplementation does not reverse decreased bone mass. Maintaining recommended vitamin D levels may be important to maintaining bone integrity (Ferlin, Schipilliti, Foresta, 2010).

The practitioner should attentively treat comorbidities, no matter the source. This includes autoimmune disease, dyslipidemia and cardiac disease, impaired glucose utilization, adrenal dysfunction, and thyroid dysfunction. Regular physical activity may mitigate motor dyspraxia (Radicioni, 2010).

Patterns of cognitive dysfunction suggests that social competence intervention may be effective in improving executive function (Skakkebaek, Wallentin, & Gravholt, 2015). For example, one feature of autism spectrum disorders that Klinefelter’s patients are known to show is patterns of reduced eye contact and attention to the eyes of others (van Rijn, 2015). Typical management strategies for psychosocial impairment are used. Psychologic interventions that assist affected males and their families to reframe negative experiences of the condition increases perception of manageability (Turriff, Levy, & Biesecker, 2015).

**Patient and Family Education**

Patients and families need two main things:

* relevant information at the correct time, and
* support systems, both personal and institutional (Bourke, Snow, Herlihy, Amor, & Metcalfe, 2014).

The practitioner should identify how much the patient and family wants to know, and meet their information appetite. Patients and families should be encouraged to seek their own resources, but also be warned about the presence of false information on the Internet (Girardin & Van Vliet, 2011).

Again, the expectant parents should receive counseling bout potential findings before prenatal diagnostic testing. They should be aware of the laws regarding terminating a pregnancy. Families may agree that pursuit of prenatal or early diagnosis is advantageous due to allowing for proactive mitigation of developmental social and cognitive delays.

Accompanying a Klinefelter’s syndrome diagnosis, the provider should utilize the principle of nondirectiveness to give unbiased information on the spectrum of phenotypic expression, the process of heredity, risk of recurrence, the probable course, and management options. This is a relatively frequent, random event, with relatively little chance of recurring (Girardin & Van Vliet, 2011).

Patients and families will face stereotypes and negative perceptions of the patient as mentally retarded and feminine (Girardin & Van Vliet, 2011). The provider may inoculate the patients against negative experiences, and perhaps furnish a framework for combatting subsequent suffering. The primary care provider may speak positively of mental health counseling, lessening any stigma the patient and family might feel.

The provider should inform families and patients of resources. For example, the provider may provide guidance on the process for obtaining educational support, which may include speech therapy, reading assistance, and special education.

It is a public health imperative that the clinician inform patients that, despite infertility, condom use is essential for prevention of sexually transmitted infections.

**Team-based Approach**

Involved medical specialties may include epidemiology, endocrinology, embryology, pediatrics, cardiology, urology, psychology, and psychiatry (Skakkebaek, Wallentin, & Gravholt, 2015). Orthopedic specialists may attend to skeletal problems as they arise.

Professional genetic counselors provide personalized help too patients and families in understanding and adapting to the diagnosis. They complement and reinforce the provider’s teaching on prevention, testing, phenotypic expression, the process of heredity, risk of recurrence, probable course of the condition, treatment options and resources. Genetic counselors provide patient advocacy, and may increase patients’ and family satisfaction with their healthcare experience. They are usually covered by insurance in the same manner as other specialists (National Society of Genetic Counselors, n.d.).

Speech therapists, reading and other academic specialists, and mental health counselors may proactively engage a Klinefelter’s syndrome patient to avoid developmental and skill delays (Girardin & Van Vliet, 2011). Mental health professionals may help affected patients build coping skills and attend to mental and emotional sequelae of the condition.

Reproductive specialists assist in establishing a pregnancy (Oates, 2011). Affected men wishing to be fathers may seek other resources, such as adoption experts. Social workers may coordinate complex needs for patients and families.

**Ethics, Legal, and Social Considerations**

Expectant parents who receive a prenatal diagnosis of Klinefelter’s syndrome may often choose whether to continue the pregnancy. In MG’s home state of Wisconsin, abortion is legal prior to 20 weeks gestation (Guttmacher Institute, 2015). The woman must receive in-person counseling and a fetal ultrasound; the provider must show and describe the anatomic features in the image. Then the woman must wait 24 hours before the abortion is performed. Minors must obtain parental permission. Public funds may only be used when the woman’s health is in danger, or when the pregnancy is the result of a sexual crime. With this topic so hotly debated, many feel that abortion services are too easy to obtain and others feel that the services are too difficult to access; participants often cannot even agree on what language to use to discuss the matter. We must ask though, what is the impact of being selective about what kind of children to have? How do the rest of us, and society as a whole, change because of this choice?

Patients and families with Klinefelter’s syndrome may share considerations with other people facing mental handicaps. One consideration is the educational environment. What special services will be available, and will affected students be separated from or integrated with the general population? How would these scenarios affect males with Klinefelter’s, and how would they affect the general population? How will tailored services be funded?

The preceding case study exhibits economic factors of accessing health care, both before, and in the era of, the Affordable Care Act. We as a society must consider how readily available to make treatments; however, the case study shows that, even when treatment is less economically exclusive, the affected patient may still not obtain treatment.

We should also consider the impact of this infertile population as part of society. The affected group is, clearly, not large enough to adversely impact human survival – but who, specifically, is not having children? Again, Klinefelter’s syndrome is largely considered random (Radicioni, 2010), and the occasional natural offspring of affected males are generally not affected (Girardin & Van Vliet, 2011). No specific demographic pattern is reported for the affected male’s family of origin; however, the condition adversely impacts the affected patient’s socioeconomic status over his lifetime (Skakkebæk, Wallentin, & Gravholt, 2015); does this mean that children of affected males will be poorer than average?

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**Genogram**

**Key**

□ male

ᴏ female

X□X deceased male

XᴏX deceased female

I connects natural offspring

: connects adopted person

---- connects married couple

-/-/-/ connects divorced couple

A&W Alive and well with no significant health issues

(Known health issues)

X□X---------------------------------XᴏX X □X---------------------------------XᴏX

Paternal grandfather Maternal grandmother

(ETOH abuse) (Schizophrenia,

I Dementia)

I I

□--------------------------------------------------------------------------------------------------------------ᴏ

Father – born 1932 Mother – born 1939

(ETOH abuse, (Colon CA – remission,

back pain, wheelchair bound, Bipolar? - undiagnosed)

Multiple MIs) I

I I I I

□------------------ᴏ ᴏ-/-/-/-/-/-/-/-/-/-/-/-/-/-□ ᴏ--------------------□ □

Older brother Oldest sister Older sister Patient

A&W, born 1965 A&W, born 1969 A&W, born 1976 A&W, born 1978

: : I I I I I

□ ᴏ ᴏ ᴏ □ □ ᴏ

A&W A&W A&W A&W A&W A&W A&W