Reproductive Health in Young Male Adults with Chronic Diseases in Childhood

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Abstract

The Centres for Disease Control and Prevention have defined a chronic diseases as an "illnesses that are prolonged, do not resolve spontaneously, and are rarely cured completely". Approximately 20% of all children have a chronic illness and 65% of them the illness is severe enough to interfere with daily activities .Failure of pubertal growth, delay or absence of sexual development, infertility and sexual dysfunction due to hypogonadism and defective spermatogenesis are well recognized disturbances among adolescents and young male adult patients with chronic diseases. The causes are multifactorial and can be due to disease itself, associated complications or drugs.

Haemoglobinopathies, endocrine disorders, gastrointestinal and renal diseases are some examples that frequently cause some degree of disability. Infertility affects the future quality of life of these patients and is a predictor of stress in current and future relationships. Health care providers often neglect the reproductive health of chronically ill adolescents and young adults, although many studies indicate that they are sexually active and interested in knowing about their future fertility.

This review article provides an overview of the literature concerning the impact of some chronic diseases in adolescents and young adults on reproductive health but will not address patients with cancer because it has been tackled adequately in the literature.MEDLINE database search of English-language medical journal articles published between 1975 and 2012 for papers related to reproductive health in adolescents and young adults with chronic diseases since childhood was done.

Several Authors, recommend that all young adult patients with severe/prolonged chronic disease in childhood should be offered reproductive health care in a specialized center with appropriate expertise, involving a multidisciplinary team, including endocrinologists, andrologists, geneticists, psychologists, urologists and specialist nurses. Adequate information must be provided to these patients about adolescent reproductive health, including types of contraception, pregnancy, sexually transmitted infections and fertility. The importance of transitional care between pediatric and adult medical care should not be ignored. In the development of this process the adolescent must be involved in decision-making regarding treatment or referral. Reproductive health medicine should take a wider view to create a physical, psychological and genetic well-being of these patients.

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Introduction

All over the world, owing to the considerable progress of medical care, the number of adolescents and young adults with chronic illnesses is going to increase. The exact prevalence of chronic conditions among adolescents is difficult to assess due to the lack of quality data focusing specifically on this age group, as well as the diversity in methodology and definitions (1,2). Five percent of children have multiple (two or more) chronic conditions and less than 1% of children have three or more such conditions (1, 2).

Boekaerts and Roder consider that a chronic disease is something which "cannot be cured, but treatment may ameliorate some consequences of the disease and prevent overall deterioration" (3).

O'Halloran *et al.* (4) used a set of criteria to define chronic conditions. They stated that chronic conditions may have a duration that has lasted, or is expected to last, at least 6 months; a pattern of recurrence, or deterioration; have a poor prognosis, produce consequences, or sequelae that impact on the individual's quality of life.

The Centers for Disease Control and Prevention have defined a chronic diseases as an "illnesses that are prolonged, do not resolve spontaneously, and are rarely cured completely" (5-7).

Among adolescents with chronic illness, some are survivors of a severe disease in childhood, some have a long-standing yet less severe condition and some have been ill since adolescence only. With appropriate management, many adolescents with chronic conditions can function well and live almost "normal lives". It is estimated that up to 98% of children diagnosed with a chronic health condition may now reach adulthood, depending on the condition (6, 7). As a result, the management of teens and young adults with a chronic illness must go beyond the strictly medical disease treatment. It should include also issues such as development, family, social support and reproductive health.

Health care providers often neglect the reproductive health of chronically ill adolescents and young adults, although many studies indicate that they are sexually active and interested in knowing about their future fertility (8, 9).

Among adults, chronic illnesses include quite a large group of widespread illnesses and a small number of rarer diseases. In contrast, the chronic illnesses of infants, children, and adolescents are characterized by only a few frequently occurring illnesses and a large assortment of different diseases with low prevalence rates.

This review article provides an overview of the literature concerning the impact of some chronic diseases in adolescents and young adults on reproductive health but will not address patients with cancer because it has been tackled adequately in the literature.

MEDLINE database search of English-language medical journal articles published between 1975 and 2012 for papers related to reproductive health in adolescents and young adults with chronic diseases since childhood was done.

Physiology of testicular function and spermatogenesis

The testes fulfil two major tasks: steroidogenesis and spermatogenesis. Steroidogenesis takes place in the Leydig (interstitial) cells, located between the seminiferous tubules. Spermatogenesis takes place in the germinal epithelium of these tubules. The germ cells undergo various stages of development from spermatogonia before spermatozoa (mature sperm) reach maturation (Figure 1) This process takes about 60 days to be produced and another 10-14 days for them to pass through the epididymis and vas deferens (10,11).

The first conscious ejaculation takes place usually 12 months after the onset of puberty at a bone age of 12.5-15.6 years. It is still not known exactly when the adolescent boy reaches a complete spermatogenesis and therefore one has to be cautious in assessing the spermatogenesis potential of the investigated subjects (12-15). A study carried out in Poland showed that normal seminal parameters are achieved 12-14 months after the first ejaculation and that a good motility of the spermatozoa is usually reached a year later (16,17).

Three categories of spermatogenesis failure or abnormal spermatogenesis are recognized (18):

1. Pretesticular, secondary to a disorder of the hypothalamic-pituitary axis
2. Testicular, maturational failure of the spermatogonium, spermatocyte, spermatid or hypospermatogenesis
3. Post-testicular, secondary to obstruction of the canalicular system which would allow the spermatozoa to leave the seminiferous tubules and join the ejaculate.

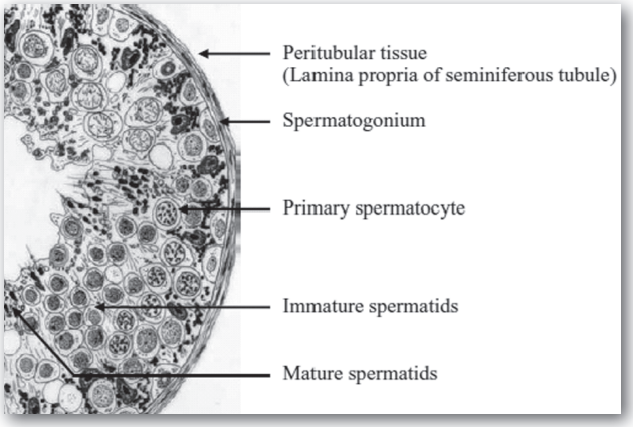

***Figure 1**: Cross-section of human testis in an young adult (From: Reproductive Biology and Endocrinology 2003, 1:107 , mod.)*

Hormonal Regulation of Spermatogenesis and Spermiogenesis

Pubertal development is the result of increasing release of GnRH by the hypothalamus, which stimulates the pituitary to release both gonadotropins (LH and FSH) in a pulsatile fashion. Kisspeptin, the product of the KISS1 gene, plays an essential role in the regulation of spermatogenesis acting primarily at the hypothalamic level of the gonadotropic axis (19).The gonadotropins stimulate the gonads (testis) to develop and produce the sex steroids (testosterone). FSH stimulates the production of sperms from the seminiferous tubules and the acquisition of LH receptors on Leydig cells. LH stimulates Leydig cells to secrete the male hormone, testosterone (20,21).

Two important negative feedback loops exist to regulate the secretion of gonadotropins. The testosterone negative feedback loop is established in fetal life and inhibits hypothalamic and pituitary production of GnRH and LH. Inhibin-B, produced by the Sertoli cell, exerts inhibitory effects on FSH secretion from the pituitary gland; however this negative feedback loop is only established at around puberty (22). Any disruption of this system or dysfunction of its components may lead to infertility (23-25).

Disorders of Pubertal Development

On average puberty starts at approximately 11 years in boys, with 99 % showing a testicular volume of 4 ml or greater by the age of 14 years (18,20).

Delayed puberty is defined as the complete lack of pubertal development in boys by the age of 14 and hypogonadism is defined as the absence of testicular enlargement (less than 4 ml) by the age of 16 years. Also, a pubertal arrest may result in hypogonadotropic hypogonadism after some spontaneous development (26-30).

There are two types of male hypogonadism, regardless of age of onset.

Primary; involves testicular failure that results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin levels.

Secondary; results from central defects of the hypothalamus or pituitary and is associated with low-to- normal gonadotropin levels (LH and FSH) and low testosterone levels .

When hypogonadism develops *before* the age of puberty, the manifestations are those of impaired puberty:

- Small testes and phallus
- Scanty pubic and axillary hair
- Disproportionately long arms and legs (from delayed epiphyseal closure)
- Persistently high-pitched voice

When hypogonadism develops *after* the age of puberty, some signs and symptoms are suggestive of male hypogonadism, while others are less clearly associated (26-29). The patient presents with:

- Very small, soft or shrinking testes,
- Loss of libido and activity,
- Decreased spontaneous erections or impotence,
- Reduction of seminal fluid or aspermia
- Reduced muscle bulk and strength , and
- Osteoporosis

Components of a complete evaluation of reproductive health

1. Medical History

The cornerstone of the evaluation of infertile man is a careful history including the current problem/complaint, age, occupation, previous seminal analysis findings, and any associated medical complication or negative impact of life style, such as cryptorchidism, testicular torsion, mumps orchitis or complications following inguinal herniorraphy, diabetes, smoking ,drugs consumption and alcoholism (26-31).

A number of sources are available to the clinician to help evaluate the reproductive risks of drugs and other agents (31).

2. Physical examination

In the physical examination particular attention should be paid to:

1. Vital signs, body height and weight (BMI), arm-span, secondary sexual characters, and examination of thyroid gland.
2. Features of hypogonadism: Complete or partial development of secondary sexual characteristics (penis length, distribution of body hair, including beard growth, axillary hair and pubic hair)
3. Testicular size: Failure of one or both of the testes to descend into the scrotum or damage to the testicles, such as by injury or after a mumps infection, may reduce sperm production. Because approximately 85% of testicular mass consists of germinal tissue, a reduced germinal cell mass would be associated with a reduced testicular size and a soft consistency.

Atrophic testes may be primary, due to an inherent testicular dysfunction, or secondary, due to a hormonal deficiency. The finding of atrophic testes with elevated FSH levels indicates germ cell failure (30,32). Normal-sized testes accompanied by normal FSH and azoospermia suggest the possibility of obstruction.The diagnosis of obstruction can be established by palpation of the vas, seminal plasma physical characteristics and by trans-rectal U/S. Men with obstructive azoospermia and congenital bilateral absence of vas deferens as well as their wives should be screened for cystic fibrosis mutations (33). Men with non obstructive azoospermia or severe oligospermia (< 5 million/ml) are at increased risk of having a definable genetic anomaly (Y-chromosome deletions).

4. Presence of varicocele: Varicocele which is varicosity of the veins around the testes which can occasionally cause infertility.
5. Presence of gynaecomastia: It may be the result of hypogonadism , medications, genetic disorders, hyperprolactinemia, or chronic liver disorders.

3. Hormonal measurements

An endocrine evaluation should be performed if sperm concentration is abnormally low, sexual function is impaired, and when other clinical findings suggest a specific endocrinopathy. The minimal initial endocrine evaluation should include measurement of serum total testosterone, prolactin, LH and FSH concentrations .

Hormone measurements can help determine whether the patient has gonadotropin deficiency (low testosterone and low or inappropriately normal LH and FSH), primary testicular failure (low testosterone, elevated LH and FSH), spermatogenic failure (normal testosterone and LH, elevated FSH), or androgen resistance (slightly increased LH and normal-slightly increased testosterone). Low gonadotropin levels associated with elevated prolactin raises the possibility of a pituitary prolactinoma, and a pituitary MRI should be performed (30).

Patients with FSH levels above normal range and normal sperm production may have a defect in spermatogenesis (30).

It has been reported that concentration of inhibin B in patients with infertility may provide useful information on spermatogenesis and possibly serve as a more direct marker of spermatogenesis than FSH (32).

4. Semen analysis

Semen analysis is a highly predictive indicator of the functional status of the male reproductive hormonal cycle, spermatogenesis and the patency of the reproductive tract.

The World Health Organization Laboratory Manual for Examination of Human Semen and Semen-Cervical Mucous Interactions is highly recommended for technical details (34).

Because semen parameters fluctuate from day to day, at least two semen samples are usually required to diagnose below-normal semen quality (30). Semen is collected by masturbation. Patients should be encouraged to abstain from ejaculation for 72 hours prior to collecting a semen sample in the laboratory. A repeat semen analysis should be requested after two to three months, bearing in mind that a complete spermatogenesis cycle lasts for 74 days.

The specimen container should be clean, although sterility is not required, and wide-mouthed, to minimize collection error. The semen sample should be processed within one hour from its production

Macroscopic semen analysis variables are volume, pH, coagulation, liquefaction, color and viscosity. Note that fresh semen is a coagulum that liquefies 5-25min after ejaculation (30).

Microscopic semen analysis includes sperm concentration, motility and morphology.

The lower reference limits (5th percentile) for semen parameters in "fertile" adult men are given in **Table 1**.

The results from the semen analysis are categorized as all parameters normal, oligozoospermia, asthenospermia (defects in motility), teratozoospermia (defects in morphology), and azoospermia (complete lack of sperm).

Volume > 1.5 mL
Sperm concentration > 15 million/mL
Total sperm count per ejaculate 39 million
Total sperm motility > 40 %
Sperm progressive motility > 32 %
Normal morphology ≥ 4%
White blood cells < 1 million/mL

***Table 1**: Lower reference limits (5th percentile) for semen parameters in "fertile" adult men*

5. Specialized clinical tests on sperm

Sperm DNA fragmentation, acrosome reaction and ROS are useful investigative tool, but are not recommended for the routine evaluation of infertility(35-37). Such assessments not only yield information on the fertilizing capacity of human spermatozoa but also their ability to support normal embryonic development. However, none of these parameters addresses sperm function and their clinical value in predicting fertility is questionable (38).

Haemoglobinopathies

The haemoglobinopathies (thalassaemias and sickle-cell disease) are the most commonly inherited genetic disorders world wide with some 240, 000 infants born annually with major haemoglobinopathies and at least 190 million carriers world wide. They are all inherited in a Mendelian recessive manner so the person with the carrier or trait state is healthy (39-41). Patients with thalassaemia and sickle-cell disease are now surviving into their fourth and fifth decades of life; however, many show problems with growth and sexual development in their adolescent years.

1. Thalassaemia

Beta-thalassaemia major (β-thal) is an inherited monogenic disorder. It is caused by a mutation at the ß-globin gene locus resulting in persistence of α-globin chain that is precipitated within erythroid precursors in the bone marrow associated with severe dyserythropoietic anaemia. Patients with thalassemias (ß-thal) can present with a broad spectrum of clinical severity, ranging from silent carriers to those with severe cases of iron overload. The severity of the clinical manifestations of these disorders relates to the amount of globin chain produced and the stability of residual chains present in excess (42).

The combination of early diagnosis, improvement in monitoring complications and advances in supportive therapy has enabled patients with thalassaemia major to have improved life expectancy (40-42).

Today many patients with ß-thal successfully survive into adult life, due to remarkable improvement of medical care and to a better understanding of pathogenesis, clinical manifestations and prevention of endocrine complications. Despite the improvement of the treatment, the involvement of the endocrine system still burdens the life of these patients. In fact, several studies have reported that as many as 51% to 66% of patients may have pubertal failure, sexual dysfunction and infertility, due to hypogonadism (40-42).

The causes of male infertility in general population are multiple while in ß-thal are classically considered to be the result of iron deposition in the endocrine glands (43-50). Other possible causes of hypogonadism in b-thal include liver disorders (45, 48,49) chronic hypoxia (50) and associated endocrine complications, such as diabetes (51).

Magnetic resonance imaging (MRI) shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function (52, 53).

Excess iron deposition in the anterior pituitary leads to degranulation of the adenohypophysis and decreased hormone storage with ensuing hypogonadism due to pituitary hyporesponsiveness to gonadotrophin releasing hormone (55-61). The pituitary damage is rarely reversible (62). The main damage of gonadotrophs in the pituitary is explained by the expression of transferrin receptors in these cells (52).

Iron overload is also present in the gonads. Testicular biopsies show hyperpigmentation of undifferentiated seminiferous tubules, a decreased number of Leydig cells and various degrees of interstitial fibrosis (58,59).

For the diagnosis and treatment of fertility issues of these patients , clinicians should take in consideration that:

1. Blood transfusion is associated with significant acute enhancement of sperm parameters and with an increased concentrations of serum testosterone, LH, FSH and IGF-I. These "acute" effects on spermiogenesis are reached with an unknown mechanism/s and suggest a number of pathways that need further human and/or experimental studies (50).
2. Iron overload induces sperm to oxidative injury and it could contribute to the impairment of sperm motility (43).In addition, an impaired prostatic secretion may be present in b-thal patients with high ferritin serum levels (60) . This is supported by the decrease of its specific markers such as zinc, citric acid and prostate specific antigen.
3. Iron chelators are suspected teratogens, and spermatogenesis in thalassaemics is, at least theoretically, occurring in a milieu of chelators, which is suboptimal for the generation of genetically intact sperm (44). A possible detrimental effect on spermatogenesis by the iron chelator desferrioxamine has been documented in these patients (45-47).
4. It is possible to induce or restore spermatogenesis with exogenous gonadotrophins in some b-thal patients (63, 64). We attempted to induce or augment pubertal development and achieve spermatogenesis in 10 gonadotrophin-deficient b-thal patients aged 15-23 years (mean 18.9). b-thal patients were treated with exogenous gonadotrophins for 1-4 years (mean 2.1). Seven patients produced sperm during HCG treatment given for 6-14 months. However, full spermatogenesis was achieved only when HMG was added to HCG regimen. In one patient, despite cessation of gonadotrophin treatment, sexual potency, libido and spermatogenetic capacity were maintained during the past 2½ years (63). Hormonal treatment of pubertal disorders in b-thal is a complex issue due to the many associated complications. Therefore, each patient has to be assessed

individually (45, 48, 49). Because of advances in fertilization and sperm banking technologies, all subjects, even those with extremely low sperm counts and motility, should be considered candidates for sperm cyropreservation (65). Fertility counselling offered to all patients prior to cryopreservation of sperm should include information about the potential of fetotoxicity and reproductive failure (44),in the light of sperm DNA damage documented in these patients (44,45). Substantially, there is an increased risk of transmitting defective DNA to the offspring (44,45), because the natural barriers to penetration of sperm with defective DNA into the oocyte are bypassed (44).

In conclusion, these patients have variable degrees of organ damage and endocrinopathies that can affect their quality of life. Hypogonadotrophic hypogonadism is the commonest endocrinopathy (44-50).

At present, one of the major problems dealing with adult patients with b-thal are "fertility" and "osteoporosis". In our experience, more and more adult thalassemic patients in their second and third decades of life, with the prospect of marriage, wish to know their ability to father a child.

Forty five percent of our thalassemic males with regular transfusional regimen, good compliance to chelation therapy and normal testicular volume (Tanner V) had abnormal motility/morphology. Those with poor compliance to chelation therapy ,arrested puberty (Tanner II-IV) and small testicular had reduced semen volume. Those with bad control, had failure of puberty, no erection or ejaculation and no seminal fluid (45,50).

There are only few studies, which describe spontaneous spermatogenesis and semen parameters in b-thal patients (43-50).

Advances in assisted reproductive techniques such as Intracytoplasmatic Sperm Injection (ICSI) in which a single spermatozoon is injected into the cytoplasm of an oocyte, have improved the prospects of childbearing in oligozoospermic thalassaemic patients. However,we believe that international guidelines are required to assist these patients because it is widely accepted that infertility and involuntary childlessness, and the decision to engage with assisted reproduction technology services as a patient, donor or surrogate can entail wide-ranging psychosocial issues (65).

2. Sickle-cell Disease

Sickle cell disease (SCD) is one of the commonest inherited diseases .The SCD is most common among people from Africa, India, the Caribbean, the Middle East, and the Mediterranean, but population movement has made this a worldwide problem(67).

In the UK, SCD affects approximately 1 in 4000 live births every year. Heterozygotes are generally asymptomatic carriers (traits), while the SCD is expressed in the homozygotes and the double heterozygotes for two abnormal haemoglobin genes or HbS and the thalassaemias (67).

The disease is caused by a point mutation in the b-globin gene resulting in a substitution from adenine to thymine, which in turn results in substitution of the amino acid valine for glutamic acid at the sixth position of the b-globin chain. This results in bs protein production which has a tendency to gel on deoxygenation. This liquid crystal distorts the red blood cells into their rigid sickle cell, leading to chronic haemolysis. The rigid cells aggregate in the microcirculation causing stasis and promoting hypoxia which leads to further sickling. It is characterized by a painful vaso-occlusive crisis resulting from the blockage of capillaries by the interaction of sickle erythrocytes, leukocytes, platelets and plasma proteins with vascular endothelium.These complications start in early life, but become more apparent with increasing age. Several factors such as infections, dehydration, fever, cold weather and stress precipitate the complications (68,69).

For the majority of patients, the mainstays of treatment are preventative and supportive. For those children with severe SCD, three major therapeutic options are currently available: blood transfusion (simple or exchange), hydroxyurea and bone marrow transplantation (67,69). Chelation therapy is routinely employed to prevent and treat iron overload in chronically transfused SCD patients (70).

Patients with sickle cell disease often have moderate to severe hypogonadism (71-81). Several mechanisms have been suggested: primary hypogonadism (71-74), hypogonadism induced by repeated testicular infarction (75) , zinc deficiency (76,77) and puberty delay (78-80) .

To our knowledge, only few studies have been published on the analyses of sperm parameters in patients with SCD (82-83). Some have reported an alterations of spermatozoa concentration, motility and morphology, others a decrease in ejaculate volume and sperm vitality (83-85). From 72 to 100% of SCD tpatients had an impairment of at least one sperm parameter (83-85).

The increases proportion of spermatids found in these patients suggest that there may be an impairment of the transformation of these immature forms into spermatozoa (86). In addition to testicular dysfunction, there may be abnormalities in the accessory sex organs, such as the

seminal vesicles and the prostate gland, particularly in view of the marked decrease in ejaculate volume (84).

Blood transfusion, in patients with SCD, is associated with significant acute enhancement of sperm parameters including total sperm count and total and progressive sperm motility (86).

Hydroxyurea (HU) significantly reduces the number of hospitalizations, vaso-occlusive crisis, and acute chest problems; thereby reducing severity of the disease (87,88). The beneficial effects of HU are due to a number of mechanisms, including inhibition of intracellular polymerization of HbS ,modification of red cell-endothelial interactions and the rheological properties of HbS-containing red cells, and via its myelosuppressive effects, particularly on neutrophils (89).

HU has been reported to impair spermatogenesis in mammals, resulting in testicular atrophy (90-92), a reversible decrease in sperm count (92-94) and abnormal sperm morphology (91,95) and motility (90).

Berthaut *et al* (96) reported data from the largest series so far of semen analyses in 44 patients with SCD before treatment with HU .They found that at least one sperm parameter was abnormal in 91% of the patients before treatment, in agreement with published literature. After HU cessation, while global results in 30 patients were not statistically different before and after HU treatment, in four individuals follow-up sperm parameters did not seem to recover quickly and the total number of spermatozoa per ejaculate fell below the normal range in about half the cases. In addition, HU may exacerbate the already SCD-induced hypogonadism due to gonadal failure (97).

In conclusion, these studies suggest that sperm cryopreservation should be offered to SCD patients before treatment with HU (96). Like ß-thal patients assisted reproductive techniques may supplementary help these patients to overcome previously untreatable causes of male infertility (66).

Miscellaneous Endocrine Illnesses

1. Thyroid dysfunctions

In the past two decades, several experimental and clinical studies have demonstrated that thyroid hormone plays an important role in testicular development and function (98-100).

Thyroid significantly impacts testicular development and that abnormal thyroid profile affects semen quality and male fertility by compromising testicular size, sperm motility and ejaculate volume because thyroid hormone receptors in the testes have been found (98,99). The presence of thyroid hormone receptors in testicular cells implies that tri-iodothyronine (T3) acts in the control of Sertoli cell proliferation and functional maturation, as well as in postnatal Leydig cell differentiation and steroidogenesis (101).

More specifically, a particular interest has grown concerning the effects of thyroid disease such as hyperthyroidism and hypothyroidism on spermatogenesis and overall male fertility (102-104).

Hyperthyroidism appears to cause alterations in the sex steroid hormone metabolism as well as in spermatogenesis and fertility. Testosterone levels are normal or increased and there are increased levels of estradiol (E2) and LH and LH response to gonadotropin-releasing hormone (GnRH), but decreased response of testosterone to hCG. There is an increased production rate of E2 and a decreased clearance of E2. Estradiol can decrease spermatogenesis by direct action on the testis (18). Oligoasthenospermia and decreased libido have been reported in 40 to 50% of cases and gynecomastia in 20 to 40% of cases (102). These abnormalities are reversible after restoration of euthyroidism (99,100).

Radioiodine therapy for hyperthyroidism or thyroid cancer may cause transient reductions in sperm count and motility, but there appears to be little risk of permanent effects provided that the cumulative dose is less than 14 MBq (103). Gonadal damage may be cumulative in those requiring multiple administrations and sperm banking should be considered in such patients (100,101).

The effects of hypothyroidism on male reproduction appear to be more subtle than those of hyperthyroidism and reversible. Severe, prolonged hypothyroidism in childhood may be associated with permanent abnormalities in gonadal function (103). Hypothyroidism in adults is associated with disturbances in the sex steroid hormone metabolism as well as infertility, although available data concerning the latter are scarce (102-104).

2. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive hereditary diseases. The impairment of cortisol synthesis leads to excessive stimulation of the adrenal glands by adrenocorticotropic hormone (ACTH), adrenal hyperplasia and excessive androgen synthesis (105,106).

21-Hydroxylase deficiency has an incidence of one in 12,000 live births for severe mutations causing classic CAH, which manifests in the neonatal period or during childhood, one in 2500 for milder mutations causing

nonclassic CAH manifesting during adolescence or early adulthood (105,106).

The syndrome is characterised by a considerable correlation between the genotype and the phenotype with the type of CYP21A2 gene mutation affecting the severity of 21-hydroxylase deficiency.

The clinical manifestations of CAH in adults result from adrenocortical and adrenomedullary insufficiency, hyperandrogenism, and the adverse effects of glucocorticosteroids used for the treatment of the condition. Non-classic CAH may sometimes be asymptomatic (105,106).

The principal goal of treatment in adult males with CAH is to improve quality of life, ensure that they remain fertile and minimise the adverse effects (107-111).

Arlt *et al* evaluated the health status of adults with CAH (112).Twenty-four of 65 men (37%) had sought fertility and 16 of 24 (67%) had been successful, reporting 25 live births, including two conceived after fertility treatment.

Testicular adrenal rest tumors (TARTs) were found in 11 of 16 patients (69%) investigated with ultrasound; only four were palpable at clinical examination. An additional four men had previously undergone unilateral orchidectomy, with histopathology reporting benign Leydig cell tumor, Leydig cell hyperplasia, and Leydig cell nodular hyperplasia (112).

Regarding fertility in the patients found to have TARTs, seven never tried, one tried for 3 yr without success, one is trying and still under treatment, and two patients tried with success, achieving one and two live births, respectively (112).

In conclusion, this study demonstrated that all adult patients with CAH should be offered care in endocrine centers with appropriate expertise, involving a multidisciplinary team, including endocrinologists, geneticists, psychologists, urologists and specialist nurses (112).

3. Insulin dependent diabetes mellitus

Juvenile diabetes is the most common metabolic disease of childhood and adolescence. Findings differ, however, with regard to the age of onset. The first manifestation is most frequently diagnosed in late childhood or early adolescence (113).The health reproduction care and follow-up of these adolescents are scanty.

Testicular dysfunction, impotence, decreased fertility potential and retrograde ejaculations are conditions that have been described in adult diabetic males (114,115).

Decreased serum testosterone due to impaired Leydig cell function and poor semen quality has been reported in some adult diabetic men, including decreased sperm motility and concentration, abnormal morphology and increased seminal plasma abnormalities (114,115).The gonadotrophin levels correlate with the markers of glycaemic control suggesting that there is a significant effect of diabetes on testicular function (115).

A complex interaction of metabolic, neurovascular and drug-related factors usually underlies the disturbance of sexual function. Oxidative stress is increased in diabetes due to overproduction of reactive oxygen species (ROS) and decreased efficiency of antioxidant defences, a process that starts very early and worsens over the course of the disease. During the development of diabetes, oxidation of lipids, proteins and DNA increase with time. Mitochondrial DNA mutations have also been reported in diabetic tissues, suggesting oxidative stress-related mitochondrial damage (116).

Conventional semen analysis (semen volume, sperm count, motility and morphology) and nuclear DNA fragmentation were assessed 27 adult diabetic (mean age 34 years) and 29 non-diabetic. Apart from significant, reduction in semen volume in diabetic men (2.6 versus 3.3 ml; $p < 0.05$), the other conventional semen parameters did not differ significantly from control subjects (114). Diabetes was associated with increased sperm DNA damage that may impair the reproductive capability of these patients (116). A deterioration of the quality of human semen occurs in adolescent diabetic patients. Neuropathy and poor metabolic control seem to be important factors of this deterioration (117).

The reproductive histories of people in a Finnish cohort of 2,819 men with type 1 diabetes and two matched controls were obtained from national population registery data. The age at onset of diabetes was associated with the pattern of reproduction. Later age at onset of diabetes was associated with a higher rate of having a first child among men (116).

Gastrointestinal Diseases

1. Celiac disease

Celiac Disease (CD) is a permanent intolerance to gluten, a protein complex contained in wheat, barley and rye, characterized by a wide clinical variability.

In genetically predisposed subjects, exposure to gluten results in a mucosal damage which, progressing through different stages of severity, causes small-intestinal mucosal atrophy (119, 120). Celiac disease occurs in

adults and children with an incidence approaching 1% of population in Western countries (120).

A diet completely free of the above cereals results in the total resolution of the clinical picture as well as in complete healing of jujenal mucosa histological lesions (120). Before treatment with a gluten free diet, men with CD have elevated total testosterone, free testosterone and LH. These changes revert to normal with a gluten free diet, suggesting reversible androgen resistance (121).

Abnormalities of sperm morphology and motility are common in both untreated and treated patients (124). Others have reported no association between CD and subfertility (125) . Celiac disease was first shown to be a reversible cause of male infertility in 1975, but the underlying mechanism was unclear (126).

It has been reported that the pathology of CD on reproduction is multifactorial in nature. These pathological manifestations can be modulated, besides gluten, by different concurrent genetic, nutritional and environmental factors. CD induces malabsorption with consequent deficiencies of micronutrients such as iron, folic acid and vitamin K, which are essential for organogenesis and fat-soluble vitamins important for spermatogenesis (127-129).

In conclusion, it is important to recognize asymptomatic CD as a possible cause of male subfertility. Therefore, CD should be considered and screening tests performed on men presenting with reproductive problems and treated accordingly.

2. Inflammatory bowel diseases

Chron's disease has been associated to oligospermia mainly in patients taking sulphasalazine (130,131). The abnormal semen parameters improve after stopping the drug (115).

Males with ulcerative colitis, in contrast, have similar semen parameters to the controls and the overall reproductive capacity is not markedly diminished (132).

3. Cystic Fibrosis (CF)

Cystic fibrosis (CF) is the most common inherited, autosomal recessive disorder in Caucasians, with a prevalence of approximately 1 in 2500 live births (133).

CF is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-activated anion channel conducting both Cl2 and HCO3 (133).

A multitude of clinical manifestations are associated with CF, which include chronic lung inflammation/ infection, pancreatic insufficiency, intestinal obstruction and infertility/subfertility in both sexes (133-135).

Over 1900 mutations have been reported in the CFTR, the gene defective in patients with cystic fibrosis. These mutations have been discovered primarily in individuals who have features consistent with the diagnosis of CF. In some cases, it has been recognized that the mutations are not causative of cystic fibrosis but are responsible for disorders with features similar to CF, and these conditions have been termed CFTR-related disorders or CFTR-RD (136,137), such as various forms of obstructive azoospermia, idiopathic pancreatitis or disseminated bronchiectasis associated with CFTR mutations uncharacteristic for CF (136,137).

Although CF is still considered a fatal disease, life expectancy has dramatically increased from 14 years of age (1969) to 32 years of age (2000) /133). Children with CF born after the year 2000 can be expected to survive well into their 50's (133,134).

Most of the men with CF (>95%) have congenital bilateral absence of vas deferens (CBAVD), which makes them infertile (135-139) Semen analysis reveals reduced ejaculate volume, low pH, low fructose concentration and azoospermia. Spermatogenesis is usually intact, therefore testicular biopsy usually is not recommended in these patients. Sufficient number of spermatozoa could be retrieved from the obstructed epididymis or is remnant (139).

With advances in assisted reproductive techniques, it is now potentially possible for these patients to father their own biological children. Spermatozoa may be retrieved from either the epididymis or the testes and combined in vitro with oocytes retrieved from the female partner. Epididymal sperm may be collected either by microsurgical or percutaneous epididymal sperm aspiration (135-138).

It is important to remember that when assisted reproductive techniques are used for such patients, there is the inevitability of transmitting a mutated cystic fibrosis trans-membrane (CFTR) gene, which increases the risk of producing an affected child and can have serious long-term implications. It is therefore mandatory to offer genetic counselling to the men with CF (and CBAVD) and their partners before carrying out assisted reproductive techniques (135-138).

Chronic Kidney Disease

Gonadal dysfunction is a frequent finding in men with chronic kidney disease and with end-stage renal disease. This is multifactorial in origin, as drugs and critical illness play a role (115,140). Testosterone deficiency, usually accompanied

by elevation of serum gonadotropin concentrations, is present in 26-66% of men with different degrees of renal failure which leads to reduced spermatogenesis (140,141). Uremia -associated hypogonadism rarely improves with initiation of dialysis (141).

These patients may be candidates for testosterone-replacement therapy, which has been shown to improve bone mineral-density and libido in men with low and low-normal testosterone levels (141,142).

However, caution is warranted because of the potential side effects of testosterone therapy, and further research is needed to more precisely define the balance of risk and benefit in patients with chronic kidney disease (142).

Approximately 20% of all children have a chronic illness and in 65% of them the illness is severe enough to interfere with daily activities (143).

Failure of pubertal growth, delay or absence of sexual development, infertility and sexual dysfunction due to hypogonadism and defective spermatogenesis are well recognized disturbances among many adolescents and young adult male patients with chronic diseases (115). The causes are multifactorial and can be due to the disease itself, associated complication/s or drugs (115).

Haemoglobinopathies, endocrine disorders, gastrointestinal and renal diseases are some examples that frequently cause some degree of disability. Infertility affects the future quality of life of these patients and is a predictor of stress in current and future relationships (144).

Recognition of potential endocrinopathies in adolescents and young adults with chronic illness is an important aspect of the care of these patients because the disturbances are frequently amenable to treatment, permitting full or partial restoration of normal growth, development and reproductive health (1,3,5,6).

Much progress has been achieved in the field of male infertility, both in the diagnostics and treatment aspects. Assisted reproductive techniques have revolutionized the treatment of male reproductive failure, allowing biological fatherhood to be achieved by many men that nature would have never permitted (145).

Conclusion

Several authors recommend that all young adult patients with severe/prolonged chronic disease in childhood should be offered reproductive health care in a specialized center with appropriate expertise, involving a multidisciplinary team, including endocrinologists, andrologists, geneticists, psychologists, urologists and specialist nurses. Adequate information must be provided to these patients about adolescent reproductive health, including types of contraception, pregnancy, sexually transmitted infections and fertility.

The importance of transitional care between pediatric and adult medical care should not be ignored. In the development of this process the adolescent must be involved in decision-making regarding treatment or referral. Reproductive health medicine should take a wider view to create a physical, psychological and genetic well-being of these patients.

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The Authors have nothing to disclose

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