Male reproduction in thalassaemia: A short overview

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Today many subjects with thalassaemia major (β-thal) successfully survive into adult life due to the remarkable improvements in 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.

The causes of male infertility in general population are multiple while in β-thal are classically considered to be the result of iron deposition in the endocrine glands.
Iron overload may be the result of economic circumstances (expense of the chelation therapy), late onset of chelation therapy or poor compliance with treatment.
Toxicity starts when the iron load in a particular tissue exceeds the tissue or blood-binding capacity of iron and free non-transferrin iron appears. The 'free iron' is a catalyst of the production of oxygen species that damage cells and peroxidize membrane lipids, leading to cell destruction.
Other possible causes of hypogonadism in β-thal include liver disorders, chronic hypoxia and associated endocrine complications, such as diabetes.

This is not a comprehensive review of male fertility problems in thalassaemia. It is not meant to be. It is, however, a short contribution written by a paediatric endocrinologist with a great interest in the subject and actively involved, in the last 30 years, in the management of male infertility in β-thal subjects.

I hope that it will be of value to all patients who wish to learn something about this subject.

The physical changes of puberty

Timing of puberty is the result of both genetic constitution and environmental influences. Chronic systemic diseases are often associated with delayed puberty. The initial physical sign of puberty is testicular enlargement (Table 1).

Table 1 Pubertal assessment according to Tanner

Penile development	Growth of pubic hair
P1: Prepubertal	PH1: Prepubertal
P2: Early puberty (enlargement of scrotum and testes, 4-5 ml, little or no enlargement of penis)	PH2: Early puberty (sparse growth)
P3: Mid puberty (enlargement of penis and further growth of testes, 8-12 ml, and scrotum)	PH3: Mid puberty (hair extends over the pubic junction)
P4: Advanced puberty (enlargement of penis in length and breadth. Increased pigmentation of scrotal skin and enlargement of testicles, 15-25 ml)	PH4: Advanced puberty (hair corresponds to adult growth but less extensive)
P5: Adult	PH5: Adult

Physiology of testicular function

The testes fulfil two tasks: steroidogenesis and spermatogenesis.
Steroidogenesis takes place in the Leydig (interstitial) cells, situated 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. This process takes about 60 days to be produced and another 10-14 days for them to pass through the epididymis and vas deferens.

Disorders of pubertal development and iron overload

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.
Delayed puberty is defined as the complete lack of pubertal development in boys by the age of 14 and hypogonadism is defined by 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.

Hypogonadotropic hypogonadism, which still remains the commonest endocrinopathy in patients with thalassaemia major, has been proven to be the result of haemosiderosis of the gonadotroph cells of the pituitary gland.

The anterior pituitary gland is particularly sensitive to free radical oxidative stresses and exposure to this. Magnetic resonance imaging (MRI) shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function. The pituitary damage is rarely reversible.

Genetic differences may influence the patient's susceptibility to hypogonadotropic hypogonadism, possibly as a result of differences in the amounts of blood transfused and/or their vulnerability to free radical damage

When hypogonadism develops *before* the age of puberty, the manifestations are those of impaired puberty:
• Small testes and phallus
• Scant pubic and axillary hair
• Disproportionately long arms and legs (from delayed epiphyseal closure)
• Persistently high-pitched voice

Some signs and symptoms are suggestive of male post- pubertal hypogonadism, while others are less clearly associated. The patient presents very small, soft or

shrinking testes, loss of libido and activity, decreased spontaneous erections or impotence, reduced muscle bulk and strength, reduction of seminal fluid or aspermia.

Semen analysis

Although semen analysis is not a test of fertility, a carefully performed 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.

The minimum number of specimens to define good or poor quality of semen is three samples over a 6-8 week interval with a consistent period of abstinence of 2-3 days.

Classical semen analysis, which includes sperm concentration, motility and morphology gives an approximate evaluation of the functional competence of spermatozoa.
• Low numbers of sperm and poor sperm movement can have an impact on fertility.
• Abnormally shaped sperm can also result in failure to conceive.
• An abnormal level of white blood cells could indicate an infection

The fertilizing potential of sperm depends not only on the functional competence of spermatozoa but also on sperm DNA integrity. Sperm with compromised DNA integrity, regardless of the degree of DNA damage, appear to have the capacity to fertilize oocytes at the same rate as normal sperm. However, the embryos produced by fertilization of an oocyte with DNA damaged sperm can not develop normally.

What do we know about fertility potential in thalassaemia?

Virtually very little is known about spermatogenesis in thalassaemia patients.
In summary, we found:

- A normal sperm count and motility in 45% of fully sexual mature β-thal subjects

- A possible detrimental effect on spermatogenesis of iron chelation therapy. Three out four patients with serum ferritin levels lower than 500 ng/ml had poor sperm motility.
- A higher degree of defective chromatin packaging in β-thal subjects with low sperm concentrations
- A low seminal plasma of zinc, citric acid and prostate specific antigen, suggesting an impaired prostatic secretion
- An increase of seminal lipoperoxidation, suggesting an increased oxidative stress of semen of these patients that could contribute to the impairment of sperm motility
- An increased DNA sperm damage and a negative correlation with sperm motility. These findings suggest that iron overload predispose sperm to oxidative injury.

Treatment

Iron chelation therapy

Combined therapy (use of two chelators on the same day), may induce negative iron balance and may reverse hypogonadism and endocrine complications in severely iron overloaded β-thal subjects.

Counselling
Sometimes certain 'lifestyle' factors may be responsible for poor semen quality. For example obesity, alcohol abuse, use of anabolic steroids and extreme sports may contribute towards poor semen quality. Another factor may be increased scrotal temperature through wearing thermal underwear, sauna or hot tub use or occupational exposure to heat sources. A considerable number of drugs can also affect the spermatogenesis.

Hormonal treatment

Hormonal treatment of pubertal disorders in thalassaemia is a complex issue due to the many associated complications; therefore, each patient has to be assessed individually. Collaboration between endocrinologists and other doctors is critical.
The treatment of delayed or arrested puberty, and hypogonadotrophic hypogonadism depends on factors such as age, severity of iron overload, damage to

the hypothalamo-pituitary-gonadal axis, chronic liver disease, and the presence of psychological problems resulting from hypogonadism.

Thalassaemics who fail to enter puberty or whose puberty is arrested before complete sexual maturation has occurred are usually considered to be sterile for life. However, we have found that this is not necessarily true and that gonadotropin treatment (hCG and hMG) can achieve spermatogenesis.

Infertility

Infertility is defined by the World Health Organization as the "inability of a sexually active, non-contracepting couple to achieve pregnancy in one year." Although no universally accepted consensus exists between specialties on the management of infertility, several algorithms have been devised to provide an initial assessment of the infertile male.

In presence of infertility , the male and female partners are evaluated to determine the cause and best treatment options.
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Today new assisted reproductive techniques (ART) offer hopes to many couples:

- intra-uterine insemination is used for mild male factor infertility problems

- intracytoplasmic sperm injection (ICSI) as a management for severe male factors or for recurrent unexplained failed in vitro fertilization (IVF) cycles. ICSI is a procedure that is performed in conjunction with IVF. With ICSI, a single sperm from the male partner is injected directly into a woman's egg (oocyte) in the laboratory. The pregnancy rate with ICSI is approximately 20% to 40% per cycle

Adoption is offered for cases with recurrent unexplained failed IVF cycles and donor insemination for azoospermia