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GUIDELINE

BSH Guideline

Guideline for the Management of Conception and Pregnancy in Thalassaemia Syndromes: A British Society for Haematology Guideline

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Summary

This comprehensive guideline, developed by a representative group of UK-based medical experts specialising in haemoglobinopathies, addresses the management of conception and pregnancy in patients with thalassaemia. A systematic search of PubMed and EMBASE using specific keywords, formed the basis of the literature review. Key terms included "thalassaemia," "pregnancy," "Cooley's anaemia," "Mediterranean anaemia," and others, covering aspects such as fertility, iron burden and ultrasonography. The guideline underwent rigorous review by prominent organisations, including the Endocrine Society, the Royal College of Obstetricians and Gynaecologists (RCOG), the United Kingdom Thalassaemia Society and the British Society of Haematology (BSH) guideline writing group. Additional feedback was solicited from a sounding board of UK haematologists, ensuring a thorough and collaborative approach. The objective of the guideline is to equip healthcare professionals with precise recommendations for managing conception and pregnancy in patients with thalassaemia.

KEYWORDS

ovulation induction, thalassaemia, spermatogenesis, puberty, pregnancy

METHODOLOGY

This guideline was compiled according to the BSH process at b-s-h.org.uk. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

REVIEW OF THE MANUSCRIPT

The review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee General Haematology Task Force, the BSH Guidelines Committee and the General haematology sounding board of BSH. It was also on the members section of the BSH website for comment. The guideline has also been reviewed by the Endocrine Society and the Royal College of Obstetricians and Gynaecologists for the Obstetric management. The national patient organisation for thalassaemia, the United Kingdom Thalassaemia Society, has reviewed and endorsed the guidelines.

We recognise the need for language that is inclusive of trans and gender-diverse patients and the variety of relationships and situations in which pregnancy takes place. Please consider the diversity of patients when reading these guidelines and ensure all people have equal access to care.

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LITERATURE SEARCH

The search was performed using the online search engine Medline (PubMed) as per the BSH literature review process.

Search terms were: ("thalassaemia") AND ("pregnancy") AND; "Cooley's anaemia"; "Mediterranean anaemia", "hypogonadotrophic hypogonadism", "ovulation induction", "assisted reproduction", "iron burden", "serum ferritin", "penicillin prophylaxis", "iron chelation", "fetal growth and measurement", "ultrasonography", "spermatogenesis induction", "chelation". Searches were also conducted using terms allogenic stem cell transplant and fertility to address specific sections.

Filters were applied to include only publications written in English, studies carried out in humans, case reports, clinical studies, clinical trials, comparative studies, evaluation studies, guidelines, meta-analysis, multicentre studies, observational studies, practice guidelines, reviews, systematic reviews, validation studies and published between 1 January 2012 and 31 August 2018, inclusive. The RCOG Green Top Guidelines GTG 66 (developed by the authors) was used to provide relevant literature prior to 2012. The RCOG GTG66 included publications identified in the Cochrane Database of Systematic Reviews, DARE, EMBASE, TRIP, Medline and PubMed. Search terms included: 'beta thalassaemia', 'Cooley's anaemia', 'Mediterranean anaemia', 'hypogonadotrophic hypogonadism', 'ovulation induction', 'assisted reproduction', 'iron burden', 'serum ferritin', 'penicillin prophylaxis', 'iron chelation', 'fetal growth and measurement' and 'ultrasonography'. The search was limited to humans and the English language, from 1980 to July 2013. A top-up literature search for the BSH was conducted on 5 February 2021 for articles published between 31 August 2018 and 5 February 2021 inclusive, using PubMed. The authors have reviewed the literature and updated references as appropriate after the top-up literature review.

Searches of individual journals were not implemented because it was felt that publications not captured during the database search process would have had limited availability and would have had little impact on the scientific community.

CRITERIA FOR REVIEW AND DATA COLLECTION

Titles and/or abstracts of publications obtained from the database searches described were manually reviewed and excluded if they did not adhere to the search criteria or refer to in vivo or in vitro data. Randomised controlled trials, case-controlled studies and well-conducted cohort studies were included if relevant.

INTRODUCTION

The thalassaemia syndromes are a spectrum of disorders ranging from severe transfusion-dependent conditions such as alpha and beta thalassaemia major to more variable non-transfusion-dependent anaemia disorders such as alpha thalassaemia intermedia (Haemoglobin H and related compound alpha thalassaemia disorders) and beta thalassaemia intermedia syndromes.[1] The global burden of thalassaemia is significant, with over 70 000 babies born with thalassaemia syndromes worldwide each year and more than 100 million individuals who are asymptomatic thalassaemia carriers.[2] In the United Kingdom, there are approximately 2000 patients with a thalassaemia syndrome registered on the National Haemoglobinopathy Registry. Most of these patients are of reproductive age; many are fertile or subfertile and will wish to have families. The challenges faced during pregnancy, due to iron overload and anaemia, are similar regardless of the genetic basis of the thalassaemia syndrome, and for the purpose of this guideline, patients will be considered based on clinical phenotype as transfusion-dependent thalassaemia (TDT) or non-transfusion-dependent thalassaemia (NTDT).[3,4]

The Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guideline 66 (GTG 66) was developed to support multidisciplinary care of thalassaemia patients from prior to conception to the postpartum period.[5] There is now an increasing body of evidence to support the multidisciplinary management of pregnancy in thalassaemia syndromes.[6–10] These guidelines focus on the patient's sex, assigned at birth as male or female. Patients who are transitioning or wish to transition should be supported appropriately, and discussion should happen around fertility preservation strategies to ensure that patients are able to have families in the future if they so wish. Same-sex couples should be offered appropriate support to conceive based on individual factors related to the couple. Partner testing should be undertaken with appropriate counselling to assess for risk of a serious haemoglobinopathy; if donor eggs or sperm are to be used, then the haemoglobinopathy status of donors should be reviewed prior to fertilisation.[11,12]

Patients receiving regular or intermittent red blood cell (RBC) transfusion develop iron overload over time and this is managed with iron chelation therapy (ICT). Inadequate ICT will result in end organ damage. The liver is the primary site of iron storage, but once sufficient iron overload occurs, iron can be deposited in the endocrine organs and the heart. Resultant complications include diabetes, hypogonadotropic hypogonadism, hypothyroidism, hypoparathyroidism and more rarely growth hormone and adrenal insufficiency.[13–15] Approximately 40% of young adults with thalassaemia are hypogonadal, and over 50% have more than one endocrinopathy.[16–18] Hypogonadotropic hypogonadism occurs because of pituitary iron overload and is the most common endocrinopathy.[19,20] Patients should undergo regular screening for development of, and appropriate replacement of, hormonal deficiencies. Patients who are hypogonadal will require support to conceive, but all endocrine complications require optimal management both preconception and during pregnancy to ensure optimal outcomes.[21–23]

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Cardiac iron deposition can result in serious life-threatening complications such as cardiac failure and cardiac arrhythmias. Cardiac iron overload is diagnosed with MRI assessment using a variety of techniques, but the most standardised and widely recognised method is the T2*.[24] The ejection fraction in thalassaemia patients is higher than those of non-thalassaemia patients due to the high output state, and thus a fall in ejection fraction, even within the normal range, can herald heart failure.[25] Cardiac failure due to iron overload can be fully reversed with ICT, and it is important that patients are aggressively and optimally managed for this fully reversible cardiomyopathy.[26] Myocardial iron clearance requires several years of sustained therapy with optimal iron chelation.[25] A cardiac T2* of >20 ms is considered optimal for pregnancy; hence, patients with TDT require careful assessment of iron burden and preconceptual optimisation to ensure a good outcome.

Patients with NTDT will have mild to moderate degrees of anaemia, and this can pose significant challenges during pregnancy. Patients may have developed iron overload; this is generally mild in the majority of patients with α NTDT but can be more severe in those with β NTDT. The severity of the anaemia can potentially affect both fetal growth and maternal health during pregnancy.[3,27] Transfusions initiated during pregnancy may be associated with an increased risk of alloimmunisation.[6,8]

Other challenges common to both TDT and NTDT disorders are the increased thrombotic risk in splenectomised patients and the presence of skeletal deformities, which may increase the risk of fetal complications during labour due to cephalopelvic disproportion as well as the maternal risk of fractures due to osteoporosis.[6,28–32] Management of pregnancy in thalassaemia syndromes therefore requires a multidisciplinary approach to ensure successful outcomes.

PRECONCEPTION OPTIMISATION IN PATIENTS WITH THALASSAEMIA

Optimisation of patients' health is important in ensuring good outcomes for pregnancy or fertility treatment (see Table 1). Patients with TDT and NTDT should have the opportunity to discuss plans for pregnancy and understand the importance of partner testing for haemoglobinopathy status.

Transfusion dependent patients

Discussion of fertility preservation and the importance of optimising chelation should be an integral part of routine clinic discussions with patients and their families from adolescence onwards, emphasising the fact that good chelation can prevent infertility and that there is limited evidence that infertility can be reversed.[9,33] Patients should be having, as part of routine care, regular MRI assessments for iron overload,[34,35] and if patients want to plan a pregnancy, a baseline scan (if not undertaken in the prior 12 months) should be undertaken and provide the basis for preconception optimisation of iron burden.

Well-chelated patients have equivalent pregnancy outcomes to patients without thalassaemia syndromes.[36,37]

Chelation regimens used outside pregnancy include desferrioxamine (DFO), deferiprone (DFP) or deferasirox (DFX). These can be used in monotherapy regimens or in combination with two chelating agents.[34,38] In the context of patients planning pregnancies, the iron burden should be optimised as much as possible prior to conception because ICT is stopped during pregnancy. DFO is the only agent that has been used safely in significant numbers of women during the period immediately prior to conception and in the second and third trimesters of pregnancy.[39]

DFP and DFX should be switched to DFO, ideally 6–12 weeks prior to planned conception. DFP and DFO have both shown some reproductive toxicity in animal studies (SPC). Case studies of spontaneous pregnancies in thalassaemia patients on oral ICT have not shown any maternal or fetal toxicity; therefore, termination of pregnancy is not mandated; however, chelation should be stopped as soon as a pregnancy is confirmed.[40–42]

In patients who do not have optimal iron parameters preconception, close attention should be paid to improving the efficacy of the chelation regimen, with consideration given to using combination therapy if monotherapy is insufficient.[26,43,44] The aim prior to pregnancy is a cardiac T2* in the normal range (>20 ms) and a liver iron below 7 mg/g/dw ideally, although pregnancy can safely be managed with lower cardiac T2* and higher liver iron levels.[5,34] Inflammatory markers such as amino-terminal pro-brain natriuretic peptide (NT-Pro-BNP) are raised in thalassaemia patients and cannot differentiate between patients with cardiac iron and those without.[45–47]

In addition to worsening iron overload due to cessation of chelation and increased transfusion requirement, the risks of pregnancy include cardiac decompensation, new-onset arrhythmias, complications of diabetes, new endocrinopathies, worsening bone health and liver decompensation.[4,48] Diabetes in pregnancy can lead to a fourfold risk of fetal anomaly and a threefold risk in perinatal mortality and can also impact adversely on cardiac function. Diabetic patients should have multidisciplinary management involving both haematology and diabetes teams preconceptually to optimise successful maternal and fetal outcomes.[49,50]

Male patients who are not fertile and require hormone replacement therapy (HRT) should aim for a well-controlled iron burden and can continue with their ICT regimen during spermatogenesis induction. Diabetes and other endocrinopathies should be optimally managed throughout spermatogenesis induction, which can take more than a year. Once adequate sperm production is achieved, chelation therapy should be switched to DFO in preparation for pregnancy and semen cryopreservation.

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TABLE 1 Preconception optimisation—summary of recommendations.

Aspect of care	Investigations/management	Aim	References	Quality and grade
Genetic counselling	Partner screening and patient genotype. Preimplantation genetic diagnosis or prenatal testing for appropriate couples		National screening standards	1B
Fertility unit assessment	Evaluation of both patient and partner, including tubal patency, sperm count, hormonal assessment		Standard practice	1B
Contraception	Adequate contraception should be used until all aspects of health required for pregnancy are optimised		Standard practice	1C
Psychological assessment/lifestyle	Evaluation of the patient and partner. Encourage smoking cessation		Standard practice	1C
Iron chelation	Optimise chelation regimen. Change chelation regime to avoid DFP or DFX within 3 months of planned conception	SF ~1000 mcg/L	(Marsella & Borgna-Pignatti[114], Di Maggio & Maggio[43], Singer & Vichinsky[39], Saliba et al[115])	1B
Transfusion	Increased red cell requirement in TDT patients. Consider transfusion in NTDT patients. Ensure extended red cell phenotype or genotype before transfusion. Rh and Kell matched units should be used in both TDT and NTDT patients.	Target Hb 100 g/L during pregnancy	(Origa[51], Origa[22], Taher[116])	1B
Cardiac	ECG, Echocardiogram, Cardiac T2*, cardiology review. Holter Monitor assessment if there is history of palpitations	Cardiac T2* >20 ms, LVEF ≥56%	Carlberg et al.[9]; Yardumian et al[117]	1B
Liver	Ferritin levels, liver R2 or T2*, USS liver (gallstones)	Liver iron concentration <7 mg/g	Yardumian A 2016	1B
Infection	Assess for Hepatitis B, C and HIV. Monitor hepatitis B antibody titre in vaccinated patients and offer immunisation for those who are not. Ensure splenectomised patients are fully vaccinated. Offer HPV vaccination to non-immunised patients		Standard practice The Green Book: Immunisation against infectious disease	1B
Endocrine	Glucose tolerance test, fructosamine, thyroid function, DEXA, vitamin D, adrenal function. Ensure calcium and vitamin D intake adequate	Fructosamine<300 nmol/L for >3 months prior to conception	Barnard and Tzoulis[50] Jensen[118]	1B
Medication	Cessation of bisphosphonates, ACE-inhibitors. Commence 5 mg folic acid. Ensure patients on DFO are taking vitamin C. Splenectomised patients should have penicillin V prophylaxis and initiate aspirin (if not already taking)		The Green Book: Immunisation against infectious disease. Chapter 7 Taher[28]	1B

Non-transfusion-dependent patients

Most patients are fertile and generally have no thalassaemia-related complications impacting on conception. Some patients may have developed iron overload due to increased iron absorption or intermittent transfusions and will require assessment of iron burden and any associated endocrinopathies.[6,32] In patients who may become pregnant, careful consideration should be given to the potential for RBC transfusion during pregnancy.[27] Red cell genotype and phenotype should be documented and reviewed, as well as any previous antibodies that may increase the risk of transfusion-related complications during pregnancy.[6,22,27,51] In patients who have already developed alloantibodies, consideration should be given to more extensive matching of blood groups to reduce the risk of new antibodies developing.[52,53]

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Pregnancy in patients who have received allogeneic stem cell transplant

Patients and families being considered for allogeneic stem cell transplantation (ASCT) should be counselled regarding the potential risk to fertility and referred to specialist fertility services to support fertility preservation. Oocyte vitrification, embryo cryopreservation and ovarian tissue cryopreservation are options for female patients to consider prior to ASCT. Semen cryopreservation is only available to those who attained puberty prior to transplant conditioning, and testicular tissue preservation is being explored as a potential fertility preservation strategy.[54,55]

Patients who have had ASCT should have genetic counselling to ensure an understanding that they will still pass on the genes for thalassaemia to their children.

The incidence of hypogonadism, delayed puberty and infertility post-ASCT varies widely in the literature but tends to be higher in females. There is a higher incidence of hypergonadotropic hypogonadism compared to hypogonadotropic hypogonadism.[56] Younger age and lower serum ferritin levels at the time of transplant were correlated with better gonadal function and outcome. Prepubertal gonadal quiescence and less iron overload appear to be the contributory factors for better outcome. Reduced-intensity conditioning has resulted in a better gonadal outcome.[57]

Diabetes and thyroid dysfunction may occur as late effects post-ASCT, and patients should be screened for these in specialist late effects clinics.

ASSESSMENT AND MANAGEMENT OF PATIENTS WITH HYPOGONADISM NEEDING SPERMATOGENESIS INDUCTION

Assessment of pubertal status should be undertaken and include testicular volume in addition to the measurement of relevant hormones.

Endocrine assessment—FSH, LH, testosterone, inhibin B and anti-Mullerian hormone (AMH)—should be measured at baseline.[58] The secretion of testosterone is diurnal, and samples should be taken fasting between 0800 and 1000. The remainder of pituitary function should also be assessed, although deficiency of other pituitary hormones is uncommon (9 am cortisol, TSH, fT4 and IGF1). Total testosterone <8.0 nmol/L is consistent with hypogonadism, with levels of 8.0–12.0 nmol/L being borderline. Gonadotrophins will be low or (inappropriately) normal in the context of hypogonadotropic hypogonadism. Elevated gonadotrophins with low testosterone point to primary testicular failure, which will not be responsive to gonadotrophin stimulation of spermatogenesis. Patients with hypergonadotropic hypogonadism should undergo diagnosis and management as per National Institute for Health and Care Excellence guideline 156 (NICE NG156).[12]

Semen analysis should be performed in all patients with evidence of hypogonadotropic hypogonadism who desire fertility and are being considered for induction of spermatogenesis.

Therapeutic management

Gonadotrophin therapy

Gonadotrophin therapy may be considered in two settings

1. As an alternative to testosterone replacement for the induction of puberty in adolescents with hypogonadotropic hypogonadism. This may result in improved testicular growth and future fertility compared to testosterone replacement.[59,60]
   Current practice is generally to initiate testosterone replacement in adolescents with thalassaemia who have failed to enter puberty. This will induce virilisation but will not stimulate testicular growth or spermatogenesis. Induction of puberty using gonadotrophin therapy may result in improved testicular growth and the initiation of spermatogenesis[59,61,62] although specific data with regard to thalassaemia is lacking. The involvement of a paediatric endocrinologist is essential. Once testicular volume has been maximised, semen analysis undertaken and consideration taken of the option of sperm banking, gonadotrophin therapy should be withdrawn, and gonadal status reassessed. Testosterone replacement therapy can then be initiated as necessary until fertility is desired.[62]

2. Gonadotrophin therapy for induction of spermatogenesis. A baseline semen analysis is recommended. HCG monotherapy is unlikely to be successful in patients with congenital hypogonadotropic hypogonadism, and the same is likely to apply to patients with iron overload who required hormonal induction of puberty. In these individuals, combined gonadotropin therapy with FSH and hCG will be required.[63–65]
   Testosterone replacement is suspended when gonadotropin therapy is introduced. For patients on testosterone gels, the switch is immediate, but for those on injectables, gonadotropins are started at the point when the next testosterone injection would have been due.
   De Sanctis and Bajoria have shown gonadotrophin therapy for spermatogenesis induction is successful in men with TDT,[23,65] with spermatogenesis achieved in 70% and 42% of patients, respectively, in the two studies. The duration of gonadotrophin treatment was 12–48 months and 6–24 months respectively. Although studies of patients with hypogonadotropic hypogonadism unrelated to thalassaemia show that baseline testicular volume is a marker for treatment success,[63] limited data available for patients with thalassaemia suggests initial testicular volume may be less predictive in this group.[65] The time

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to first appearance of sperm was longer in thalassaemic patients despite the use of comparable treatment protocols.[23,65]

Protocol for spermatogenesis

Initial treatment with LH equivalent

Luteinising hormone (LH) stimulates testosterone production by the testicular Leydig cells, resulting in intratesticular testosterone concentrations many times higher than in the peripheral circulation, which is necessary for spermatogenesis.

Human chorionic gonadotrophin (hCG) has LH equivalent activity and is used therapeutically as an LH equivalent due to its far longer half-life. In a minority of patients with hypogonadotropic hypogonadism, hCG treatment alone may be sufficient for spermatogenesis to occur[66]; however, this is unlikely where the onset of hypogonadotropic hypogonadism is before or during puberty.

In the UK the available hCG preparations are Ovitrelle and Gonasi.

HCG is patient-administered subcutaneously by injection at a dose of 1500–2500 units twice or thrice weekly. The blood tests to monitor are serum levels of testosterone, which should be measured every 1–3 months, aiming to maintain concentrations within the normal range. If subnormal or supernormal concentrations are initially achieved, the hCG dose should be adjusted accordingly. Serum oestradiol levels also increase (via testicular steroidogenesis) during hCG therapy and may cause breast tenderness in a minority of patients. Consideration should be given to adding an aromatase inhibitor in these patients to prevent gynaecomastia.

Once normal values are achieved, semen analysis should be performed every 2–3 months. The dose of hCG should not be adjusted based on semen analysis results.

Addition of FSH equivalent

If azoospermia persists 6 months after serum testosterone concentration has been optimised by hCG, FSH or human menopausal gonadotrophin (hMG/menotrophin) should be initiated at a starting dose of 75 units three times weekly by injection, and subsequently adjusted to achieve physiological serum FSH levels, for example 4–8 iu/L. Doses can be titrated up to a maximum dose of 300 iu thrice weekly. Consider adding FSH/hMG at the start of hCG therapy in patients who have incomplete or absent puberty.

Semen analysis should be repeated every 3 months.

Duration of treatment

Patients remaining azoospermic after 24 months of combined hCG/hMG treatment are unlikely to respond to continued gonadotrophin treatment but can be considered for microsurgical testicular sperm extraction (microTESE). Otherwise, gonadotrophin treatment can be withdrawn and testosterone replacement recommenced.

Where spermatogenesis is achieved, combined hCG/hMG should be continued until pregnancy is achieved. In one study, the median time to natural conception from the initiation of gonadotrophin treatment was 28 months (range 21.6–38.5 months).[63] Assisted conception should be offered where spermatogenesis is achieved, and natural conception has not occurred after 12 months, as per NICE NG156 recommendations.[12]

Recommendations

Gonadal status should be assessed in all patients with thalassaemia, commencing at the age of puberty, in conjunction with paediatric endocrinologists. (1A)
Combined gonadotrophin therapy may be considered for the induction of puberty and may be superior to testosterone replacement due to its impact on testes volume and quality of life. Testosterone replacement may then be initiated as needed. (2C)
If gonadotrophin therapy is required for spermatogenesis induction, regular monitoring of response should be undertaken, with reduction or increase of dose, or additional therapy added as indicated. (1B)
Assisted conception should be considered where spermatogenesis is achieved, and natural conception has not occurred by 12 months, or sooner when the female partner is in her mid-30s or older. (1B)
Unless microTESE is being considered, gonadotrophin treatment can be withdrawn, and testosterone replacement commenced in patients remaining azoospermic after 24 months of combined hCG/hMG treatment. (1C)

ASSESSMENT AND MANAGEMENT OF PATIENTS WITH HYPOGONADISM NEEDING OVULATION INDUCTION

Many patients with TDT in the UK have moved through puberty naturally due to the impact of optimal chelation regimens and a well-controlled iron burden during childhood. If pubertal induction is required in adolescence, reference should be made to clinical guidelines.[67,68] A significant number of older patients are hypogonadal and therefore will need fertility support for conception. The fertility specialist plays a vital role in the management of patients with thalassaemia syndromes in two respects: first, treatment with ovulation induction using injectable gonadotrophins is the mainstay in the management of anovulation secondary to pituitary iron overload; second, preimplantation genetic testing is used to identify non-thalassaemic embryos prior to a clinical pregnancy in a high-risk couple.

The sequelae of suboptimal ICT with subsequent deposition of iron in the pituitary will eventually lead to pituitary failure. Without the pituitary release of gonadotrophins, ovulation will not occur, and the ovary will be quiescent unless activated by gonadotrophins. It is not uncommon for

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such patients to be labelled as 'menopausal', a devastating diagnosis at a young age, but this diagnosis cannot be made until the ovaries are challenged with gonadotrophins.[69]

In the absence of a functional pituitary, it is necessary to replace the endogenous gonadotrophins with exogenous subcutaneous gonadotrophins. There are no suitable oral agents.

It is essential that a full fertility workup is undertaken prior to treatment with gonadotrophins for both partners. NICE (NG 156) guidelines (which are focused on heterosexual couples) stipulate the minimal investigations are a semen analysis (after 3 days of abstinence) for the male partner[12] and for the female partner follicular phase (cycle days 2–5) oestradiol (E2), FSH and LH. Ovulation should be estimated with a 7-day premenstrual progesterone (P4) assay. However, as the patient will be amenorrhoeic, blood tests should be performed at any stage once there has been elimination of their maintenance oestrogen/progestogen. Patients with hypergonadotropic hypogonadism should be managed as per NICE NG 156.

A transvaginal ultrasound (TVS) should be performed estimating ovarian volume, morphology and antral follicle count, as well as confirmation of uterine morphology. Care should be taken in counselling patients following TVS as the ovarian reserve can appear to be decreased, with ovarian volume and antral follicle count reduced because the ovary had not been stimulated.[23,69] AMH levels in patients with TDT are reported to be lower than age-matched controls.[70]

Tubal patency testing is performed to rule out tubal disease by hysterosalpingogram (HSG), hysteron-contrast-salpingography (HYCOSY) or laparoscopy and chromotubation (dependent on clinical features and local pathways).

Prior to the initiation of treatment, the patient needs to have fully informed consent relating to the potential risks and complications of treatment, namely: over/under response, requirement for monitoring by ultrasound and blood tests and most importantly, the possibility of multiple pregnancy. This final complication is very important given that patients will already be at increased obstetric risk. It is good practice to discuss the chance of success of treatment, which is most closely related to the age of the patient at the time of conception.

The aim of ovulation induction is the maturation of a single follicle. In order to start treatment, it is essential to undertake a baseline ultrasound to check that there is no ovarian activity (i.e. there are no follicles greater than 10 mm) and that the endometrium is no greater than 4 mm thick. If the endometrium is thickened, then a withdrawal bleed can be induced with oral progestogen (for example 5 mg medroxyprogesterone, taken twice daily for 5 days).[71]

Following confirmation of ovarian quiescence and an endometrium of ≤4 mm, self-administration of exogenous hMG daily is commenced. TVS is used to measure follicular size, and once a dominant follicle reaches a size of 18 mm with an endometrial thickness of at least 7 mm, a trigger injection is given, which promotes follicle rupture and ovulation approximately 38 h later. Multiple pregnancy will always be a possible outcome, and a patient should not have a trigger injection if more than two follicles of greater than 14 mm are present on the day of trigger without clear and documented counselling.[12] Couples are encouraged to have unprotected intercourse daily for 2 days commencing on the day of trigger.[72] Intrauterine insemination (IUI) is not routinely used unless there are separate fertility indications; IUI would normally be reserved for those with psychosexual issues or when donor sperm is required.[12]

If the treatment is successful, the earliest a urinary pregnancy test can be performed is approximately 15 days following the trigger injection. If the treatment is unsuccessful, then treatment can restart on the second day of the menstrual cycle. See Table 2 for an example of an ovulation induction schedule.

Patients who have failure of induction or conception after six cycles of ovulation induction should be discussed at a multidisciplinary team meeting (MDT) and alternative treatment modalities considered.[72]

Recommendations

A full fertility workup of both partners should be undertaken prior to any ovulation induction therapy. (1B)
Patients should be fully informed of individualised risk factors both relating to assisted conception, underlying thalassaemia syndrome and any associated complications prior to treatment. (1B)
Patients who have failure of treatment or conception after 6 cycles should be discussed in an MDT. (1B)
Multiple pregnancy will always be a possible outcome, and patients should not have a trigger injection if more than two follicles of greater than 14 mm are present on the day of trigger without clear and documented counselling. (1B)

MANAGEMENT OF PREGNANT PATIENTS

Pregnancy outcomes with thalassaemia have improved with advances in transfusion and ICT[73] and transplantation.[74]

Preconception optimisation of iron burden is critical, as cardiac failure in patients with pre-existing cardiac iron overload and new endocrinopathies can develop when chelation is paused during pregnancy.[10,75] MRI Cardiac T2* assessments can be undertaken safely in pregnant patients if required. Patients who have successfully reversed myocardial iron overload may develop arrhythmias and should be carefully questioned about palpitations during pregnancy.[37,76] These are high-risk pregnancies requiring an MDT to deliver general and thalassaemia-specific care with shared decision-making. This should include an obstetrician, a midwife experienced in high-risk pregnancies and a haematologist linked to a specialist haemoglobinopathy team, with additional specialist input from a cardiologist and/or diabetologist as required.

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Antenatal care should follow NICE Guidelines (NG201).[77] See Table 3 for the schedule of antenatal care.

Preconceptual high-dose folic acid (5 mg daily) starting 3 months prior to conception reduces the risk of neural tube defects[78,79] and should be continued throughout pregnancy. Currently, UK guidelines recommend that splenectomised patients with thalassaemia syndromes require penicillin prophylaxis as they are susceptible to infection by encapsulated bacteria[80–82] for example *Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae type b*. Their vaccination status should also be updated, and human papilloma virus (HPV) vaccination offered if not already immunised (Table 3). All patients should have vitamin D levels optimised and continue their routine supplementation during pregnancy.

The risk of pregnancy-induced hypertension (PIH) and pre-eclampsia (PET) is increased in thalassaemia syndromes.[48] Aspirin prophylaxis with 75–150 mg daily in the evening is recommended from around 12 weeks of gestation until 36 weeks.[83–85]

Assisted conception patients need a first trimester viability scan as miscarriage and fetal loss rates are high.[86] Third-trimester growth scans should be performed for early detection of fetal growth restriction (FGR) to allow planned transfusion and appropriate timing of delivery to reduce perinatal morbidity and mortality.[87]

Recommendations

Pregnant patients with thalassaemia should be reviewed monthly until 28 weeks of gestation and fortnightly thereafter. The MDT should provide routine as well as specialist antenatal care (1C).

Pregnant patients with TDT who have cardiac T2* > 20 ms prior to conception require specialist cardiac assessment early in the third trimester of gestation and further review thereafter as appropriate (1C).

Monitor thyroid function in pregnant patients with thalassaemia and hypothyroidism (1B).

Monitor monthly serum fructosamine in pregnant patients with thalassaemia and diabetes (1C).

Initiate folic acid 5 mg daily preconceptually to prevent neural tube defects and continue throughout pregnancy. (1A)

Initiate aspirin 75–150 mg daily from 12 weeks. (1A)

Offer an early viability ultrasound scan at 7–9 weeks of gestation. (1C)

Offer serial fetal growth scans every 4 weeks from 24 weeks of gestation. (1C)

Offer anaesthetic assessment in the third trimester of pregnancy. (2D)

Transfusion

Physiological plasma volume expansion in pregnancy exacerbates anaemia, leading to increased transfusion requirements in patients with TDT and the initiation of transfusion in late pregnancy in some patients with NTDT.[6,88,89] The aim is to maintain pretransfusion Hb above 100 g/L to avoid maternal and fetal morbidity. Severe maternal anaemia may affect placental function and predispose to FGR, low birthweight and preterm births.[27,88–90] Pre-emptive intervention may reduce the risk of FGR in some but not all patients, and other factors impacting on FGR need to be assessed and

TABLE 2 Example of ovulation induction schedule.

Time of intervention	Intervention	Details	Grade and level
Baseline	Transvaginal US scan	Assess pelvis Endometrium <4 mm and no follicle >10 mm	1B
Initiation of therapy	Initiation of hMG (Menopur or Meriofert)[a]	75 iu daily	1B
Days 10–12 postinitiation of stimulation	Assessment of follicles	No follicles >10 mm: continue same dose for a further 5 days and reassess[b]	1B
Days 10–21	Assessment of follicles and trigger injection	If less than 2 follicles >14 mm on day of trigger then trigger with 5000 iu hCG or choriogonadotropin alfa (e.g. Ovitrelle)[c]	1B
Day 7 after trigger injection	Measure serum progesterone	Levels of more than 30 nmol/L are confirmatory[d]	1B
Days 14–18 after trigger	Measure blood (day 14/15) or urine BHCG (17/18)	Confirmation of pregnancy	1C
Day 2 of withdrawal bleed	Option to initiate next ovulation induction cycle if unsuccessful		
Clinical review		If no follicular development achieved or 6 cycles of successful ovulation but no pregnancy	1C

Note: Whittington Hospital protocol used for TDT patients who are hypogonadal.

[a]If recombinant FSH medication (e.g. GonalF) is being used then it is essential to add in recombinant LH activity.

[b]Continue low-dose stimulation for at least 21 days before considering increasing the dose to 150 iu/75 iu alternate days.

[c]Multiple pregnancy will always be a possible outcome, and a patient should not have a trigger injection if more than two follicles of greater than 14 mm are present on the day of trigger without clear and documented counselling.

[d]Progesterone support is not necessary as long as ovulation has been confirmed.

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managed.[89,91] See Table 4 for indications for transfusion during pregnancy.

Recommendation

Ensure asymptomatic patients with NTDT have a clear management plan regarding transfusion in late pregnancy in their obstetric care plan. (1C)

Thromboprophylaxis

VTE risk is raised in thalassaemia syndromes, particularly in patients with beta NTDT who have undergone splenectomy,[92,93] because the resulting endogenous erythropoiesis remains unsuppressed without transfusion.[93] Data from a large cohort of patients with beta NTDT has shown that the thrombosis risk is highest in splenectomised patients with raised platelet counts.[28] Aspirin reduces VTE risk in splenectomised patients and is therefore recommended in patients with raised platelet counts.[28,94–97] Patients with a prior history of thrombosis should be managed as per RCOG GTG 37a recommendations for patients with additional risk factors.[98] The pro-thrombotic state in patients with alpha NTDT is less clearly defined,[99,100] and patients should be managed on an individualised risk assessment basis.[98]

VTE risk assessment should take place at the initial antenatal visit at 7–12 weeks of gestation (Booking Visit), 28 weeks of gestation and during any admissions, including delivery and postpartum, using a recognised risk assessment tool to guide decisions.[98] Antenatal VTE risk has been shown to increase with admissions, particularly those with more than a 3-day length of stay[101] and in the third trimester.[102,103]

Recommendations

Patients with thalassaemia who are splenectomised OR have a platelet count above 600×10^9/L should be offered low-molecular-weight heparin (LMWH) thromboprophylaxis in addition to low-dose aspirin 75–150 mg daily. (1A)
Consider LMWH thromboprophylaxis from 28 weeks of gestation to 6 weeks. Postpartum or throughout pregnancy if additional risk factors are present. (2B)
All pregnant patients with thalassaemia require LMWH during hospital admissions. (1B)

Chelation therapy

Optimal chelation promotes pregnancy outcomes comparable to patients without thalassaemia syndromes.[36] There is no safety data to support first-trimester chelation therapy, and DFO is the only chelation agent with an evidence base for use in the second and third trimesters.[9,39] Pregnant patients with significant myocardial iron loading and a cardiac T2* of <8 ms are at high risk of cardiac decompensation, which may present as worsening symptoms of shortness of breath and leg oedema (including new-onset orthopnoea and paroxysmal nocturnal dyspnoea).[24,26] Acute presentation with heart failure symptoms in the first trimester is associated with adverse clinical outcomes. Palpitations should prompt an urgent cardiac assessment even in the absence of current myocardial iron overload, as older patients with historical cardiac iron overload are at increasing risk of arrhythmias.[104] A falling ejection fraction or increasing ventricular volumes on echocardiography will suggest an increasing risk of developing heart failure.[105] Chelation therapy is required if cardiac T2* < 10 ms or if there are signs of cardiac decompensation (LVEF <56%).[34] Desferrioxamine infusion is the treatment of choice.[26,106] See Table 5 for recommendations for chelation therapy during pregnancy.

Recommendations

Pregnant patients with existing myocardial iron loading need first-trimester specialist cardiology review. (1B)
Imaging for assessment of iron burden and cardiac function should be undertaken if there are no scans in the 12 months prior to conception (2B)
Women with myocardial iron loading should undergo regular cardiology review with careful monitoring of ejection fraction during the pregnancy, as signs of cardiac decompensation are the primary indications for intervention with chelation therapy. (1B)
Patients with no myocardial iron loading should be assessed early in the third trimester of gestation to formulate a delivery plan based on cardiology advice (1B)
Patients presenting with palpitations should be assessed for arrhythmias (1B)
Those women at highest risk of cardiac decompensation (T2* < 10 ms) should commence low-dose subcutaneous desferrioxamine (20 mg/kg/day) on a minimum of 4–5 days a week under joint haematology and cardiology guidance from 20 to 24 weeks of gestation (1B)

Intrapartum care

Follow local and national guidelines for inducing labour and intrapartum care in uncomplicated cases as per NICE NG207 and NG121.[107,108] Patients with TDT will have had 9 months of no chelation, and there have been reports of patients developing cardiac failure and arrhythmias in the peripartum/postpartum period.[73,76,109] Peripartum chelation therapy is indicated in patients with TDT to reduce circulating toxic non-transferrin-bound iron, which can cause free radical damage and cardiac dysrhythmia during the stress of labour.[110–112]

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TABLE 3 Schedule of antenatal care.

Appointment	Care for patients with thalassaemia in pregnancy
Booking appointment: see multidisciplinary team (MDT)	Information, education and advice about pregnancy in a patient with thalassaemia Review partner results and discuss Prenatal Diagnosis if appropriate Refer to diabetic antenatal team if diabetic Assess endocrine, hepatic and cardiac status if this has not been done preconceptually. Review TDT patients for cardiac and liver iron and LVEF. If not undertaken in 12 months prior to conception arrange Echo for Left ventricular ejection fraction (LVEF), MRI for cardiac T2* and liver iron burden. Abdominal ultrasound as baseline for NTDT to assess spleen, liver and gall stones. Baseline full blood count, renal and liver function tests, urine protein/creatinine ratio, ferritin, B12, folate and blood group and antibody screen, red cell phenotype and extended genotype if not already done Check thyroid function in each trimester if hypothyroid VTE risk assessment—splenectomised higher risk Prescribe 75–150 mg aspirin daily in evening and folic acid 5 mg daily if not already taking this. Discuss vaccinations if splenectomised—Pneumovax, influenza, Sars-CoV 2, *Haemophilus influenzae type b* (Hib) and Meningitis C combined vaccination, Meningitis A, C Y,W and Meningitis B. Discuss HPV vaccination if not immunised. Penicillin prophylaxis—Penicillin V 250 mg bd (or erythromycin if allergic)
7–9 weeks	Offer viability scan
10–14 weeks	First trimester ultrasound scan
16 weeks—MDT + midwife	Routine review as per NICE antenatal guideline Glucose tolerance test (GTT) if high BMI or previous borderline GTT. If not available then fasting and random glucose at same time intervals
20 weeks—MDT + midwife	Routine review as per NICE antenatal guideline NG201
20–24 weeks	Cardiac iron overload: If T2* <10 ms: Commence low-dose desferrioxamine (20 mg/kg/d) on 4–5 days per week under haematology guidance If T2* > 10 but <20 ms—assess individual risk and consider desferrioxamine If T2* > 20 ms—not for desferrioxamine unless severe hepatic iron overload Check thyroid function
24 weeks—MDT + midwife	Routine review. Ultrasound for fetal growth and amniotic fluid volume
26–28 weeks	Non-diabetic patients for GTT. For diabetics, aim for monthly fructosamine <300 nmol/L
28 weeks—MDT + midwife	Routine review. Ultrasound for fetal biometry Specialist cardiology review. Formulate delivery plan based on cardiac function Consider VTE thromboprophylaxis
30 weeks—midwife	Routine review as per NICE antenatal guideline
32 weeks—MDT + midwife	Routine review. Ultrasound for fetal growth/amniotic fluid volume
34 weeks—midwife	Routine review
36 weeks—MDT + midwife	Ultrasound for fetal growth and amniotic fluid volume Review aspirin use and continuation. Discuss timing and mode of delivery Management of labour and delivery Analgesia and anaesthesia Care of baby after birth Referral for Obstetric Anaesthetic review Delivery care plan formulated and documented in the notes
38 weeks—midwife and obstetrician	Routine review. Offer induction of labour if diabetic. Ensure desferrioxamine is available
39 weeks—midwife	Routine review
40 weeks—obstetrician	Routine review
41 weeks—obstetrician	For a non-diabetic patient with a normally grown baby offer induction in accordance with the NICE guideline for induction of labour

Note: Appointments correspond to UK antenatal care schedules but should be adapted to the appointment schedules in different nations.

Recommendations

Inform the MDT (senior midwife, senior obstetric, anaesthetic and haematology staff) on admission to the delivery suite. (1D)

If red cell antibodies are present or haemoglobin <100 g/L, cross-match blood on admission. Otherwise, a blood group and save sample are sufficient. (1D)

In TDT patients, IV DFO 2 g over 24 h should be administered throughout labour. (2D)

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TABLE 4 Indications for transfusion during pregnancy.

Indication	Recommendation	References	Grade/level
TDT	Continue with regular top up with pretransfusion Hb >100 g/L	Standard practice	1B
NTDT + materno-fetal complication Symptomatic anaemia Evidence of fetal growth restriction	Top up transfusion, aim for post-transfusion Hb 120 g/L Maintain pre transfusion Hb >100 g/L	Nassar et al.[89] Levy et al.[91]	1B 1C
NTDT untransfused Hb >80 g/L at 36 weeks of gestation Hb < 80 g/L at 36 weeks of gestation Postnatal	Transfusion can be avoided before delivery Consider 1–2 unit top up at 37–38 weeks Cross-match 2 units on admission to labour ward Transfuse as necessary	Nassar et al[89] Origa[27] Voskaridou[6]	1C 1C 1C

TABLE 5 Recommendations for chelation therapy in pregnancy.

Cardiac indications	Intensification therapy	Grade of evidence
Severe myocardial iron loading (cardiac T2* < 10 ms)	Low-dose subcutaneous DFO (20 mg/kg/day) on a minimum of 4–5 days a week by joint haematology–cardiology team from 20 to 24 weeks of gestation	1C
Cardiac decompensation LVEF fall >10% from baseline Heart failure Cardiac arrhythmia	Desferrioxamine IV 24 h infusion and consider optimal doses of 40–50 mg/kg/day	1B
Severe hepatic iron loading	Consider low-dose chelation from 20 weeks of gestation based on MDT opinion on severity of iron burden and risk of developing endocrine complication or cardiac toxicity	1D

Continuous intrapartum electronic fetal heart rate monitoring is recommended. (1D)
Thalassaemia alone is not an indication for a caesarean section. (1D)
Ensure active management of the third stage of labour to minimise blood loss (1A)

Postpartum care

Routine postnatal care should follow national guidance from NICE NG194.[113] Breastfeeding should be encouraged, as DFO is not orally absorbed. Data are lacking for DFX and DFP, which are absorbed orally.

Thalassaemia patients are at high risk of VTE, particularly splenectomised patients with NTDT. See Table 6 for postnatal care for NTDT women transfused during pregnancy.

Although lactation is a physiological state of hypo-oestrogenism (serum levels 50–125 pmol/L), patients with profound hypogonadism and undetectable levels postpartum may struggle to breastfeed unless re-prescribed oestradiol-only HRT at very low dose, for example 25 mcg patches. See Table 7 for recommendations for chelation during breastfeeding.

Recommendations

Splenectomised patients should receive LMWH for 6 weeks after delivery. (1C)
Assess iron burden at 3 months postpartum unless myocardial iron overload necessitates earlier assessment. (1C)
Consider prescribing oestradiol-only HRT at low doses to support breastfeeding in hypogonadal patients. (2D)

TABLE 6 Postnatal care of NTDT patients transfused during pregnancy.

Formal postnatal assessment of the iron burden: serum ferritin, MRI T2* heart and liver iron quantification
Individualised decision to optimise iron burden: if Liver iron >5 mg/g/dw chelation to be discussed and initiated based on severity of iron and patient plans for breastfeeding.
Resume preconception general management regimen

TABLE 7 Chelation therapy and breastfeeding.

Breastfeeding	Not breastfeeding
Continue DFO infusion after labour until discharge from hospital. DFO 40–60 mg/kg/day s/c on 5 days a week by 6 weeks postpartum	IV or s/c DFO until discharge from hospital Resume prepregnancy chelation regimen as soon as feasible

Contraception

The full range of contraceptive options is feasible. The choice should be individualised to maximise compliance and efficacy.

CONCLUSIONS

Over the last few decades, there has been great progress in understanding the pathophysiology and treatment of fertility and pregnancy problems in patients with thalassaemia syndromes. The ability to have a family should be an achievable goal for most patients, but it requires a

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multidisciplinary team effort to ensure optimal outcomes for patients.

The mainstay of prevention of fertility issues remains meticulous iron chelation. Pubertal development should be assessed, and early interventions should be undertaken where necessary. Close monitoring of complications in pregnancy is essential, and iron chelation if required in the second and third trimesters, along with optimising the transfusion protocol and prophylactic medication, will maximise the chances of a successful pregnancy outcome.

AUTHOR CONTRIBUTIONS

Farrukh Shah, Shivan Pancham, Sarah Nicolle and Mumta Garg developed the PICO, and wrote the thalassaemia-specific components of the guideline; Karen Anthony wrote the spermatogenesis induction section; Gidon Lieberman wrote the ovulation induction section; and Amma Kyei Mensah and Farrukh Shah wrote the management of pregnancy section.

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N/A.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force, and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/guidelines/).

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