

Management of infertility in patients with thalassaemia

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The consequences of thalassaemia major and of its treatment are many, affecting a number of systems within the body. The reproductive system is no exception and many women who suffer from the disorder find themselves troubled by absent or infrequent menstrual periods, failure of ovulation and infertility. Progress in understanding the reasons why these phenomena occur, along with significant improvements in the management of anaemia and iron overload have improved the prospects of such a patient being able to start a family, although concerns about the safety of pregnancy and childbirth in the more severely affected patients remain.

The textbooks tell us that patients with thalassaemia are infertile because of the effects of iron accumulation on the hypothalamus and pituitary glands at the base of the brain. If the hypothalamus fails to produce sufficient GnRH (gonadotropin releasing hormone) or the pituitary fails to produce enough FSH (follicle stimulating hormone) and LH (luteinising hormone), the hormone drive to the ovaries to ovulate, or to the testes to produce sperm, is lacking and the woman or man can become infertile. Lack of FSH and LH is termed hypogonadotropic hypogonadism, and in women is associated with a lack of oestrogen hormone. Young girls with this condition may fail to go through puberty normally, either with no periods at all or with infrequent periods. Others will not see absence of periods until they are older, depending on the severity of their disorder. Men with thalassaemia are only rarely lacking in testosterone so they usually have normal facial and body hair growth, and normal erections, although their sperm quality may be suboptimum.

Investigation of infertility and absent periods in a woman with thalassaemia will involve blood tests, an ultrasound scan of the pelvis and an MRI (magnetic resonance imaging) of the hypothalamus and pituitary. None of these are particularly unpleasant, apart from the claustrophobia that some patients experience during the MRI scan. Sedation can be used if necessary in such cases. The likely results of these tests will be a low level of FSH, LH and oestrogens in the blood sample, a small uterus and ovaries seen on ultrasound and possibly evidence of pituitary damage on MRI. Such tests are usually easy to interpret and explain why the patient is having problems. Doctors may also give a single injection (or a nasal sniff) of GnRH to see whether this produces a rise in FSH and LH in the bloodstream. This is termed a GnRH challenge test, is free of side effects and can be useful in planning treatment.

More recently, it has become clear that some patients with thalassaemia also suffer from iron accumulation in the ovaries or testes. Hormone treatment is less likely to be effective here, since the ability of the woman to ovulate or the man to make sperm is irrevocably damaged. These patients will have a different hormone profile in their blood tests and will be warned ahead of treatment that there are low chances of success. Thankfully these cases seem uncommon.

Infertility is a problem for a couple, and it is important to remember to check the male partner's sperm count if the woman is affected, or conversely to check that she ovulates and has healthy uterus and fallopian tubes if the man is affected. Such tests are routine in a fertility clinic setting and can be organised by an interested GP in some cases. We would also want to be sure that the woman has had a recent normal smear test, is immune to rubella (German measles), and screening for chlamydia, hepatitis B & C and HIV might be offered in addition, particularly if IVF is planned.

Perhaps the most important aspect of the management of infertility in the patient with thalassaemia is to make sure that the health of the patient is optimised before treatment begins. The essentials of pre-treatment assessment are listed in table 1, and require a close liaison between the team of doctors and nurses managing the thalassaemia, and the fertility clinic. It is advisable to refer to a clinic that is based in a hospital setting, within the NHS in UK, rather than to a free standing clinic out of the hospital system, for reasons of patient safety.

Pre-treatment medication also needs careful review. Folic acid supplementation, possibly in higher than routine doses, should be started. Some medications commonly used to treat patients with thalassaemia are possibly unsafe in early pregnancy, including desferrioxamine, biphosphonates (for bone protection), high dose vitamin C and ACE inhibitors (for high blood pressure). These medications should only be stopped by the lead clinician in the thalassaemia team, and not by patients without prior discussion with their doctors. Thalassaemia patients with diabetes can safely continue Metformin, but may need to switch to insulin in pregnancy as diabetic control may deteriorate. Careful monitoring will be needed. Calcium and vitamin D supplements can be continued.

So how might a fertility clinic go about treating infertility in a patient with thalassaemia? The answer will depend on the cause of the problem. If the routine investigations reveal hypogonadal hypogonadism then the simplest approach is to provide a once daily injection of FSH and LH. This can be done using a subcutaneous injection through a pen device and is not as unpleasant as it sounds. By replacing FSH and LH, the ovaries (or testes) will begin to work again, since they have been lying dormant rather than being destroyed. The woman will ovulate, often with the help of a single injection of hCG (human chorionic gonadotropin) hormone to ensure the egg is released, and can conceive naturally after intercourse at the correct stage of the menstrual cycle. The clinic will monitor the ovaries response to the drugs by ultrasound scans and blood tests – the scans can see the egg follicle growing in the ovary and the blood tests monitor the hormones produced by the growing egg follicle.

There are two significant risks to this approach. The major problem is that the drugs are powerful and can often induce growth of two or more follicles, with risk of twin or triplet pregnancy. Most of the triplets and quads reported in the UK press in recent years have been caused by this treatment, known as ovulation induction, rather than by IVF. Multiple pregnancies have many drawbacks, the most significant being the high risk of premature birth and need for admission to a neonatal intensive care unit. Although many babies will come through this ordeal unscathed, some, particularly the very premature, may have a long term handicap such as cerebral palsy, and some will not survive. It is obviously best to avoid this risk if possible, and responsible clinics will use low doses of drugs with careful monitoring to do their best to produce 'one

baby at a time'. The website of the Human Fertilisation and Embryology Authority has useful information on this topic (www.hfea.gov.uk). The second complication which can result from overdosage with these powerful drugs is OHSS (ovarian hyperstimulation syndrome). The ovaries enlarge and the woman experiences fluid retention with bloating, breathlessness and nausea. Although uncommon in ovulation induction, serious cases require hospital admission and would be particularly complicated to manage in a patient already unwell with thalassaemia. Again, these treatments can be safe if carried out carefully with close liaison with the medical team.

The chances of a pregnancy and live birth after ovulation induction depend on the response of the ovaries to the drugs, and on the age of the woman. Although seemingly unfair, biology makes it very difficult for women over 40 to achieve a healthy live birth, with rapid increases in rates of infertility, miscarriage and chromosome problems such as Down's syndrome above this age. For this reason, women with thalassaemia who wish to have children should discuss their plans with their doctors and be seen in a fertility clinic before 35 when possible.

The response of the ovaries or testes to injections of FSH and LH may be surprisingly poor. This would indicate damage to the ovaries or testes themselves, and treatment may be unsuccessful. If this is the case then little can be done, other than to consider treatment with donated sperm or eggs. The clinic would provide counselling to the couple involved, with careful explanation of the benefits and drawbacks to this approach before treatment was given.

Should ovulation induction fail to result in pregnancy despite satisfactory ovulation, or if there are other infertility factors involved, then the clinic may suggest IVF (in vitro fertilisation). IVF has come a long way since the birth of Louise Brown 30 years ago this year, and is more straightforward and less stressful than many believe. Again, the safest clinics for patients with thalassaemia are those which are hospital based. IVF again involves a daily injection of FSH, possibly with use of a nasal spray or injection of a second drug, a GnRH analogue, to prevent early ovulation. The FSH injections last for 10 – 14 days and are followed by a single injection of hCG and then collection of eggs from the woman's ovaries. Egg collection is done using a needle guided by ultrasound scan control. The scanner is a long thin probe that is placed into the vagina. The ovaries can be easily seen on the scanner and the needle runs inside the probe and is pushed through the top of the vagina into the ovary. This involves a sharp pain in the lower part of the tummy, so the procedure is carried out under anaesthetic or sedation. It takes 10 – 30 minutes to do, and will produce anything from one or two to over twenty eggs.

The male partner will be asked to produce a sperm sample on the same day as egg collection, and the laboratory scientist (embryologist) will incubate the eggs with the sperm and induce the egg to fertilise. Fertilised eggs (embryos) are grown in the lab for 2 – 5 days. The best one or two embryos will then be replaced into the cavity of the womb (uterus) in a procedure similar to having a smear test taken, a quick and fairly painless, if emotionally charged, procedure. The couple then have to wait for two weeks to see if they have a pregnancy. The clinic will often prescribe a daily progestogen during this time, given as a vaginal pessary, which may help implantation.

If the pregnancy test is positive then there is still a possibility of miscarriage or, rarely, an ectopic pregnancy. A good clinic will perform early pregnancy scans to check that the pregnancy is healthy before sending the couple for antenatal care through their GP. Early pregnancy scanning will also check if there is a twin pregnancy!

Younger patients and those with medical problems that would be made worse by twins (including thalassaemia) would be well advised to have a single embryo transfer to avoid risk of a multiple pregnancy. Although the chances of a baby are reduced with single embryo transfer, the second embryo can be frozen and replaced later in the woman's natural monthly cycle, often without drugs and without the stress of an egg collection. This "one plus one" approach will give a similar chance of pregnancy to the two embryo transfer, without significant risk of twins.

The chance of a live birth after a single cycle of IVF, based on the average of all treatments in UK in 2006, falls from over 28% for women under 35, to less than 10% for women over 40. Again, useful information can be obtained from www.hfea.gov.uk.

Preimplantation genetic diagnosis (PGD) is a new approach which aims to avoid the chances of a baby having both copies of the gene for thalassaemia. IVF allows embryos to be studied in the laboratory. One or two cells are removed from the embryo and analysed to see if they have normal or thalassaemic genes. Only those embryos that are clear of thalassaemia genes would then be replaced. The technology needed to carry out these tests is complex but becoming more widely available in UK. www.laboratorigenoma.it is a useful website that describes PGD in more detail.

Of course, having a positive pregnancy test is only the end of one chapter, not the whole book. Pregnancy can be complicated in women with thalassaemia and close liaison with the medical team is essential. Many centres will have a dedicated Consultant Obstetrician who works with this group of patients. It is particularly important to monitor cardiac function closely, to maintain haemoglobin levels at or above 10g/dl and to check blood pressure and for diabetes regularly. Ultrasound will be used to monitor foetal growth. As some women with thalassaemia are of short stature, there is an increased need for Caesarean delivery. In the largest UK case series published to date, Susan Tuck and her colleagues at the Royal Free Hospital in London reported 24 live births from 29 pregnancies. Complications included deterioration in cardiac and liver function, and in diabetes. Sadly, there were two deaths from cardiac disease, highlighting the need for high level medical care for this group of patients. Some of the more severely affected patients with thalassaemia may be best advised to avoid pregnancy because the risk to their life, and potentially also to that of their unborn baby, is too great.

One continuing problem is that the UK NHS has little interest in infertility, and many patients are surprised to learn that they will be expected to pay for their own treatment. Politicians from both major parties have repeatedly promised to improve NHS support but little progress has been made. The position varies greatly across the UK, being determined entirely at local level by PCTs (Primary Care Trusts). Patients who are contemplating treatment can find out about their eligibility for funding from

their GP or fertility clinic. Costs of private IVF vary considerably and it can be difficult to establish the true cost of treatment from some websites of private clinics. It is important to establish exactly how much a cycle of treatment will cost, including drugs, scans, consultations and many other “add-ons” before starting treatment.

There have been many improvements in the medical management of thalassaemia in recent years. Many patients can expect a near normal lifespan and can enjoy a good quality of life. For many of us, this includes having a family and seeing one’s children grow. With a careful, collaborative approach, most women with thalassaemia should be able to be helped to conceive and to have a successful pregnancy.

Table 1 – Pre treatment assessment of patients with thalassaemia

- Optimise chelation
- Cardiac function
- Liver function
- Thyroid function
- Virology
- Optimise diabetic control
- Review medication
- Screen for acquired red cell antibodies (risk of haemolytic disease)
- Check male for haemoglobinopathy
- Arrange genetic counselling if necessary