



FERTILITY AND PREGNANCY IN THALASSEMIA: Q&A with Dr. Farzana Sayani



ABOUT DR. SAYANI

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Dr. Sayani joined the Division of Hematology/Oncology at the University of Pennsylvania in Philadelphia in 2012. Prior to arriving at Penn, she had established and was Director of the Thalassemia and Sickle Cell Program at the University of Calgary. At Penn, she has established the Penn Comprehensive Adult Thalassemia Program, and developed a successful transition program for patients with thalassemia from Children's Hospital of Philadelphia. She serves as the Director of the Penn Comprehensive Adult Thalassemia Program and the Penn Comprehensive Sickle Cell Program.

I. FERTILITY

What are the main causes of infertility in women and men with thalassemia?

Iron overload in the pituitary gland is the main cause of infertility in women and men with thalassemia. The pituitary gland normally helps to regulate proper functioning of the ovaries and testes. Iron-related damage to the pituitary can lead to abnormalities in ovulation (the release of eggs from the ovaries) and sperm production. Pituitary dysfunction is observed in approximately 50-80% of patients with iron overload. It is therefore important for individuals with thalassemia

to be optimally chelated from a young age in order to minimize any damage to the pituitary, and to allow for normal sexual development and fertility.

Age is also a contributing factor to infertility, especially in women with thalassemia. Women with Thalassemia Major appear to have premature ovarian aging (early cessation of egg production) compared to women of similar age without thalassemia. Thus it is important to begin discussions with your provider early so that evaluations can begin and interventions – including iron chelation – can be optimized.



Other iron-overload associated complications, such as hypothyroidism (in which the thyroid gland doesn't produce enough thyroid hormone) and diabetes, can also contribute to infertility in thalassemia.

Iron accumulation in the ovaries and testes can also have an impact on egg and sperm production. However, iron accumulation in the pituitary seems to have a much greater impact on patients' fertility.

In addition to thalassemia-associated causes of infertility, women and men with thalassemia can also suffer from other non-thalassemia-related causes of infertility.

Which patients are most likely to experience infertility – those who experienced significant iron overload as adults, or those who experienced iron overload in childhood that led to a delay in puberty?

Infertility can occur in patients with any history of significant iron overload – whether it occurred in childhood or in adulthood. However, the extent of the problems will depend on when the pituitary damage occurred. If severe iron overload is present in the prepubescent years, puberty may be delayed and menstrual periods may not begin for a girl. However, if iron overload develops after puberty, a young woman may complete pubertal development, but may experience challenges with fertility later on. Thus, optimal chelation from a young age is vital to ensure normal pubertal development, which greatly improves one's likelihood of spontaneously conceiving a child. With improvements in chelation and monitoring of iron overload, hypogonadism (when the testes or ovaries produce little or no sex hormones) and delayed puberty is now seen less often in adolescents, and the hope is that fewer of these patients will end up needing assistance in order to have children.

How is fertility assessed in adult male and female patients? When is it appropriate for a patient to have a fertility assessment performed – only after having difficulty conceiving, or as

soon as a patient decides that he/she would like to start a family?

Adult males and females with thalassemia who are thinking of starting a family should have their fertility evaluated by a fertility specialist – especially if they have a prior history of severe iron overload. In a woman with irregular or no menstrual cycles, the assessment should be performed as soon as the patient decides she would like to start a family. Since fertility decreases with increasing patient age, and since many fertility treatments can take time to work, earlier evaluation by a fertility expert is recommended. If a female with thalassemia and normal menstrual cycles, or a male with thalassemia has not been able to conceive within 6 months of trying, an evaluation by a fertility expert is recommended.

In general, a fertility expert will evaluate all potential causes of infertility – whether or not they are related to thalassemia. Typically, both partners (male and female) are evaluated. The fertility expert will assess whether there are any hormonal deficiencies, problems with ovulation or sperm production, abnormalities in sperm motility, or abnormalities of the uterus (womb), ovaries or testicles.

How effective is hormone replacement therapy in overcoming infertility in both male and female patients? What other fertility treatments are available?

The damage in many iron-overloaded patients occurs at the level of the pituitary. Because the ovaries and testes are still functional, ovulation and sperm production can often be induced by hormonal treatments that supply the hormones which are missing due to pituitary dysfunction.

In women with thalassemia, induction of ovulation with various hormonal treatments has a success rate of approximately 80%, as long as there are no abnormalities in the uterus or fallopian tubes (tubes which carry eggs from the ovary to the uterus). Several different ovulation induction drugs and protocols are available. Most ovulation induction protocols use standard medications such as clomiphene citrate or



hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) to stimulate development of follicles, and human chorionic gonadotropin (hCG) and LH to trigger ovulation. Induction of ovulation is associated with the risk of ovarian hyperstimulation syndrome – a rare, but life-threatening, condition. Induction of ovulation also increases the likelihood of twin or triplet pregnancies by somewhere between 1.6% to 18.9%, and increases the risks associated with a multiple birth pregnancy. It is best to work closely with a team of fertility experts if you decide to embark on this journey.

The induction of sperm production in male patients with thalassemia is much more difficult, with success rates of only 10-15% in patients with a history of moderate to severe iron overload. For male patients, the treatment process generally involves regular hormonal injections together with frequent semen analyses, and may take up to 2 years of treatment to result in adequate sperm production. If the treatment regimen has not resulted in adequate sperm production after 2 years, the likelihood of eventual success is unfortunately very low.

What are some of the assisted reproductive technology options currently available to patients wishing to start a family?

After stimulation of ovulation or sperm production, there are several available conception options including: (1) natural conception, (2) intra-uterine insemination (IUI) or (3) in vitro fertilization (IVF). In intra-uterine insemination, sperm is placed directly inside a woman's uterus to facilitate fertilization. In IVF, the egg and sperm are combined in a laboratory dish, and the resulting embryo is then transferred into the mother's uterus. Several additional techniques can also be incorporated into IVF for improved outcomes: Intra-cytoplasmic sperm injection (ICSI) directly injects sperm into the egg, which can result in improved conception rates when low sperm count or defects in sperm motility are the underlying cause of male infertility. For couples who are at risk of having a child with beta thalassemia, pre-implantation genetic diagnosis (PGD) can be combined with IVF to select

embryos which are free of a clinically significant form of thalassemia for implantation into the woman's uterus. For a female patient with significant complications who might be at high risk for carrying a pregnancy, surrogacy is also an option: her egg and her partner's sperm can be combined in the laboratory, and then transferred to the uterus of a pre-arranged surrogate who would then carry the pregnancy to term.

Since there are many options available to aid with conception, it is important to work closely with your thalassemia team, your gynecologist, fertility specialists, and a genetic counselor to ensure you have all the information on the many choices available. It is important to understand the benefits and risks, the success and failure rates, and the costs of each of the options before proceeding. These are very personal and emotional decisions. Your team will help and support you through this difficult process.

For patients who wish to expand their families but who are not able to conceive on their own or with assisted reproductive technology, what other options are available to them?

For couples in which both partners have Thalassemia Intermedia or Thalassemia Major, there is a high risk of having a child with a significant form of thalassemia. In these cases, finding either an egg or sperm donor who does not carry a thalassemia mutation – followed by IVF and implantation – may be an option to consider. This allows a couple to have a child that is genetically related to one of the parents without the risk of inheriting thalassemia. A sperm donor is generally preferred in this scenario due to the ease of collecting sperm and the lower associated costs.

Adoption is another option for expanding one's family for the following types of patients: (i) those who are not able to conceive on their own or with assisted reproductive technologies; (ii) female patients with severe organ damage for whom pregnancy may be high-risk, (iii) parents at high risk of having a child with Beta Thalassemia Major, or (iv) couples who wish to adopt in order to give a home to a child in need.



II. PREGNANCY

What testing should be performed when a woman with thalassemia is first beginning to consider the possibility of pregnancy?

A planned pregnancy is key to minimizing risks to the mother and the baby. Before conception, the following should be considered:

- The partner should undergo carrier testing for thalassemia and hemoglobinopathy status, and if the partner turns out to be a thalassemia carrier, the couple should be referred to a genetic counselor
- Fertility assessment as described above may be important based on risk of hypogonadism
- Iron overload status should be evaluated by serum ferritin levels, liver MRI and cardiac MRI (T2*). Ideally, the liver iron concentration should be less than 7 mg/g dry weight and the cardiac T2* greater than 20 milliseconds before attempting to conceive.
- All women should have their cardiac function evaluated by a cardiologist using electrocardiogram (ECG), 24-hour Holter monitor, echocardiogram and cardiac MRI. Pregnancy is discouraged if there are any abnormalities of heart function or rhythm due to the high risk of death.
- Liver function evaluation with biochemical testing is important. If there has been a history of high iron burden or hepatitis C infection, further testing and evaluation by a liver specialist is important.
- Evaluation by an endocrinologist with an emphasis on bone health and vitamin D levels, and screening for diabetes, hypothyroidism and other hormone abnormalities should be performed before conception and treated as needed
- Patients should be screened for infections prior to pregnancy including for HIV, hepatitis B and C, and rubella
- Medications – including iron chelators – should be reviewed and adjusted as needed. Since the demand for folic acid increases during pregnancy, all women with thalassemia should be on folic acid supplementation prior to conception to prevent neural tube defects in the fetus.

What percentage of women with thalassemia in North America/the U.K. have ever been pregnant, at last estimate? What has enabled the large increase in pregnancies in women with thalassemia in recent years?

In the past, pregnancies in patients with thalassemia were rare due to pituitary dysfunction and infertility associated with iron overload. A 2004 publication by the Thalassemia Clinical Research Network reported pregnancy in only 8% of North American female patients (Cunningham, 2004). However, the number of pregnancies in patients with thalassemia has increased since that time due to improvements in chelation, transfusion therapy, methods of monitoring iron overload, and the availability of comprehensive care. A 2013 publication by the Thalassemia Clinical Research Network showed that the number of pregnancies had increased to 25% of female patients in North America and the U.K. (Thompson, 2013).

In general, women with non-transfusion dependent thalassemia (NTDT) are more likely to become spontaneously pregnant than women with transfusion dependent thalassemia (TDT). Women with TDT are more likely to require assisted reproductive treatments. Fewer complications are observed during pregnancy in patients with low liver iron levels and no cardiac iron. Collaboration with an experienced Maternal Fetal Medicine (MFM) team – with close monitoring of both mother and baby – has also contributed to fewer complications during pregnancy in women with thalassemia.

What are the most common complications in women with thalassemia who become pregnant? How are these pregnancy-related complications managed? Do these complications typically resolve after the mother has given birth?

Women with thalassemia who have a history of cardiac iron overload may be at risk for developing poor cardiac function and even cardiac failure if



they become pregnant. This is because the mother's metabolic demand and blood volume increases during pregnancy – which puts an additional burden on the heart. Pregnant individuals with compromised heart function due to iron overload are therefore at higher risk of heart rhythm abnormalities, heart failure, and even death. It is therefore important to have a thorough evaluation of cardiac function before trying to become pregnant. A complete evaluation by a cardiologist including electrocardiogram (ECG), echocardiogram, 24-hour Holter monitor, and T2* MRI assessment for cardiac iron are recommended. Ideally, the cardiac T2* should be greater than 20 milliseconds before pregnancy is attempted. Generally, women with a cardiac T2* < 10 milliseconds or other evidence of heart dysfunction are encouraged to chelate aggressively to reduce iron burden before attempting pregnancy. During pregnancy, patients should be closely followed by a cardiologist and evaluated every trimester by ECG and echocardiogram – or sooner if symptoms develop. After delivery, a cardiac MRI T2* and cardiac evaluation should be performed again.

Pregnancy in general increases the risk of developing blood clots. Women with thalassemia, especially those with non-transfusion-dependent thalassemia who have had their spleens removed, are at higher risk of developing blood clots. Other factors that increase the risk of clotting include prior history of a clot or an inherited predisposition to clotting. Although no guidelines are available for managing blood clots in pregnancy in women with thalassemia, we generally aim to prevent clot formation by administering a prophylactic (preventative) dose of blood thinners during pregnancy and for the 6-8 weeks after delivery. It is important to have a personal evaluation of your risk of developing blood clots with your hematologist.

It is also essential to evaluate iron burden in the liver prior to pregnancy so as to minimize possible liver complications. In addition, the lower the liver iron level, the longer the pregnant mother may be able to hold chelation during pregnancy and following childbirth, since oral iron chelators are not recommended during pregnancy and while breastfeeding.

Prior to pregnancy, it is important to be evaluated by an endocrinologist to optimize bone health and to manage any problems with low thyroid function or diabetes. Bone mineral density testing and correction

of vitamin D deficiency are important for optimal bone health. Individuals taking bisphosphonates for osteoporosis should stop therapy for at least 6 months prior to conception. Patients with diabetes should strive for good control of blood sugars before and during pregnancy. Due to pancreatic iron deposition, even patients without diabetes prior to pregnancy are at risk of developing diabetes during pregnancy (this is called “gestational diabetes”). Pregnant women with thalassemia should thus undergo earlier-than-usual screening for gestational diabetes at 16-18 weeks of gestation. If patients are negative at this time, they should be screened again at 28 weeks.

General pregnancy-related complications such as urinary tract infections, kidney stones, gallstones, and placental complications have been described in pregnant women with thalassemia at approximately the same rate as in the general population.

It is thus important to plan for pregnancy, and to screen and monitor for complications prior to conception, during pregnancy and following childbirth. Family planning is important whether a patient chooses spontaneous conception or assisted reproduction, in order to reduce the risks to mother and baby.

Is pregnancy in thalassemia always considered high-risk for the mother? Are there any patients for whom pregnancy would not be advised?

Pregnancy should always be considered high-risk for the mother, since patients continue to receive transfusions and to take various medications. There is also the potential to develop further complications.

From a thalassemia perspective, pregnancy is generally not advised for women with severe cardiac iron overload and heart failure or arrhythmia. Deaths have occurred in pregnant women, both during and after pregnancy. These deaths have been attributed to high cardiac iron and resulting cardiac dysfunction. Severe cardiac complications and death may be prevented with aggressive chelation prior to pregnancy, along with careful cardiac iron monitoring.

Is thalassemia also considered high risk for the developing fetus? Is there a need for increased fetal monitoring?



Complications for a fetus being carried by a mother with thalassemia may include: intrauterine growth retardation (in which the unborn baby is smaller than it should be due to delayed growth), low birth weight, and prematurity. In the case of multiple pregnancy (where more than one fetus is growing in the mother's womb), additional complications may be present. Prematurity is generally related to multiple pregnancies. Close follow-up with a high-risk obstetrical team is key to ensuring a safe pregnancy in thalassemia.

Why is it recommended that pregnant women with thalassemia discontinue chelation throughout the pregnancy?

In general, chelators are not recommended during pregnancy. Current recommendations advocate stopping all chelation as soon as pregnancy is confirmed, and holding it throughout pregnancy, due to concern of birth defects. Animal studies have revealed bone changes in offspring that were exposed to large doses of deferoxamine (Desferal) during fetal development. Increased kidney abnormalities were seen in animals exposed to deferasirox (Exjade/Jadenu) and deferiprone (Ferriprox) during fetal development. However, in women who accidentally continued with oral chelation therapy for some time prior to discovering that they were pregnant, no abnormalities were observed in their children. Nevertheless – due to minimal evidence from clinical studies – use of oral chelators is generally not recommended during pregnancy.

If a woman with thalassemia has been well chelated prior to conception – with low liver iron, no cardiac iron, and no organ dysfunction – chelation can generally be held for the 9 months of pregnancy. However, in certain women, especially those with a prior history of cardiac iron, cardiac dysfunction, or high liver iron, chelation with deferoxamine (Desferal) in the late second and third trimesters has been used without major side effects. In each case, the evaluation of benefits and risks is important and should include input from a hematologist.

Are mothers with thalassemia discouraged from using oral chelators while they are breastfeeding? Is desferal

an acceptable chelation option while breastfeeding?

Oral chelators such as deferiprone (Ferriprox) and deferasirox (Exjade/Jadenu) are not recommended while breastfeeding due to lack of safety data. Deferoxamine (Desferal) can be used while breastfeeding since it is a large molecule and is generally not absorbed by the baby.

Does the growing fetus lead to a dramatic increase in the mother's transfusion requirements – especially in later stages of pregnancy? Do female patients who are normally non-transfusion-dependent sometimes find that they require transfusions during pregnancy?

Blood requirements may increase during pregnancy, especially as one enters the third trimester. Pregnant individuals with transfusion-dependent-thalassemia (TDT) should continue regular transfusions to maintain a pre-transfusion hemoglobin goal greater than 10 g/dL in order to reduce the likelihood of low birth weight and preterm delivery. As pregnancy progresses and maternal blood volume increases, some women may prefer to receive low-volume transfusions more frequently. This may help to reduce fluid retention, and may also help with fatigue – especially in the third trimester.

Women with non-transfusion-dependent thalassemia (NTDT) may require transfusions during pregnancy, especially since the hemoglobin level typically drops by approximately 2 g/dL in the 3rd trimester. The hemoglobin level drops in all pregnant women due to a dramatic expansion of blood plasma, which makes the red blood cells suspended in the plasma more “dilute”/less concentrated. This is a normal phenomenon in all pregnant women regardless of thalassemia diagnosis. However, since the baseline hemoglobin level for an NTDT patient is lower than normal, the normal decrease in hemoglobin during pregnancy may result in a hemoglobin level of 7-9 g/dL, which may contribute to symptoms of fatigue and may impair fetal oxygenation. Such women may benefit from transfusion support during pregnancy. For most women with NTDT, transfusions can be stopped again after pregnancy.



Are the majority of women with thalassemia able to carry a pregnancy to full-term?

Published registry data shows that most pregnancies in women with thalassemia are delivered at full term, around 37.7 weeks. Most of the preterm births are due to carrying twins/multiple pregnancies or are undertaken for precautionary reasons.

How common is the need for C-section, especially if the mother with thalassemia is small in size?

Generally, thalassemia should not be considered an automatic indication for a Cesarean delivery. Each patient should be individually evaluated by the obstetrical team. The most common reason for Cesarean delivery occurs when the mother's pelvis is considered small for a vaginal delivery. If there are no risk factors, it is reasonable for a woman to attempt a vaginal delivery with close monitoring by the obstetrician, with quick conversion to a C-section if medically indicated.

Are there any special needs for a mother with thalassemia post-pregnancy?

Immediately after childbirth, preventative blood thinners to reduce the risk of venous blood clots are key. Medications that were held during pregnancy should be re-evaluated and restarted if indicated.

After childbirth, the mother will need to have her liver and cardiac iron status evaluated for appropriate chelation management. If any complications developed during pregnancy, close monitoring with a comprehensive team is important. It is also important to discuss birth control options following childbirth.

Breastfeeding of infants is encouraged. Deferoxamine (Desferal) is not absorbed orally and appears to be safe during breastfeeding. However, use of the oral chelators deferasirox (Exjade/Jadenu) and deferiprone (Ferriprox) is not recommended during breastfeeding due to lack of safety data.

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