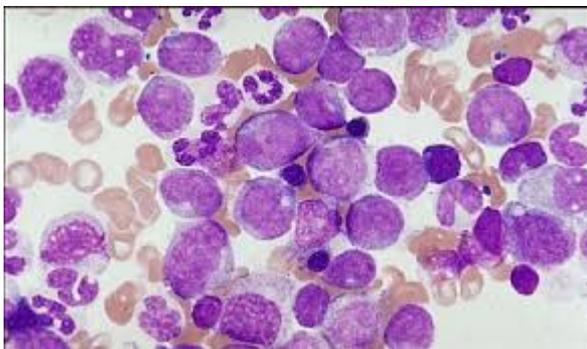


Fertility in Women Diagnosed with Chronic Myeloid Leukemia

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Women and men diagnosed with chronic myeloid leukemia should consider fertility issues and safety of pregnancy while under treatment. Chronic myeloid leukemia (CML) is formed of malignant cells from the bone marrow. It may later spread to the blood stream or other organs. It may also progress to a fast growing stage-acute leukemia. It is diagnosed in 2000 women and 2800 men yearly in The US, mostly during their adult years. Most individuals diagnosed with CML carry an abnormal chromosomal arrangement called Philadelphia chromosome. Many patients do not have any symptoms. CML is suspected from blood



counts and confirmed by examining blood smears and bone marrow examination.

Newer drugs like imatinib, dasatinib and nilotinib have changed the treatment of CML dramatically. More than 90% of patients that received these medications survived for 5 years or more. These belong to a group of medications called tyrosine kinase inhibitors (TKIs). These medication slow the propagation of lymphoma cells. Their side effects are less than standard chemotherapy. Response to treatment is assessed using blood counts, the presence of Philadelphia chromosome and molecular genetics tests for a specific gene. Some individuals require stem cell transplantation. Transplantation requires treatment with high dose chemotherapy and total body

irradiation, both are associated with very high risk for ovarian failure.

Effects of TKIs on fertility. *Animal studies* indicate that exposure to TKIs during adult life was not associated with impaired fertility in males and females. Exposure before puberty lead to reduced sperm production in males. There has been few case reports of low sperm count and early ovarian failure after exposure to imatinib in *humans*. This was not reported in large studies. Because of the possible effects of imatinib on fertility and because all individuals treated for CML are at risk for progressive disease requiring stem cell transplantation, men and women diagnosed with CML should consider fertility preservation. Men should consider sperm freezing. Women should consider embryo cryopreservation (if they have a partner) or egg freezing.

Effects of leukemia on pregnancy. In general pregnancy itself does not appear to affect the prognosis for leukemia There is no evidence that brief exposure to imatinib in early pregnancy is associated with adverse outcomes or abnormalities in the babies. There are no extensive data, however on the effects of imatinib and data on the effects of newer TKIs dasatinib and nilotinib are very sparse. Women are usually advised to use a birth control method while on these medications. In one study two of 16 babies had minor abnormalities (hypospadias in one baby and rotation of small intestine in one baby) that were surgically repaired. Women who were in remission and chose to stop imatinib during pregnancy, had 40 to 50% chance of showing evidence of propagation of the leukemia cells. The majority of them though achieved remission again after re-starting treatment.

Children born to men who are actively taking imatinib at the time of conception appear healthy and current advice is not to discontinue treatment. This is based on outcomes of 60 pregnancies reported worldwide in female partners of imatinib-treated men. In contrast the data relating to

children born to women exposed to imatinib during pregnancy are less encouraging. Although numbers are small-12 congenital anomalies were found among 125 pregnancies-there has been a cluster of rare congenital malformations such that imatinib cannot be safely recommended, particularly during the period of organ formation in the baby-first 8 to 12 weeks.

Women interested in getting pregnant while on imatinib and other TKIs should co-ordinate their specific care between oncologists and reproductive endocrinologist so that they attempt pregnancy while in remission for ideally 1-2 years and in the same time minimize the period of time while off treatment. Alternative treatments than TKIs can be used during pregnancy. After delivery, TKIs are restarted and breast-feeding is discouraged as the medicine is excreted in milk. Read more at <http://nycivf.org>

Endometriosis: Fertility Options are Clear

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Endometriosis means tissue of the lining of the uterus is present outside the its normal boundaries. It can involve the pelvic lining, the ovaries (endometrioma), the fallopian tubes, the intestine and the muscle of the uterus (adenomyosis). As menstruation takes place in the uterus, these deposits menstruate into itself, become distended and causes pain (pain with menstruation, chronic pelvic pain, pain with intercourse, urination or defecation). Moreover, because

of its chemical effects or associated pelvic scarring endometriosis may cause infertility.

Accurate diagnosis of endometriosis requires laparoscopy and biopsy of the areas suspicious because of its appearance. If you are suspect you have endometriosis (usually because of pelvic pain) and want to get pregnant or having difficulty becoming pregnant you face a small dilemma. You are usually given different recommendations from different headquarters, depending on their expertise and biases. Examples of such recommendations:

'Lets do laparoscopy to diagnose endometriosis, remove any endometriosis we find as well as remove any scarring'

'Lets give you medications for endometriosis'

The questions is which recommendation is "good for your specific case".

Few basic principals about endometriosis treatment

These are not disputed principals, just facts related to the treatment of endometriosis in general.

1. Accurate diagnosis of endometriosis requires a laparoscopy and pathological examination of tissue biopsies obtained.
2. Medical treatment of endometriosis does not allow you to get pregnant while you are using it: oral contraceptive pills, synthetic progesteron, danazol and GnRH agonists (lupron) prevent ovulation. While you are taking these medications you will mostly not ovulate so you will not get pregnant.
3. Endometriomas (endometriotic cysts of the ovary) do not respond to medical treatment. Moreover their removal mostly require removal of a part of the ovary, because they are firmly attached. Thus their removal can lower the number of eggs remaining in the ovaries (ovarian reserve).

Treatment of infertility associated with endometriosis

Though each specific situation may require a different course of action as recommended by your physician, there are general guiding principals for treatment of infertility when endometriosis is suspected.

1. **Infertility investigation:** do not make any treatment decisions without a full fertility workup. Do not proceed unless you know your partner sperm analysis, obtained the results of ovarian reserve tests, tested if your fallopian tubes are open or not via an HSG as well as general preconception lab tests. Why? if you undergo surgical treatment for endometriosis and later discovered that your partner has very low sperm count requiring IVF and ICSI, then surgery had no potential to help you get pregnant.

2. **What is your priority treating infertility or treating pain?** This is important because medical treatment, although effective in treating pain cannot help you with infertility because it mostly prevents ovulation. Please note that the best treatment for pain associated with infertility is pregnancy. The large amounts of progesterone produced during pregnancy suppresses endometriosis, sometimes for years after delivery.

3. **Resection of endometrioma;** If a cyst consistent with endometriosis is seen on ultrasound be very careful with a recommendation to resect that cyst. Resection requires surgery. it reduces ovarian reserve because of removal of ovarian tissue. Unless the cyst is suspicious of malignancy or complication they are better left alone with observation while proceeding directly to fertility treatment e.g IVF. There is no evidence that removal of the cyst improves IVF success. On the contrary, removal of the cyst is associated with low response in that ovary.

4. Laparoscopic surgery for mild and minimal endometriosis:

There are two studies that showed an improvement in pregnancy rate after laparoscopy for mild endometriosis. To put this in perspective, yes laparoscopy for infertility and mild endometriosis and infertility is an option but the magnitude of benefit in this case is limited at best. You first have to undergo surgery (with its possible complications). If endometriosis is found and ablated you would get a small bump in pregnancy rate in the year following surgery. The surgery may also help you with pain. On the contrary, endometriosis may not be found and you still have to try after surgery. Considering all the risks and benefits, the odds for pregnancy is not dramatically improved.

5. An alternative approach to mild and minimal endometriosis:

The general thinking about infertility associated with minimal and mild endometriosis is that it is unexplained infertility. In these cases there is no mechanical distortion of pelvic organs and fallopian tubes are open. If sperm analysis is within normal enhancing fertility could be achieved through stimulation of the ovary to produce multiple eggs followed by IUI or IVF. This approach avoids surgery with its potential complication. IVF carries approximately three times the odds of pregnancy and can control the risk for multiple pregnancy, compared to IUI.

6. **Moderate to severe endometriosis:** These cause distortion or blocking of the fallopian tubes. Surgery is an option but its much more complicated than mild cases and has the risk of injury to the intestine, ureter, fallopian tubes, ovaries..Scarring also may recur after surgery. An alternative approach is to proceed to IVF. It avoids major surgery and can address tubal, male and ovulatory factors. IVF success is not reduced in women with endometriosis.

7. **Adenomyosis (endometriosis of the uterus):** MRI is sometimes needed for accurate diagnosis of adenomyosis. Adenomyosis is a surgical disease and its cure require removal of the whole

uterus. This is because it cannot be shelled out of the uterus like a fibroid. Better ignored and proceed with fertility treatment.

Do not make any decisions related to infertility before a complete workup; sperm analysis, ovarian reserve tests and fallopian tube patency test. Avoid surgery in the ovary as it may reduce ovarian reserve. There is no established evidence that the chance for successful fertility treatment is reduced in women with endometriosis. Laparoscopic surgery is an option but is associated with surgical complications.

Fertility Treatment Options

Fertility Treatment Options: What Are Infertility Treatments?

Following detailed fertility investigation of the male tubal and ovarian factors, patient and her reproductive endocrinologist decide together on the optimal [fertility treatment options](#).

Factors to consider in selecting the best **fertility treatment options** include:

Sperm source

1. Is there a male partner: if so what is the ejaculate volume, sperm concentration, motility and shape? if >10 million moving sperm then pregnancy through intercourse or IUI is possible. Lower numbers indicates [IVF](#) or ICSI. If azospermia (no sperm in the ejaculate) then surgical

sperm retrieval may be needed (TESE) or donor sperm can be used.

2. If there is no male partner: anonymous or known donor sperm is used

Tubal Factor

1. Open fallopian tubes allow for natural conception or IUI.
2. Blocked fallopian tubes require IVF. Sometimes tubes can be fixed using tubal surgery.
3. Blocked and dilated fallopian tubes (Hydrosalpinx) require surgical removal of the dilated tubes followed by IVF. Dilated tubes are very difficult to fix and can leak fluid into the uterine cavity and prevent implantation of the embryo.

Ovarian Factor

1. Women who do not ovulate due to polycystic ovary syndrome (PCOS): ovulation can be induced using oral medications (clomid or letrozole) or injection medications (gonadotropins). This is usually combined with IUI.
2. Women who do not ovulate due to defect in the master gland in the brain (Hypothalamic amenorrhea): ovulation can be induced using injection medications (gonadotropins). This is usually combined with IUI.
3. Women diminished ovarian reserve and unexplained (idiopathic) infertility commonly have lower quality eggs and may benefit from inducing multiple ovulation followed by IUI or IVF, to increase the chance that one of the eggs is healthy (chromosomally normal).

Donor Eggs

1. Donor eggs are needed in women with low egg reserve that fail multiple IVF cycles after menopause or those who carry some genetic abnormalities.

2. Donor eggs can enable same sex male couples parent a child (together with a gestational carrier).

Gestational carriers

1. Gestational carriers enable women to parent a child if the uterus is absent or was removed due to a disease e.g endometrial cancer or if the lining of the uterus is damaged e.g intrauterine scarring due to prior scrapping.
2. Gestational carrier enable women who cannot get pregnant to parent a child e.g history of breast cancer
3. Gestational carriers enable same sex male couples to parent a child.

Genetic analysis of the eggs or embryos (PGD)

1. Women and men with risk of conceiving a child with a specific genetic disorder e.g cystic fibrosis, sickle cell anemia should consider testing their embryos before transfer into the uterus (PGD)
2. PGD can also be used for selecting the sex of the baby for family balancing.
3. PGD can be used to test the chromosomes of the embryo to increase the chance for pregnancy in women select women but its efficacy for that purpose is still being investigated.

Fertility Preservation

1. Women at risk for diminished fertility due to a medical problem or treatment e.g breast cancer can freeze their eggs or embryos to use later
2. Men at risk for azospermia due to genetic factors, cancer and cancer treatment can freeze sperm for use later
3. Many other techniques for fertility preservation can also be applied to adults and children to preserve reproductive organs and tissue.

Many [fertility treatment choices](#) exist to help women and men conceive a child. One or more of these methods can be tailored to each

i. individual circumstances:

singles women or men,

heterosexual couples or

same sex couples.

ii. reproductive aim:

wants to get pregnant now versus later,

wants one child only or accepts twins,

wants to conceive a child of certain sex,

will use own uterus or a gestational carrier,

will use own gametes- sperm or egg or donor gametes.

To learn more about [fertility treatment options please visit \[nycivf.org\]\(http://nycivf.org\)](#)

Idiopathic Infertility
Treatment: what do you need

to know

Idiopathic Infertility Treatment: what do you need to know

Idiopathic infertility (unexplained infertility) is defined as inability to conceive after trying for 6 months in women 35y or older and one year for women younger than 35, with no tubal, ovarian or male factor infertility. This diagnosis of idiopathic infertility is established after open fallopian tubes are detected in HSG or laparoscopy, regular ovulation is detected from history, lab tests and ultrasound and sperm is near normal on sperm analysis. These fertility tests can be performed within few days. Note that good health and physical fitness..etc are not factors here. Many women with terrible general health do conceive. On the other hand, many women in excellent physical fitness and sound health have extreme difficulty conceiving even with fertility treatment. Having difficulty getting pregnant without an apparent cause applies to a large category of the sub-fertile population and is puzzling to couples trying to conceive. The consensus of opinion among reproductive endocrinologist can divide the underlying factors for unexplained infertility into

1. Chromosomal abnormalities in the egg (low egg quality)

Abnormal eggs are present in every woman, albeit to a varying degree. Older women has more abnormal eggs. In addition, the fewer eggs you have the higher the proportion of abnormal eggs. There is no *non-invasive test* for egg quality and history, age, blood tests for ovarian reserve and antral follicle count detected on vaginal ultrasound are the most used methods.

Factors that point to low egg quality

1. Advanced maternal age,
2. Diminished ovarian reserve (e.g high FSH, low AMH), also prior surgery in the ovaries, smoking, family history of early menopause and exposure to chemotherapy
3. Early pregnancy loss before a fetal heart activity is detected (chemical pregnancy, blighted ovum),
4. Abnormal chromosomes of the products of conception and
5. Abnormal chromosome configuration of male or female partner e.g chromosome translocation. Less than 5% of couples miscarry due to a translocation in the male or female partner.

2. Other factors: may be more prevalent in younger patient and include mild endometriosis, immunological factors as anti-sperm antibodies, abnormality in cervical mucus, abnormalities in the cavity of the uterus and endometrial lining. Generally, these are not considered major factors in idiopathic infertility. Mostly oral medication produce few or only one follicles, thus they do not increase the chance that one or more eggs are healthy leading to a pregnancy.

Treatment Options for Idiopathic Infertility

Oral medication – IUI or expectant treatment (intercourse)

Oral medications are either clomid (clomiphene citrate) or an aromatase inhibitor (mostly letrozole) are used. This is followed by intercourse or intrauterine insemination (IUI). The pregnancy rate is about 5% to 7% per treatment cycle. There is no evidence that oral medications followed by IUI are superior to just intercourse in treatment of unexplained infertility. The risk for multiple pregnancy is about 8%. However, because oral medication (clomid) widespread use, mostly without ultrasound monitoring, they are probably

responsible for more multiple pregnancy than any other fertility treatment.

Injection medications – IUI

This **treatment** should probably be avoided in the majority of couples because of a. No added benefit: Pregnancy rate is not significantly higher than Clomid-IUI cycles; 9% pregnancy rate per treatment cycle and drops to 5% in women >38y. b. Risks: notably multiple pregnancy (two or more babies; 30%) and higher order multiple pregnancy (three or more babies; 3 to 8%). Multiple pregnancy has significant risks to the mother and babies. Preterm delivery can be associated with permanent neurological and intellectual defects in the babies. This risk can be minimized with careful stimulation under supervision of a reproductive endocrinologist, but cannot be completely prevented.

In Vitro Fertilization (IVF)

a. The pregnancy rate per an IVF treatment cycle is approximately 30% on average, three times that of IUI. The specific pregnancy rate is dependent on female age. The time to conception is also shorter than any other fertility treatment modality. The higher success rate can be further extended through the use of frozen embryos in couples that have good quality embryos available for freezing. The cumulative pregnancies resulting from fresh transfer and subsequent frozen-thaw embryo transfer can result in a very high odds for pregnancy. Frozen embryos can be used years after their creation, when ovarian reserve has considerably diminished. The contribution of IVF to treatment success becomes more pronounced in older women >38 years as the success of ovarian stimulation – IUI drops considerably. b. The risk for twins and higher order multiple pregnancy can be greatly minimized through single embryo transfer (1% twins and no higher order multiple pregnancy). In other words *if you want to get pregnant faster, with one baby and at higher*

chance for success per treatment cycle strongly consider IVF with single embryo transfer.

Infertility Treatment Strategy for Idiopathic Infertility

Conventional fertility treatment: “expectant management → clomid / letrozole- IUI x2 to 3 cycles → gonadotropin – IUI x3 cycles → IVF ” is the old method of treatment for unexplained infertility Modern treatment of Unexplained infertility: “ expectant management or oral medication – IUI → IVF preferably with single embryo transfer “. Women 38 years and older modern treatment strategy suggests Immediate IVF as the initial fertility treatment. The modern paradigm for fertility treatment will lead to pregnancy faster, is more successful, minimize multiple pregnancy and is more cost effective (lower dollar cost per baby). The majority of women (>70%) with unexplained infertility especially women with normal ovarian reserve will succeed in delivering a baby.