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DOB:

Controlled Ovarian Stimulation and Intrauterine Insemination

Intrauterine Insemination

This consent is intended to inform you about timed intercourse (TIC), controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) process at the Columbia University Fertility Center (the Fertility Center). This consent will inform you about the potential risks to both patients and potential offspring. While this consent is comprehensive, there are circumstances that cannot be foreseen, that may have a negative effect on your cycle.

We will be testing all patients for COVID-19. The protocol is changing rapidly as information on this virus is changing rapidly. Speak to your care coordinator team concerning the latest protocol. Please be aware if you test positive at any time during the course of treatment the cycle may be delayed by a few weeks or cancelled.

Timed intercourse is a simple treatment option for infertility. It involves monitoring your ovarian cycle via ultrasound and hormone testing and then having sexual intercourse around the time you are predicted to ovulate. Your ovulation window is 2-3 days around a positive ovulation kit or after trigger with hCG. Timed intercourse may be used in conjunction with IUI.

Controlled ovarian hyperstimulation with intrauterine insemination (COS/IUI) has become an established treatment for many forms of infertility. The main goal of IUI is to allow a patient the opportunity to become pregnant using her own eggs and sperm from her partner or from a donor. This is an elective procedure designed to result in the patient's pregnancy when other treatments have failed or are not appropriate.

This consent reviews the COS/IUI process, including the risks that this treatment might pose to you and your offspring. While we try to disclose all known risks, there may be risks of COS/IUI, which are not yet clarified or even suspected at this time.

A COS/IUI cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs (COS).
- Timed release of the eggs from the ovary or ovaries.
- Insemination of uterus with sperm (IUI) using a small catheter.
- Occasional support of the uterine lining with hormones to permit and sustain pregnancy.

Controlled Ovarian Hyperstimulation

- The success of COS/IUI largely depends on growing multiple eggs at once.
- You may be given fertility drugs, ether orally or by injection to stimulate the growth and maturation of egg follicles to produce more than one egg.
- Additional medications are occasionally used to support the lining of the uterus following ovulation and include progesterone and estradiol You may have a strong response from the medication or a very little/ inadequate response.

Clomiphene Citrate: (Clomid, Serophene) is an oral agent that acts by inhibiting the action of estrogen on the hypothalamus. It binds to estrogen receptors and stays bound for long periods. This prevents normal receptor recycling and causes an effective reduction in hypothalamic estrogen receptor number. Since estrogen can no longer effectively feedback on the hypothalamus, GnRH secretion becomes more pulsatile, which results in increased pituitary gonadotropin (FSH, LH) release. Increased gonadotropin levels cause growth of the ovarian follicle, followed by follicular rupture, otherwise known as ovulation. Clomiphene can lead to multiple ovulation, and hence increasing the chance of twins (5-8% of births instead of normal ~2%). In comparison to purified FSH, the rate of ovarian hyperstimulation syndrome is low.

Common adverse drug reactions associated with the use of clomiphene (≥ 1% of patients) include, hot flashes, abdominal discomfort, visual blurring (dose-dependent), and/or reversible ovarian enlargement and cyst formation. Infrequent adverse

effects (0.1–1% of patients) include abnormal uterine bleeding, nausea, and/or vomiting. Rare adverse effects (<0.1% of patients) include reversible alopecia and/or ovarian hyperstimulation syndrome.
Letrozole: (Femara) is also an oral agent used for ovulation induction by fertility doctors since 2001; having less side effects than clomiphene citrate (**Clomid**) for the patient and may pose less risk for multiple gestation. However, a Canadian study presented at the American Society for Reproductive Medicine 2005 Conference suggests that it may increase the risk of birth defects compared with a control group, however a more detailed follow-up study found no basis for concern when Letrozole is used for ovulation induction (and other studies since then have shown similar results). The prescribed treatment of Letrozole for ovulation induction remains an "off-label" use. Either clomiphene or letrozole can result in growth of multiple follicles, and your doctor may recommend cancellation of your cycle and avoiding intercourse if the concern for multiple pregnancy is too high as a result. Either of these medications can result in a thin uterine lining—which studies suggest may not affect the likelihood of a cycle working.

Gonadotropins or injectable "fertility drugs": (Follistim®, Gonal-F®, and Menopur®): These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of eight or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Luveris®, recombinant LH, can also be given as a separate injection in addition to FSH or alternatively, low-dose hCG can be used. These medications are administered by subcutaneous or intramuscular injection. Proper dosage of these drugs and the timing of egg release require monitoring of the ovarian response, usually by way of blood tests and ultrasound examinations during the ovarian stimulation. As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be there an allergic reaction to these drugs. The intent of giving these medications is to mature multiple follicles, and many patients experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2.0 % of patients will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to the Patient section which follows]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, and nausea.

Even with pre-treatment attempts to assess response, and even more so with abnormal pre-treatment evaluations of ovarian reserve, the stimulation may result in very few follicles developing, the end-result may be few or no eggs obtained at egg release or even cancellation of the treatment cycle.

Some research suggested that the risk of ovarian tumors might increase in women who take any fertility drugs over long periods. These studies had significant flaws, which limited the strength of the conclusions. Studies that are more recent have not confirmed this risk. A major risk factor for ovarian cancer is infertility per se, suggesting that early reports may have falsely attributed the risk resulting from infertility to the use of medications to overcome it. In these studies, conception lowered the risk of ovarian tumors to that of fertile women.

Human chorionic gonadotropin: ***(hCG)*** (Profasi®, Novarel®, Pregnyl®, and Ovidrel®): hCG is a natural hormone occasionally used in COS/IUI to induce the eggs to become mature and fertilizable; it is prescribed when concern exists that a natural LH surge has not occurred in order to facilitate the timing of the insemination. The timing of this medication is critical to release of mature eggs. Potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort.

Progesterone, and in some cases, estradiol**:** Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg release in some patients, the ovaries will not produce adequate amounts of these hormones for long enough to support a pregnancy. Typically, hormones to support pregnancy are used following treatment with gonadotropin medications, not with clomiphene or Letrozole. Accordingly, supplemental progesterone, and in some cases estradiol, are given to ensure adequate hormonal support of the uterine lining. Progesterone is given by injection or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories) after insemination. Typically, progesterone is continued for some weeks after a pregnancy has been confirmed. Progesterone

has not been associated with an increase in fetal abnormalities. Side effects of progesterone include depression, sleepiness, and allergic reaction; and if given by intra-muscular injection includes the additional risk of infection or pain at the application site. Estradiol, if given, can be by oral, trans-dermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the injection site if given by the trans-dermal route and the risk of blood clots or stroke.

The Intrauterine Insemination Procedure

Intrauterine insemination, or IUI, is a procedure where sperm is introduced directly into the uterine cavity using a small catheter, around the time of ovulation, in the hope of producing a pregnancy. Before the IUI, the sperm specimen will need to be prepared by the laboratory. You will be asked to identify the specimen as part of the program chain-of-custody. Once ready, the physician will introduce a speculum into the vagina to visualize the cervix. A mild cleaning solution may be used to clean the cervix and surrounding vaginal tissue. The washed sperm will be in a syringe with a tiny catheter attached. The catheter is passed through the cervix and then the sperm injected into the uterus. The catheter and speculum will be removed and you will be asked to rest for a short period.

Infection: Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the catheter. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after IUI is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Very rarely severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are rarely used before the IUI procedure to reduce the risk of pelvic or abdominal infection in patients at higher risk of this complication. Despite the use of antibiotics, there is no way to eliminate this risk completely.

Bleeding/cramping: The catheter passes through the cervix and into the uterine cavity. Both of these structures contain small blood vessels. The incidence of uterine bleeding problems has been estimated to be less than 0.1%. Cramping occurs in approximately 5% of inseminations and may be relieved by the use of nonsteroidal anti-inflammatory agents such as ibuprofen and Naprosyn.

Hormonal Support of Uterine Lining

Successful attachment of embryos to the uterine lining depends on adequate hormonal support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. However, in COS/IUI cycles in which medication is administered, this support is not always adequate. Therefore, progesterone is routinely given, and some clinics prescribe estradiol. Progesterone is given by the intramuscular or vaginal route. Estradiol is given by the oral, vaginal, or intramuscular route. The duration of this support is from two to ten weeks.

Risks to the Patient

Ovarian Hyperstimulation Syndrome (OHSS): This is the most severe side effect of stimulating the ovaries. Signs of OHSS include increased ovarian size, nausea, vomiting, and a buildup of fluid in the stomach. You may also have trouble breathing. In some cases, OHSS increases the level of red blood cells, and causes kidney and liver problems. In the most severe cases, it can cause blood clots, kidney failure, or death. All of these complications occur very rarely (in only 0.2% of all treatment cycles).

Cancer: Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers

are too small to achieve statistical significance, but it is at least possible that use of fertility drugs may indeed cause some increased risk of uterine cancer.

Risks of Pregnancy: Getting pregnant through assisted reproduction technology (ART) comes with certain risks. This is partly because women using assisted reproduction are often older than those who might get pregnant on their own. In addition, the cause of the infertility itself may be to blame. There may be other risks linked to ART that are not known at this time. Please see the table below for certain known risks. The table lists risks of IVF, which are similar to the risks of IUI in studies.

Maternal Risks	**Absolute Risk (%) in IVF-conceived Pregnancies**	**Relative Risk (vs. non IVF-conceived Pregnancies)**
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
Placenta previa	2.4%	2.9 (1.5--5.4)
Placental abruption	2.2%	2.4 (1.1--5.2)
Gestational diabetes	6.8%	2.0 (1.4--3.0)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

In this table, the Absolute Risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a Relative Risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the "Confidence Interval") indicate the range in which the actual Relative Risk lies.

Risks of Multiple Gestation

Multiple gestation in general has an increased risk of pregnancy problems. The most important maternal complications associated with multiple gestation are premature delivery ("early delivery" accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations), pre-eclampsia (high blood pressure and protein in the urine), diabetes of pregnancy (gestational diabetes), excessive bleeding at delivery and placental disorders are more common. Other problems more common with multiple pregnancy include gallbladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Triplets and above increase the risk to the mother of more significant complications including post-partum hemorrhage and transfusion.

Placenta previa and vasa previa are more common complications in multiple gestations. Abruptio placenta also is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries. Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity and chronic lung disease) as well as those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. Rearing of twins and high-order multiples may generate physical, emotional, and financial stresses, and the incidence of maternal depression and anxiety is increased in women raising multiples. At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus or mother. No excess perinatal or maternal morbidity has been described resulting from a "vanishing" embryo. Demise of a single fetus in a twin pregnancy after the first trimester is more common when they share a placenta, ranging in incidence from 0.5% to 6.8%, and may cause harm to the remaining fetus. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

Multiple fetuses (including twins) that share the same placenta have additional risks. Twin-twin transfusion syndrome in which there is an imbalance of circulation between the fetuses may occur in up to 20% of twins sharing a placenta. Excess

or insufficient amniotic fluid may result from twin-to-twin transfusion syndrome. Twins sharing the same placenta have a higher frequency of birth defects compared to pregnancies having two placentas. Twins sharing the same placenta appear to occur more frequently after blastocyst transfer.

Risks to Your Baby

Assisted reproduction babies may be at a slightly higher risk for birth defects and genetic defects, and has a slightly increased risk of multiple pregnancy. Many of these statistics involve patients doing IVF, which has similar risks to offspring as IUI, stemming largely from the fact that many risks have been shown to arise from the condition of infertility itself.

Overall Risks: Clomiphene was introduced in the 1960s, and the first IVF baby was born in 1978. Since then, more than 5 million children around the world have been born through IVF, and presumably many times that number from TIC and IUI cycles Studies have shown that these children are quite healthy. In fact, some experts believe having a child through ART is now just as safe as having a child naturally.

Assisted reproduction single babies are often born about 2 days earlier than naturally conceived babies and they are about 5% more likely to weigh less than 5 pounds, 8 ounces (2,500 grams) than a naturally conceived single baby.

Birth Defects: The risk of birth defects through normal birth is about 4.4 %, and it is about 3% for severe birth defects; no higher risks are seen in frozen embryo or donor egg cycles.

Imprinting Disorders: These are rare disorders caused by whether the genes from the mother or the genes from the father are working. Studies do not agree on whether these disorders are associated with IVF. Even if they are, these disorders are extremely rare (1 out of 15,000 people).

Childhood Cancers: Most studies do not suggest any extra risk, except for retinoblastoma (a cancer behind the eye): One study did report an increased risk after IVF treatment, but further studies did not find an increased risk.

Infant Development: Most studies of long-term developmental outcomes have been reassuring so far. Most children are doing well. However, these studies are hard to do, and they have some limitations. Many developmental issues arise mostly from prematurity and low birth weight as a result of multiple pregnancy.

The Option of Multifetal Pregnancy Reduction (Selective Reduction)

The more fetuses there are in the uterus, the greater the chance of a problem. Patients with twins or more have 3 choices:

- Continue on with the pregnancy (with all the risks that have already been stated),
- End the pregnancy
- Reduce the number of fetuses (terminate one or more of the fetuses) to lower the health risks to mother and child.

Reducing the number of fetuses lowers the risk of some complications: This can be a difficult decision to make. The main danger is losing the entire pregnancy. The odds of losing the entire pregnancy are about 1 in 100 (1%). The odds of losing the entire pregnancy are greater if there are more than 3 fetuses present before the procedure is done. Raising twins or higher multiples may cause physical, emotional, and financial stresses. The chance of having depression and anxiety is higher in women raising multiples. Patients may consider working with mental health professionals who are specially trained in the area of infertility care, as well as with their health care team, to minimize the emotional impact of infertility.

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Informed Consent

Signing this consent indicates that this consent has been read in its entirety, all of your questions have been answered and the information is understood. If you have questions or concerns or require additional clarification, please contact your physician/ nurse team before signing. This consent is valid for one year from the date it is signed. This consent may be rescinded at any time by any of the signed parties. In the event that any of the signed parties withdraw from participation, then this consent is nullified and will require consultation with a Columbia University Fertility Center physician and the resigning of all pertinent consents.

Additional consents will be signed at the time of the actual IUI and will include consents for inseminating sperm and the placement of the insemination catheter.

Partner Name _____
(If applicable)

Signatures:

Patient: _____ Date: _____

Partner: _____ Date: _____
(If applicable)