NewYork-Presbyterian
Columbia University Medical Center

ColumbiaDoctors
Center for Women's Reproductive Care

1790 Broadway
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www.columbiafertility.org

Informed Consent for Laboratory Assisted Reproduction: Controlled Ovarian Stimulation and Intrauterine Insemination

1. Please place your initials below to indicate which components of controlled ovarian Stimulation (COS) and intrauterine insemination (IUI) treatment you agree to undertake in your upcoming treatment cycle. Also, initial each page to indicate that you have read and understand the information provided. If you do not understand the information provided, please speak with your treating physician. There are a few locations within the consent form where you are being asked to make a decision. Please initial your choice and sign where requested.
2. This consent form is valid for one year from the time of its signed and dated execution. It may be rescinded by any of the signed parties at any time. If consent is rescinded, then a new and complete consent must be executed prior to reinitiating therapy by all parties.
3. Separate procedural consents will be necessary to execute in addition to this COS/IUI consent in order to effect treatment. Included would be consents for inseminating sperm and the placement of the insemination catheter.

Partner Name: _____

Patient Signature	Partner Signature (If applicable)	Date
_____	_____	_____ (COS/IUI)

Witness Name	Witness Signature	Date
_____	_____	_____

Initials: Patient: _____Partner *(if applicable)*: _____

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OVERVIEW

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 from start to finish, including the risks that this treatment might pose to you and your offspring. While best efforts have been made to disclose all known risks, there may be risks of COS/IUI which are not yet clarified or even suspected at the time of this writing.

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

OUTLINE OF CONSENT FOR COS/IUI

A. Technique of COS/IUI
    a. Core elements and their risk
        1. Medications for COS/IUI Treatment
        2. Intrauterine insemination
        3. Hormonal support of uterine lining
B. Risks to woman
    a. Ovarian hyperstimulation
    b. Timed insemination
    c. Pregnancy
C. Risks to offspring
    a. Overall risks
    b. Birth defects
    c. Multiple pregnancy
D. Ethical / religious concerns
E. Psychosocial risks
F. Legal considerations and legal counseling
G. Alternatives to COS/IUI

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A. TECHNIQUE OF COS/IUI

a. Core elements and their risk

1. Medications for COS/IUI Treatment

- The success of COS/IUI largely depends on growing multiple eggs at once
- Oral agents which increase native pulsatility of the hormones FSH/LH or the use of injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose
- Additional medications are occasionally used to support the lining of the uterus following ovulation and include progesterone and estradiol
- An overly vigorous ovarian response can occur, or conversely an inadequate response

Medications may include the following (not a complete list):

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 of time. 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 (3-5% of births instead of normal ~1%). 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 that has been used for ovulation induction by fertility doctors since 2001; having less side-effects than clomiphene citrate (Clomid) for the patient and may possess less risk for multiple gestation. However, a Canadian study presented at the American Society of 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 was used for ovulation induction. The prescribed treatment of letrozole for ovulation induction remains an "off-label" use.

- **Gonadotropins, or injectable "fertility drugs" (Follistim®, Gonal-F®, Bravelle®, Menopur®):** These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 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 given by subcutaneous or intramuscular injection. Proper dosage of these drugs and the timing of egg release require

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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 women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2.0 % of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section which follows]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

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 may increase in women who take any fertility drugs over a long period of time. These studies had significant flaws which limited the strength of the conclusions. More recent studies 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®, Ovidrel®):** hCG is a natural hormone occasionally used in COS/IUI to induce the eggs to become mature and fertilizable. 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. It is prescribed when concern exists that a natural LH surge has not occurred in order to facilitate the timing of the insemination.
- **Progesterone, and in some cases, estradiol:** Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg release in some women, the ovaries will not produce adequate amounts of these hormones for long enough to fully support a pregnancy. Typically hormones to support pregnancy are only 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 usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories) after insemination. Progesterone is often 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, 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.

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2. Intrauterine insemination

- Eggs are released from the ovary and presumably picked up by the fallopian tubes
- Intrauterine insemination of prepared sperm is performed using a small catheter
- Injury and infection are exceedingly rare

Intrauterine insemination, or IUI, is a procedure where sperm is introduced directly into the uterine cavity around the time of ovulation, in the hope of producing a pregnancy.

Before the IUI, the sperm specimen will need to be prepared. You will be asked to identify the specimen to ensure that it is the correct one. 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. A small amount of the washed sperm will be drawn into 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 then be removed and you may be asked to rest for a short period of time.

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 in at risk patients, 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.

c. Hormonal support of uterine lining

- Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support
- Estrogen and progesterone produced by the body as a direct result of the orally administered drugs used to stimulate the ovaries is typically adequate and do not need supplementation.
- In cycles using gonadotropins, progesterone is commonly prescribed to supplement the luteal phase.

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 parenterally administered

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gonadotropins are administered, this support is not always adequate. Therefore, progesterone is routinely given, and some clinics also 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 2 to 10 weeks.

B. RISKS TO THE WOMAN

a. Ovarian Hyperstimulation Syndrome

To increase the number of eggs that develop, either orally administered agents or a series of hormone shots are given. The hormones used in this regimen are known to have, or suspected of having a variety of side effects, some minor and some potentially major.

The most serious side effect of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). Its symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure, or death. The severe cases affect only a very small percentage of women who undergo COS/IUI—0.2 percent or less of all treatment cycles—and the very severe are an even smaller percentage. Only about 1.4 in 100,000 cycles has lead to kidney failure, for example. OHSS occurs at two stages: early, 1 to 5 days after egg release (as a result of the hCG trigger); and late, 10 to 15 days after release (as a result of the hCG if pregnancy occurs). The risk of severe complications is about 4 to 12 times higher if pregnancy occurs which is why sometimes no insemination is performed to reduce the possibility of this occurring.

b. 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.

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C. RISKS TO OFFSPRING

- IUI babies may be at a slight increased risk for birth defects
- The risk for a multiple pregnancy is significantly higher for patients undergoing IUI, even when oral agents are used
- Multiple pregnancies are the greatest risk for babies following IUI
- Some risk may result from the underlying conditions responsible for the infertile state

a. Overall Risks

Ovarian hyperstimulation using a variety of pharmaceutical agents has been widely practiced for nearly 40 years, and millions of children have been born worldwide following COS/IUI treatments. Numerous studies have been conducted to assess the overall health of COS/IUI children and the majority of studies on the safety of COS/IUI have been reassuring. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for COS/IUI babies as compared to naturally conceived babies.

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that COS/IUI method engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after COS/IUI prove to be true, the absolute risk of any abnormal outcome appears to be small.

b. Birth Defects.

The risk of birth defects in the normal population is 2-3 %. In COS/IUI babies the birth defect rate may be 2.6-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between COS/IUI treatment and specific types of birth defects.

c. Risks of a Multiple Pregnancy

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Others include gall bladder 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.

Prematurity accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations. Moreover, IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

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. 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

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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.

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.

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. It is not clear to what extent these risks are affected by IVF per se.

The Option of Selective Reduction: Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. The greater the number of fetuses within the uterus, the greater is the risk for adverse perinatal and maternal outcomes. Patients with more than twins are faced with the options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, or reducing the number of fetuses in an effort to decrease the risk of maternal and perinatal morbidity and mortality. Multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates profound ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggest that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%.

In general, the risk of loss after MFPR increases if the number of fetuses at the beginning of the procedure is more than three. While there is little difference between the loss rates observed when the final number of viable fetuses is two or one, the loss rate is higher in pregnancies reduced to triplets. Pregnancies that are reduced to twins appear to do as well as spontaneously conceived twin gestations, although an increased risk of having a small for gestational age fetus is increased when the starting number is over four. The benefit of MFPR can be documented in triplet and higher-order gestations because reduction prolongs the length of gestation of the surviving fetuses. (This has been demonstrated for triplets; triplets have a 30-35% risk of birth under 32 weeks compared to twins which is 7 to 10%).

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D. ETHICAL AND RELIGIOUS CONSIDERATIONS

Infertility treatment can raise concerns and questions of an ethical or religious nature for some patients. The technique COS/IUI involves the creation of human embryos inside the body by sperm produced and processed outside the body (typically by masturbation), and can involve the production of excess embryos and/or 'high-order' multiple pregnancy (triplets or more). We encourage patients and their spouses or partners who so desire to consult with trusted members of their religious or ethics community for guidance on their infertility treatment.

E. PSYCHOSOCIAL EFFECTS

A diagnosis of infertility can be a devastating and life-altering event that impacts on many aspects of a patient's life. Infertility and its treatment can affect a patient and her spouse or partner medically, financially, socially, emotionally and psychologically. Feelings of anxiousness, depression, isolation, and helplessness are not uncommon among patients undergoing infertility treatment. Strained and stressful relations with spouses, partners and other loved ones are not uncommon as treatment progresses.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany infertility. In addition to working with our health care team to minimize the emotional impacts of infertility treatments, patients may also consider working with mental health professionals who are specially trained in the area of infertility care.

While it is normal to experience emotional ups and downs when pursuing infertility treatment, it is important to recognize when these feelings are of a severe nature. If you experience any of the following symptoms over a prolonged period of time, you may benefit from working with a mental health professional:

- Loss of interest in usual activities
- Depression that doesn't lift
- Strained interpersonal relationships (with partner, family, friends and/or colleagues)
- Difficulty thinking of anything other than your infertility
- High levels of anxiety
- Diminished ability to accomplish tasks
- Difficulty with concentration
- Change in your sleep patterns (difficulty falling asleep or staying asleep, early morning awakening, sleeping more than usual for you)
- Change in your appetite or weight (increase or decrease)
- Increased use of drugs or alcohol
- Thoughts about death or suicide
- Social isolation
- Persistent feelings of pessimism, guilt, or worthlessness

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F. LEGAL CONSIDERATIONS

The law regarding parent-child status of any resulting child(ren) is, or may be, unsettled in the state in which either the patient, spouse, partner, or any donor currently or in the future lives, or the state in which the ART Program is located. We acknowledge that the ART Program has not given us legal advice, that we are not relying on the ART Program to give us any legal advice, and that we have been informed that we may wish to consult a lawyer who is experienced in the areas of reproductive law and embryo cryopreservation and disposition if we have any questions or concerns about the present or future status of our embryos, our individual or joint access to them, our individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.

G. ALTERNATIVES TO COS/IUI

There are alternatives to COS/IUI treatment including adoption or not pursuing treatment as possible options.

References:

Ovarian hyperstimulation syndrome. The Practice Committees of the American Society for Reproductive Medicine. Fertil Steril 2006; 86 (suppl 4): S178-S183.

Risks of pregnancy

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Risks to offspring

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

- Multiple pregnancy associated with infertility therapy. The Practice Committees of the American Society for Reproductive Medicine Fertil Steril 2006; 86 (suppl 4): S106-S110.

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