Gestational Surrogacy Medical Overview

In Gestational Surrogacy, the Surrogate Mother undergoes in vitro fertilization (IVF) and embryo transfer to become pregnant. The eggs used under a Gestational Surrogacy are not that of the Surrogate Mother. The sperm used is from the Intended Father or a sperm donor. The Surrogate Mother has no genetic relationship to the child born from a Gestational Surrogacy.

In Gestational Surrogacy with an Egg Donor, the Surrogate Mother becomes pregnant through IFF/ET using eggs from a donor other than the Intended Mother. The Surrogate has no genetic relationship to the child born from a Gestational Surrogacy.

Medical Screening

Gestational Surrogates recruited by Simple Surrogacy, LLC are carefully screened by your clinic of choice using the guidelines provided by The American Society for Reproductive Medicine. The screening encompasses a review of their detailed medical history, a physical exam, comprehensive laboratory testing and medical screening. Multidisciplinary consultations with internists and specialists, psychologists, geneticists may also be required.

If there has been no previous work-up or if the testing is outdated, the Traditional Surrogate's work-up may include:

Gestational Surrogate Screening

· Initial consultation with a Reproductive Endocrinologist
· Physical examination
· Gynecological Exam
· Blood count and chemistry
· Blood type and RH
· Drug toxicology
· Screening for rubella, cytomegalovirus, , toxoplasmosis
· HIV Antibody
· Hepatitis A, B and C Surface Antigen
· RPR for Syphilis
· Cytomegalovirus (CMV)
· Cervical Cultures for Gonorrhea, Chlamydia, Ureaplasma, and Mycoplasma.
· Genetic Testing for Cystic Fibrosis, Tay Sachs Disease, Sickle Cell Disease, and Thalassemia.
· FSH - cycle day 2 or 3
· Group B Strep

· Hysterosalpingogram or Sono-hysterosalpingogram
· Consultation with the IVF nurse coordinator regarding the treatment protocol, medication and teaching of injections. Review and sign the consent forms.

Intended Parent(s)Screening

Your primary physician may have already performed the work-up of the Intended Parent(s) referred for surrogacy. The philosophy at Simple Surrogacy is not to duplicate testing, thus, Intended Parent(s) are encouraged to obtain copies of their previous testing to avoid duplication. Testing for the Intended Father includes but are not limited to psychological evaluation, std testing, hysteroscopy, mock transfer, mock cycle, and blood work.
If there has been no previous work-up or if the testing is outdated, the Intended Father's work-up may include:
If there has been no previous work-up or if the testing is outdated, the couple's work-up may include:
· Initial consultation of the couple with a staff physician of the program to review previous medical records
· Physical examination
· Consultation with the IVF nurse coordinator regarding the treatment protocol, medication and teaching of injections
· Review and sign the consent forms

<u>Female laboratory testing</u>
· Rubella Immunity
· Blood type and Rh
· HIV antibody
· Hepatitis B and C surface antigen
· RPR for Syphilis
· Cytomegalovirus (CMV)
· Cervical cultures for Gonorrhea, Chlamydia, Ureaplasma, and Mycoplasma (when appropriate).
· FSH - cycle day 2 or 3

<u>Male laboratory testing</u>
·Blood type and RH
· HIV antibody
· Hepatitis B and C surface antigen
· RPR for Syphilis
· CMV
· Genetic Testing for Cystic Fibrosis, Tay Sachs Disease, Sickle Cell Disease, and Thalassemia.

· Semen analysis (within the past 6 months)
· Sperm Count
· Motility

Counseling

The role of counseling is to prepare all parties involved in the treatment and to consider all factors which may influence the outcome. Counseling ensures that everyone is confident and comfortable with their participation and trusts each other. Counseling also minimizes foreseeable risks, thereby avoiding the placement of unacceptable burdens on any of the parties, including the future child. Some clinics will require that a Minnesota Multiphasic Personality Inventory (MMPI) be completed by a Traditional Surrogate Mother before entrance into their medical program. The MMPI is one of the most frequently used personality tests in the mental health fields. This assessment, or test, was designed to help identify personal, social, and behavioral problems in psychiatric patients. The test helps provide relevant information to aid in problem identification, diagnosis, and treatment planning for the patient.

Gestational Surrogate/Intended Parent(s) Suggestions

During the treatment cycle both the Surrogate and Intended Parent(s) should eat healthy food, take vitamin supplements and refrain from smoking, drinking, and drug use. All parties should not take any additional medication other than that prescribed by the Reproductive Endocrinologist/Physician.

· Be open and honest regarding expectations and hopes throughout the process.
· Refrain from sexual intercourse during the cycling process.

Cycling

Once the contracts are complete and testing has finished, the Surrogate and the Egg Donor (who can be the Intended Mother or a donor) synchronize their cycles. This is usually with birth control pills. About 14 days into the birth control pills, both Surrogate and Egg Donor will start Lupron. Lupron is a subcutaneous (just under the skin) injection to shut down the body's normal hormone production used to control the cycle and ensure the Surrogate's uterus is ready to receive the embryos at the exact time for the best chance of success.

The Surrogate is usually about a week or so ahead of the Egg Donor to ensure her uterus will be ready when the eggs are retrieved and fertilized, and because they can keep the SM in a holding pattern for up to 2 weeks once her uterine lining is at optimum.

When the menstrual cycle starts while on Lupron, the Lupron dose is usually decreased by half and the Surrogate will start adding Estrogen replacement to the mix (in the form of pills, patches, or shots depending on the doctor). Some doctors have you take other medications as well (Dexamethasone to suppress male hormones to increase implantation, antibiotics to guard against any infection that might have gone undiagnosed, etc.)

The Egg Donor starts on injectable fertility hormones on her cycle day 3 to stimulate her ovaries to produce several eggs as opposed to just 1 or 2. Fertility hormones continue anywhere from 7 to 12 days depending on the Egg Donor's response to the hormones. The Egg Donor is checked about 3 times a week via ultrasound and blood tests to determine her response to the drugs. Once the follicles are the right size (about 18-20mm) she is given an HCG shot which induces an LH surge which also matures the eggs. Thirty-six hours after the HCG shot the egg retrieval is performed. Up until this time, the date/time of the transfer is flexible.

The eggs retrieved are fertilized with sperm from either the Intended Father or a sperm donor and incubated for 2-5 days. Lupron usually stops the day before egg retrieval in the Surrogate. Progesterone replacement (most often in the form of intramuscular injections, but sometimes with suppositories or Crinone gel) starts the day of the retrieval and continues until the 12th week of pregnancy or a negative pregnancy test. Estrogen replacement also continues until the 12th week of pregnancy (when the placenta takes over hormone production). Because the Surrogate was on Lupron and had natural hormones were suppressed, The Surrogate will need to take external sources of these very important hormones in order to maintain any pregnancy that occurs.

When the fertilized embryos are at the proper stage, they are loaded into a special syringe with a thin flexible catheter at the end. The catheter is inserted thru the cervix into the uterine cavity (sometimes with the assistance of abdominal ultrasound to ensure EXACT placement of the embryos) where the embryos are "injected". Most doctors will only transfer three to four 2-day old embryos or two 5-day embryos. Any unused embryos are frozen for a future attempt if a pregnancy doesn't result from the fresh cycle. Bed rest of anywhere from 2 hours to 3 days is usually required immediately following embryo transfer.

A Quantitative HCG in which the amount of pregnancy hormone is measured is usually done 14 days post egg retrieval. At that time they are looking for the HCG level to be about 50 or better. Anything over 200 is usually indicative of a multiple pregnancy. The Surrogate will have a second quantitative HCG test two days later to verify that the pregnancy hormone numbers are going up (they should double about every 2 days). If the quantitative HCG is negative, all external hormones are discontinued and a menstrual cycle will usually start within 5 days.

If a pregnancy has occurred (Congratulations!), an ultrasound is usually done about 6-7 weeks to check for a heartbeat and again around 12 weeks before being released to a regular OB/GYN. Usually during this time, hormone levels are checked several times to ensure that the proper levels are being maintained to ensure the pregnancy continues. Once the placenta starts taking over the hormone production, the Surrogate is weaned off the hormone replacements.
The rest of the pregnancy would be the same as any other pregnancy.

The information provided above is for general information purposes to the Clients of Simple Surrogacy and should not be construed in any way as health or medical advice or treatment recommendations.

PGD TESTING FACTS AND QUESTIONS

(Pre-implantation Genetic Diagnosis)

Does Pre-implantation Genetic Diagnosis have a role to play in Embryo Selection?

The concept of performing of PGD/ Fluorescence in-situ Hybridization (FISH) to exclude numerical chromosome abnormalities (aneuploidy) in order to select the "best embryos" for transfer is undoubtedly flawed and such practice should be discouraged. In contrast the performance of PGD using comparative genomic hybridization (CGH) for the identification of chromosomally (numerically) normal (euploid) embryos is a completely different consideration and is emerging as a valuable tool that might significantly improve implantation potential, reduce multiple births and , markedly reduce the risk of miscarriage and chromosomal birth defect. The following considerations will assist in better assessing the role of PGD in the selection of embryos for transfer:

1. Trauma to the embryo (through PGD) is always a potential problem. However this is far less likely when PGD is done for CGH than when FISH is performed: Here is why…..PGD for FISH requires maintaining blastomere chromosomes intact for specific analysis. This explains why 2 cells are often biopsied rather than one and why in the hands of the inexperienced, there is a greater potential to traumatize surrounding blastomeres and compromise the embryo. While nothing is more important than expertise (which requires a degree of experience and dexterity that is often lacking), the level of expertise needed to perform an atraumatic single blastomere biopsy for CGH is far less. The reason is that CGH targets DNA and unlike with FISH does not require that the chromosomes be maintained intact. Thus the removal of a single cell for PGD/CGH requires less dexterity and there is a lesser potential for causing trauma to the embryo.

2. FISH does not assess all 23 chromosome pairs for numerical chromosomal abnormalities (aneuploidy): Commercially available FISH, while capable of targeting no more than 12 chromosome pairs, usually only evaluates 8-9 pairs. Moreover, even 12-probe FISH fails to assess several chromosome pairs commonly associated with lethal aneuploidy. CGH on the other hand, accesses all chromosome pairs (i.e. full karyotyping).

Humans have an inordinately high incidence of egg aneuploidy which occurs primarily during meiosis which takes place in the hours leading up to ovulation or egg retrieval. Our own studies where CGH was performed on the first polar body (PB-1) of the mature egg (MII) have shown that in women <35Y, about 2/3 of the eggs are aneuploid (often complex aneuploid, i.e involving >1 chromosome pair). Preliminary data where PB-1 biopsy (with CGH) was performed on the eggs of older women suggests that the incidence of aneuploidy increased progressively as women age beyond 35Y such that at 40Y about 4/5 eggs are aneuploid and at 45Y the incidence of post-meiotic egg aneuploidy might even be as high as 9/10. In addition we have observed

that the complexity of the oocyte aneuploidy increases (involving a greater number of chromosome pairs (i.e. chaotic aneuploidy with advancing maternal age.
It has been shown that when 9-probe PGD/FISH performed on embryos derived from the eggs of young women (<35Y) indicates no evidence of aneuploidy, there remains a 47% chance that aneuploidy resides in the untested chromosomes. The comparable error rate in women over 40Y is greater than 55%. This serves to explain why PGD with FISH in order to diagnose embryo aneuploidy, becomes progressively less reliable with advancing maternal age..

3. Performance of PGD when there are few Embryos available is both redundant and unnecessary. The following facts suggest the need for discretion when it comes to PGD/CGH performed to fully karyotype embryos so as to select the best one's for transfer to the uterus:
· We have already shown that while achieving the blastocyst stage does not exclude embryo aneuploidy, failure to reach blastocyst means that such embryos were almost certainly aneuploid and unworthy of transfer or preservation,
· Taking embryos to the blastocyst stage automatically culls out many severely aneuploid embryos in the process
· Because of the inevitability of an age-related increase in the incidence of egg aneuploidy, women with advancing age beyond 39Y are far less likely to have multiple pregnancies and the likelihood of high order multiple pregnancy (triplets or greater) is negligible beyond the age of 40Y regardless of the number of (unselected) embryos transferred. It follows that where fewer than 6 biopsiable day 3 embryos (i.e 6-9 cells) are obtained from women over 35Y it is probably wiser (in most cases) to allow them to develop to blastocyst and in the process cull out many obviously aneuploid embryos… whereupon those reaching the blastocyst stage can be transferred.
It is a fact that the full karyotyping of a single day 3 blastomere will not completely exclude the possibility of aneuploidy in the other blastomeres of that embryo. Aneuploidy can sometimes arise sporadically during regular cell division (i.e mitosis) as a consequence of abnormal chromosome dispersion. Thus it is possible even in cases where full karyotyping (CGH) reveals the tested single blastomere to be euploid that one or more of the untested blastomeres might be aneuploid. This so called mitotic aneuploidy is
referred to as mosaicism. Conversely, the finding through CGH that a single blastomere is aneuploid, does not inevitably mean that all the entire embryo is aneuploid since the aneuploidy affecting the randomly selected single could (albeit rare) have resulted from mitotic (rather than meiotic) aneuploidy. So, a single mitotically aneuploid cell might in fact be a "loner" with the remaining cells being euploid.
Mosaicism commonly arises in blastocysts and in further advanced healthy concepti. In such cases it affects a small percentage of the total number of cells and the aneuploidy usually proves to be harmless. Perhaps such mitotically aneuploid cells ("overwhelmed" by the majority of its euploid neighbor cells) undergo accelerated death (apoptosis) and are so kept in check. In contrast, when mitotic aneuploidy occurs in early embryos (e.g. by day 3) the percentage of

aneuploid cells in the later embryo is likely to be so high as to render ultimate embryo viability unlikely.

What is true and indeed relevant is that the detection of a single euploid single cell in the 3 day embryo provides valuable and irrefutable evidence that:

· The egg of origin was euploid

· The fertilizing sperm was euploid and,

· Fertilization took place in an orderly fashion.

Against this background, it is important to understand that the diagnosis of "embryo competency based upon single cell (blastomere) full karyotyping (i.e. by CGH) is a presumptive diagnosis that is likely to be accurate in about 80% of cases. Furthermore, even if the embryo is fully euploid throughout uterine receptivity and technical prowess in performing the embryo transfer, can preclude a successful pregnancy. That is why, based on available limited (albeit growing) data, we currently project a 60-70% viable pregnancy rate when ≤ 2 CGH normal embryos are transferred to a "presumably receptive" uterus. Time will undoubtedly refine and modify these statistical projections.

In summary: PGD/FISH for gender selection and for the diagnosis of translocations is of indisputable relevance. However, the performance of PGD/FISH for the diagnosis of embryo aneuploidy has little if any value in selecting the" best embryos" for transfer. Full embryo karyotyping (by CGH) is optimally suited to the selection of the most "competent" concepti for transfer. The following indications should be considered in deciding upon PGD/CGH for embryo selection:

1. Cases where there are >5, 6-9 cell day 3 embryos (derived from egg providers <39Y) available. Here the decision as to which one should be transferred is pivotal.
2. In cases of unexplained repeated IVF failure where it is necessary for diagnostic purposes to differentiate between an implantation versus an embryo factor
3. In selected cases of unexplained recurrent pregnancy loss ; to differentiate between an implantation versus an embryo factor
4. In certain cases of male factor infertility when trying to decide whether to proceed to DS. In such cases it is sometimes necessary to perform both PB-1 and blastomere CGH
5. To stockpile euploid, "competent" embryos over time in older women undergoing IVF
6. For egg donation at a distance where the recipient prefers to limit the time away from home. Here St-IVF will per permit fertilization of donor eggs while she waits for the results
7. Cases where expensive treatments such as IVIG, and or surgical/medical treatments in preparation for pregnancy could be deferred until "competent euploid embryos have been safely cryo banked for subsequent dispensation