

MicroSort®

A Division of the Genetics & IVF Institute

3015 Williams Drive, Suite 101
Fairfax, Virginia 22031

800-277-6607 Fax: 703-995-4928
E-mail: microsort@givf.com

MicroSort® Separation of X- and Y-Sperm PATIENT CONSENT TO PARTICIPATE

Introduction

We are volunteering to be subjects in a multi-center research study. Before agreeing to participate, it is important that we read and understand the information in this form. This form is designed to provide us information that we should know about this study. It describes the study's purpose, procedures, benefits and risks. It also describes alternative procedures and our right to withdraw from the study at any time.

This information is provided to us so that we can make an informed decision about whether to participate in this study. We should take as much time as we wish to make our decision about signing this informed consent. We are free to ask any questions we may have about this research study before agreeing to participate in it.

Purpose of Research Study

The purpose of this research study is to evaluate the safety and effectiveness of a new technique to sort sperm to increase the likelihood of conceiving a baby of the desired gender. This new technique is known as MicroSort.

Certain couples who have had a child with a sex-linked or sex-limited disease, or who have a family history of a sex-linked or sex-limited disease, may be at increased risk of bearing children affected with the disorder. For example, if a woman is a carrier of an X-linked disease (i.e., classic hemophilia), the chance that a male child will be affected is 50% in every pregnancy. The chance that a female child will be a carrier is 50% in every pregnancy. Most carriers of X-linked diseases are clinically normal. If carrier women could increase the likelihood of female offspring prior to conception by selecting X chromosome-bearing (female) sperm, they could reduce the risk of having affected sons. There are also some sex-linked or sex-limited genetic disorders in which a couple could reduce the risk of passing on the disorder to their offspring by selecting Y chromosome-bearing (male) sperm. In addition, certain couples with a majority of children of one sex may wish to increase the probability of having another child of the opposite sex (example: a couple with 1 or more boys who would like to have a girl).

MicroSort Separation of X- and Y-Sperm

PATIENT CONSENT TO PARTICIPATE

Increasing the probability of having a child of a particular gender can now be accomplished by sperm sorting followed by artificial insemination or *in vitro* fertilization (IVF) using MicroSort separated (sorted) sperm. This research program provides us the opportunity to have sperm sorted and to have an artificial insemination or IVF cycle using the sorted sperm.

Study Procedures

If agreement is made to participate in this program, both husband and wife will be tested for HIV, hepatitis B and hepatitis C. The husband will also provide a semen sample for evaluation and sorting. A semen donor may be chosen for the sorting, if medically indicated.

Sperm are sorted into a sample that is enriched (the percentage increased) for the desired sperm using a flow cytometer (cell sorting device). To obtain a sperm cell sample enriched in either X-(female) or Y-(male) bearing sperm cells, MicroSort exploits the fact that X-bearing sperm cells have 2.8% more total DNA content than Y-bearing sperm. Human sperm cells are treated with a non-cytotoxic, non-intercalating (not inserted within, outside) DNA stain (Hoechst 33342) and processed through a specialized flow cytometer instrument that uses an ultraviolet laser. The treated sperm cells are briefly exposed to ultraviolet light from the laser, which causes the stain to fluoresce. Since X-bearing (female) sperm cells contain more DNA and thus more stain than Y-bearing (male) sperm, the female sperm fluoresce brighter than the male sperm. The flow cytometer detects and separates the X- and Y-bearing sperm based upon their fluorescence. The gender-enriched sample may then be used in combination with various assisted reproductive technologies, such as intrauterine insemination (IUI), *in vitro* fertilization (IVF), or IVF with intracytoplasmic sperm injection (ICSI).

The average purity of 2570 sorts (August 1994 to December 2002) for X- bearing sperm was 87.6%. The average purity of 555 sorts for Y-bearing sperm was 69.3%. The actual percentage of female fetuses after sorting for a girl (XSORT®) is 91%. The actual percentage of male fetuses after sorting for a boy (YSORT®) is 76%. The mean number of total motile sperm cells available prior to processing was 192.6 million. After processing, the average number of total motile cells was 169.7 thousand sperm. Due to the relatively low number of motile sperm cells available after processing, an assisted reproductive technology treatment such as IVF, ICSI or IUI is considered necessary in order to conceive.

Pregnancy rates vary significantly from patient to patient based on factors such as age, sperm quality, egg quality, tubal disease, and prior infertility as well as by the type of procedure that is being performed. As of December 2002, the clinical pregnancy rate after IUI was 15% / cycle with 271 women achieving a pregnancy after 1824 inseminations. The clinical pregnancy rate for IVF (includes ICSI) was 34%/cycle with 169 women achieving a pregnancy after 502 embryo transfers. Pregnancy rates have been 34 %/cycle using frozen embryos with 17 women conceiving after 50 attempts.

If we agree to participate in this program, the wife will undergo an insemination or an IVF cycle using the enriched sorted sperm. A separate informed consent for either artificial insemination or for IVF must also be signed.

Follow-up Evaluations

If we become pregnant following a reproductive procedure with sorted sperm, we agree to participate in a long-term follow-up program to collect information about the health of our child (or children). A summary letter of the care we received and an outline of the clinical trial follow-up requirements will be sent to my obstetrician. We agree to sign forms to release to MicroSort the medical records for prenatal care and our child's (our children's) birth and pediatric records. MicroSort will review these records to learn more about the pregnancy and health of children conceived from a sorted sperm sample. If an early miscarriage occurs, we agree to request a chromosomal analysis on the fetal tissue, if available. If there is a late pregnancy loss, we agree to request an autopsy with chromosomal analysis. If we have prenatal testing such as an amniocentesis or chorionic villi sampling, we will send MicroSort a copy of the results for review. We agree to maintain our contact with MicroSort every 3 months during the pregnancy, and for at least one year after our child's (or children's) birth. Notification can be accomplished through email at MicroSort@GIVF.com or by calling (703) 289-4220. We agree to provide change of address information if applicable.

Risks and Discomforts

This technique has been effective in sorting the sperm in multiple animal species. The method does involve the exposure of sperm to a DNA-binding dye and very briefly to ultraviolet light; one or both of these could cause DNA damage in the sperm. However, numerous normal animals have now been born after sperm sorting with this technique. Based on these animal experiments, there is no evidence that this type of sperm sorting increases the risk of birth defects. Additional laboratory studies are ongoing to help further understand any potential risk to sperm from MicroSort[®] treatment.

Since sperm sorting is new, there may be risks from the study that are currently unknown or unforeseen, including risks to an embryo or fetus. It is not known if sperm that are sorted with MicroSort are associated with an increased risk of congenital malformations, developmental delays, genetic damage induced diseases including cancers, ectopic pregnancy, reduced implantation and pregnancy rates, increased rates of spontaneous abortion, or other unknown risks. Clinical experience, to date, with MicroSort pregnancies have resulted in some major and minor congenital abnormalities. The expected major malformation rate is 4% in the general population. To date, a 2.3% major malformation rate (aneuploidies, such as Downs Syndrome are included) and 2.6% minor malformation rate has been noted in children born using sorted sperm. In addition to the malformations noted at birth, of 457 pregnancies there were 5 cases of spontaneous abortion associated with chromosomal abnormalities and 5 pregnancies

MicroSort Separation of X- and Y-Sperm

PATIENT CONSENT TO PARTICIPATE

were found to exhibit abnormalities based on prenatal testing. At this time, there is insufficient information to draw conclusions about whether these abnormalities are caused by the MicroSort technology.

MicroSort will not assume any responsibility or liability for participant’s travel, medication or treatment costs in the event the MicroSort laboratory is unable to sort a semen sample due to any unexpected condition, such as; equipment failure, power outage or any situation that would deem the laboratory unsafe or un-operational. For those couples using a frozen specimen, there are certain inherent risks in the process of freezing, sorting, refreezing, and shipping sperm specimens (the ultimate consequence of which could be failure of fertilization). These risks include, but are not limited to, damage to the sperm during the freezing, sorting, refreezing, and thawing process; handling during shipment; loss during shipment; and liquid nitrogen tank failure during shipment and storage. MicroSort will not assume any responsibility or liability for participant’s travel, medication or treatment costs in the event that sorted, frozen sperm is deemed unusable due to no motility post thaw.

We understand and accept that MicroSort and the Genetics & IVF Institute, its physicians, clinicians, laboratory directors, and laboratory personnel do not assume responsibility or liability for the condition or survival of the sorted sperm specimen or the physical, mental, or other characteristics of any child or children born as a result of the use of the sorted sperm. We agree to indemnify, hold harmless, and provide defense from any claim, demand, cause, or action for damages or otherwise asserted against MicroSort, the Genetics & IVF Institute, or its officers, directors, laboratory personnel, agents and contractors arising out of the freezing, sorting, refreezing, storage, shipping, handling, thawing and any other action involving the receipt and handling of the sperm samples.

Potential Benefits to Us and Others

MicroSort sperm separation is a new technology that does not result in complete exclusion of undesired sperm from the sperm sample used for the insemination; therefore, we may not conceive a child of the desired gender. In the case of sorting for X-bearing sperm, a male child could still be conceived in this procedure; and in the case of sorting for Y-bearing sperm, a female child could still be conceived.

The current separation technology (June 1994 - December 2002) has resulted in an average increase in the percent of X-bearing sperm from 50% in the unsorted sample to 87.6% in the sorted sample (the other 12.4% having the Y chromosome or undetermined). This increase would be expected to make it approximately 7 times more likely to have a female than a male child ($87.6 / 12.4 = 7.06$). The increase in the percent of Y-bearing sperm is from 50% in the unsorted sample to an average of 69.3% in the sorted sample (the other 30.7% having the X chromosome or undetermined). This increase would be expected to make it over 2 times more likely to have a male than a female child ($69.3 / 30.7 = 2.25$)

We may benefit by participating in this study although a benefit cannot be guaranteed. We may be able to increase the likelihood of conceiving a child (or children) of the desired gender. If we have a family history of a sex-linked or sex-limited genetic disease, we may be able to prevent our child (or children) from having the disorder. Our participation in this program may provide new and useful information in medical science and may aid in the development of new techniques to help other couples select the gender of their children.

Alternative Treatments

There are no other methods approved by the U.S. Food and Drug Administration (FDA) to increase the likelihood of conceiving a child of the desired gender.

We do understand that there are methods to detect X-linked or sex-linked disorders that involve post-conceptual DNA analysis performed on tissue obtained by amniocentesis or chorionic villus sampling. It has been explained to us that if a specific DNA alteration has been identified in our family, then this will allow direct and highly accurate fetal diagnosis. Alternatively, the gender of the fetus can be determined by chromosomal analysis or mid-trimester obstetrical ultrasound study. We also understand that the only way to prevent the birth of an affected child with post-conceptual diagnosis is by termination of such a pregnancy.

Confidentiality

If we agree to participate in this study, our identities will remain as confidential as possible within the limits of a study. Information from this study may be submitted to the FDA, or it may be submitted to the governmental agencies of other countries where the device may be considered for approval. The FDA may inspect our medical records, including those of our child (or children). The results of this research study may be presented at meetings or in publications, but our identities will not be disclosed in these presentations. MicroSort and the FDA must treat all patient names as confidential.

Compensation

We will not be paid or financially compensated to participate in this research study. We will be responsible for all associated fees and payment. By signing this agreement, we acknowledge that we have been made aware of the costs of our care in the program and agree to be fully responsible for them, including any additional costs of collection in the event of nonpayment. We also understand that we are financially responsible for any other medical costs incurred at the Genetics & IVF Institute or any collaborating facility.

Study-Related Injury

In the event that we believe participation in this study led to injury, we should contact Dr. Donald Marazzo at (703) 698-7355 and he will review the matter with us, identify any medical resources which may be available to us and assist us in obtaining appropriate medical care. We understand that MicroSort and the Federal Government does not have any programs to provide compensation for persons participating in research projects who experience injury. If we require information about our rights as research subjects, we may contact Tricia Nugent at the Genetics & IVF Institute IRB at (703) 698-7355.

If an injury occurs as a result of participating in the study, we will be required to file a claim through our insurance company, and there will be no compensation for us from Genetics & IVF Institute. Emergency medical treatment is provided by Institute personnel whenever possible or by our personal physician or local emergency room.

New Information

Any significant new findings discovered during the course of this research study that may relate to our willingness to participate in this study will be provided to us.

Our Rights as Subjects

If we have any questions about this study or if we experience an adverse effect that we believe may be related to our study participation, we should contact Dr. Donald Marazzo at (703) 698-7355.

If we require information about our rights as research subjects, we may contact the Genetics & IVF Institutional Review Board Coordinator, Tricia Nugent, at (703) 698-7355.

Voluntary Participation/Withdrawal

Our participation in this research study is entirely voluntary. We may refuse to participate or withdraw from participation at any time without penalty or loss of benefits to which we are otherwise entitled. Neither our withdrawal from this study, nor our refusal to participate, will affect our ability to receive future medical care from MicroSort.

Our decision whether or not to participate is voluntary and will not prejudice our future medical care. If we decide to participate, we are free to discontinue participation at any time, for any reason, without prejudice. However, if we choose to withdraw, I understand that MicroSort and the Genetics & IVF Institute may elect not to release my sorted semen or embryos created with sorted semen after withdrawing from the clinical trial. Due to the constraints of the clinical trial, if I choose to transfer my sorted semen or

embryos (resulting from the use of sorted semen) it may only be transferred to a collaborating facility that is in good standing with MicroSort.

MicroSort may end our participation in the research study without our consent. This may occur if it appears to be medically harmful to us, if we fail to follow directions for participating in the study, if we do not meet the study requirements, or if the study is canceled. This specific research study is expected to have a 4-year duration and will include enrollment of 3500 patients.

Consent to Participate

This Informed Consent/Authorization will be governed by the laws of the Commonwealth of Virginia.

We have read the above information, the Patient Information Packet, and have had an opportunity to ask any questions and all of our questions have been answered.

We have received a copy of this consent form. We voluntarily consent to participation in this research study and specifically request that the sperm be sorted for enrichment of the gender indicated below for the reason indicated below. We understand that this consent is valid for a maximum of 12 treatment cycles.

Check and initial one selection regarding the type of sperm sorting desired:

<input type="checkbox"/> XSort [®] (female)	<input type="checkbox"/> YSort [®] (male)
_____ (husband's initials)	_____ (husband's initials)
_____ (wife's initials)	_____ (wife's initials)

Check one selection, fill in the blanks, and initial regarding the reason for participation:

Genetic Disease Prevention (name of disease: _____)
 _____ (husband's initials) _____ (wife's initials)

Family Balancing (previous children: # of sons _____, # of daughters _____)
 _____ (husband's initials) _____ (wife's initials)

Husband's Name: _____

Wife's Name: _____

Address: _____

City: _____ State: _____

Postal Code: _____ Country: _____

Home Phone: _____ Work: _____

Clinician's name: _____

Facility Name: _____

Signature of Husband Date

Signature of Wife Date

Signature of Clinician Date

Signature of Witness Date