

CONSENT FOR PREIMPLANTATION GENETIC DIAGNOSIS (PGD) OF ANEUPLOIDY

Palm Beach Center for Reproductive Medicine/Palmetto Fertility Center of South Florida

PURPOSE

The purpose of this procedure is to select and transfer into the uterus only embryos that do not have recognizable chromosomal abnormalities.

BACKGROUND

Chromosomes are structures found in the center or nucleus of cells. A human typically has 46 chromosomes or 23 pairs. An embryo receives 23 chromosomes from the sperm and 23 from the egg. Chromosomes are made of genes, which contain the information that instructs the body how to function. Having extra or missing chromosome(s) (called aneuploidy) can result in lack of implantation of an embryo, pregnancy loss, and other conditions such as infertility and Down Syndrome.

PGD of aneuploidy is being offered to patients undergoing in-vitro fertilization (IVF) who are 35 years old or older. Patients in this age group are at increased risk of miscarriage or birth defects. PGD may reduce these risks. PGD of aneuploidy may also assist the embryologists to select embryos more likely to result in a pregnancy. PGD of aneuploidy may also be used for patients of all ages who have unexplained failure to conceive despite several IVF cycles. Other patients who may benefit are patients with a history of miscarriages, especially when testing reveals no clear explanation. Patients who have had an aneuploid pregnancy in the past may also want to consider PGD of aneuploidy.

PROCEDURE

The entire procedure consists of five different steps, usually performed by different experts and laboratories. (i) The first part is in vitro Fertilization (IVF) during which embryos are produced. This part occurs at Palm Beach Center for Reproductive Medicine/Palmetto Fertility Center. (ii) The second part is embryo biopsy, during which one cell of the embryo is removed to be analyzed. This is done by at Palmetto Fertility Center. (iii) The processing of the cell, in this case called cell fixation, is performed by at Palmetto Fertility Center. (iv) The analysis of the cell is performed by an outside reference laboratory. (v) The final step, the transfer of the embryos to the female patient, is done by the physicians at the Palmetto Fertility Center.

BIOPSY AND FIXATION OF BLASTOMERES

A blastomere is a cell from an embryo. To test the blastomere, an embryologist from the Palmetto Fertility Center makes an opening in the covering of the embryo on the third day of development when the embryo has 5 to 10 cells. A blastomere is removed via aspiration with a pipette. The embryo is returned to an incubator and the cell that was removed from the embryo is fixed to a glass slide and sent to an outside reference laboratory for analysis. Please read and sign the consent form for embryo biopsy and fixation which will explain the risks of this procedure.

CELL TRANSPORT

After the cells have been biopsied and fixed, the Palmetto Fertility Center sends the slides to an outside reference laboratory for analysis. Same-day or next-morning delivery couriers are used for transportation.

ANALYSIS

The fixed cells are analyzed by an outside reference laboratory using a technique called *fluorescent in-situ hybridization* or FISH. This technique uses probes, small pieces of DNA that

are a match for the chromosomes to be analyzed, to count the chromosomes present. These probes are attached to molecules that are like microscopic colors. The probes are applied to the biopsied cell and attach to the chromosomes. Under a microscope, the numbers of chromosomes, identified by color, are counted and the geneticist can tell normal cells from cells with aneuploidy. Testing of the cells destroys them because they must be glued to a glass slide and repeatedly heated and cooled. Therefore, the cells cannot be used for another purpose or returned to the embryo. The slides are kept for future reference. This analysis is accomplished in one day.

LIMITATIONS

The reference laboratory is unable to study all of the chromosomes or the structure of the chromosomes via PGD. Because of these limits, prenatal testing after the IVF/PGD cycle is strongly advised in order to confirm the diagnosis and review the number and structure of all the chromosomes. Prenatal testing may be done in the first trimester via chorionic villous sampling (CVS) or during the second trimester via amniocentesis. CVS is a procedure done in the late first trimester that takes cells from the placenta and analyzes them for chromosomal abnormalities. Amniocentesis is a procedure usually done between 15 and 20 weeks of pregnancy that takes fluid from around the baby and analyzes the baby's cells in the fluid for chromosomal abnormalities.

RISKS

THE RISK OF EMBRYO BIOPSY

PGD does not guarantee the birth of a normal baby. It is unknown whether biopsied embryos implant less than embryos that have not been biopsied. Embryo biopsy may lower implantation rates slightly in the absence of an abnormal test result, but selection of chromosomally normal embryos via PGD of aneuploidy may more than compensate any negative effect of embryo biopsy and increase the probability that the embryos transferred will implant.

If an embryo is damaged by the procedure it will stop growing and will not be suitable for transfer into the uterus. The risk of damaging an embryo during removal of the cell(s) is less than 1%. The future fetus will be complete even if one or two cells are removed from the embryo. The procedure may delay cell division for a few hours, after which the embryo continues its development. As of June 2003, more than 1000 babies have been born from IVF with PGD with no reported increase of congenital abnormalities above the general population rate. The rate of malformations in the general population is 3-5%. This procedure, however, has not been performed enough yet to rule out any detrimental effect. Thus it is still strongly recommended that you have chorionic villus sampling or an amniocentesis performed.

THE RISKS OF FIXATION

After embryo biopsy, the biopsied cell is glued (fixed) to a glass slide and an acid solution removes all but the center of the cell, called the nucleus, which contains the chromosomes to be studied. After this process, the cells are no longer viable in any way and can only be used for analysis. A fraction of cells may not have a test result. Some cells may not have a nucleus and will not yield a result. In addition, some cells may be lost during the fixation process, whereas others may have suboptimal fixation rendering the cell inadequate for analysis. Embryos without analysis may still be replaced, but the advantages of PGD may not apply.

THE RISK OF TRANSPORT

Once the cells are fixed, a third party transports the cells to the reference laboratory for analysis. This is done using same day or next morning delivery services. Weather and air travel conditions

may delay the reception of samples. In about 1/1000 cases, samples do not arrive in the reference laboratory. Even more rarely, 1/3000, samples may be damaged during transport.

THE RISKS OF THE PGD ANALYSIS

The risk of a clinical misdiagnosis, that is the occurrence of a fetus or baby with chromosome abnormalities after a PGD procedure, is less than 1%. This risk seems lower than the one found without PGD or in natural conceptions in women of advanced maternal age. Due to the chance of misdiagnosis, as well as the presence of types of aneuploidy for which we do not test, we recommend prenatal testing by CVS or amniocentesis. CVS and amniocentesis offer higher accuracy and lower misdiagnosis rates than PGD.

NO EMBRYOS FOR FREEZING- If most of your embryos that are tested are found to be abnormal, you may only have a few embryos for transfer, and none left for freezing. This is common.

NO NORMAL EMBRYOS- None of the embryos may be normal according to the test and there may not be an embryo replacement. The likelihood that this will happen is dependent on your age and other factors.

NO DIAGNOSIS AND PARTIAL DIAGNOSIS- Due to how the cell was fixed, or because the cell lacked a nucleus, some embryos will not have a diagnosis. Embryos without a result can still be replaced, but all the possible advantages of PGD will not apply. In addition, sometimes the analysis may not be clear for one of the chromosomes being tested. Again, this embryo could be replaced, but the possible advantages of PGD may not apply.

Because of the possibility of misdiagnosis, your pregnancy should be carefully monitored. Between 10 to 18 weeks, we strongly recommend that you have chorionic villous sampling (CVS) or an amniocentesis performed. The fetus should also be monitored with ultrasound examination to check its growth and development. There is no guarantee that a child will be normal after IVF with PGD.

POSSIBLE BENEFITS:

In most cases, aneuploid embryos are indistinguishable morphologically and developmentally from chromosomally normal ones. Thus, without genetically testing them, an embryologist cannot differentiate normal embryos from aneuploid embryos and could transfer aneuploid embryos to you.

Most chromosomally abnormal embryos either do not implant or spontaneously abort shortly after implantation. The probability of conceiving a healthy child may increase if PGD is applied.

PGD of aneuploidy has been reported to double implantation rates in some studies. The test may reduce pregnancy loss and increase the chance of having a baby.

PGD will not cause you any physical discomfort other than what is experienced during a regular IVF cycle.

ALTERNATIVES

Alternatives to PGD during pregnancy include standard prenatal testing for abnormalities (chorionic villous sampling, amniocentesis, and ultrasound examination). You are not obligated to undergo PGD even if your physician recommends it. You should have prenatal testing when you become pregnant. The risks, benefits and alternatives of this testing should be discussed

thoroughly with your genetic counselor, obstetrician or the person performing/ordering the tests. If you desire referral to a genetic counselor, please inform us. *Although these tests may serve as alternatives to PGD, PGD is not a substitute for routine prenatal testing.*

COSTS

Fees for PGD are in addition to the cost of the IVF cycle. The Finance Department at Dr. Graubert's facility or the staff at Dr. Roseff's center will advise you of the fees. If the PGD procedure is paid for but not performed, your payment will be refunded less the cancellation fee. You are also responsible for any additional medical costs incurred as a result of complications or other medical care required as a result of receiving PGD. Insurance coverage for all or any part of this total procedure may not be available, and it is your personal responsibility for payment of such costs including hospital and laboratory charges, and physician's professional fees.

CONFIDENTIALITY:

Confidentiality of your records will be maintained at all times. Only personnel of the reference laboratory and at Palm Beach Center for Reproductive Medicine/Palmetto Fertility Center will have access to your records. Also the Department of Health and the Food and Drug Administration (FDA) may inspect the records.

GENETIC CONSULTATION BEFORE PGD:

It is recommended that you have a consultation with a genetic counselor before undergoing PGD. This can be arranged by Palm Beach Center for Reproductive Medicine, or directly through the reference laboratory.

SPECIMEN RETENTION:

The cells to be tested will be destroyed during the process of the analysis. This will usually occur within 5 days of the biopsy. In case the test was not performed for any unusual reason, the sample will be destroyed within 60 days of reception, as stipulated by standard Laboratory rules.

FOLLOW-UP

Testing of a pregnancy can be done via chorionic villous sampling (CVS) or amniocentesis. Your obstetrician, or someone he or she refers you to, can perform these tests. If prenatal diagnostic testing is not performed, chromosome analysis should be performed on umbilical cord blood at the time of delivery. If a pregnancy loss occurs, we request that chromosome studies be performed on the loss. All results from genetic testing of the pregnancy or the child up to the age of one year will be forwarded to the PGD Program Coordinator at the outside reference laboratory. This information will remain confidential and will be used to monitor outcomes of the PGD program.

We have read the entire consent form, or it has been read to us. We understand that PGD has benefits and risks, some of which may be unknown at this time. We want to proceed with PGD for aneuploidy.

We also understand that undergoing PGD for aneuploidy *does not eliminate* the need for standard prenatal testing such as chorionic villous sampling (CVS) or amniocentesis. The need for these tests *remains the same* whether or not PGD for aneuploidy is performed. We understand that if we have questions about CVS or amniocentesis we may ask our obstetrician or we may request a referral to a genetic counselor.

We have been given an opportunity to ask questions about the PGD procedure and the contents of this consent form. If we think of additional questions, we may contact our physician, genetic counselor or nurse.

Female Partner's Signature

Date

Male Partner's Signature

Date

Witness' Signature

Date

You may request a copy of this form for your records.