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Answers for Recurrent Pregnancy Loss

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Consent for Pre-implantation Gestic Diagnosis (PGD)
For Single Gene Disorders by PCR Analysis

PURPOSE AND BACKGROUND

Currently, the only way to determine whether or not an embryo is affected by a genetic disorder is to wait until pregnancy has begun and then perform a prenatal test, such as chronic villus sampling (CVS) or amniocentesis. These procedures involve sampling fetal cells from within the womb during the first trimester or second trimester of pregnancy, respectively. The cells are then analyzed to determine whether an inherited disorder is present in the developing fetus. If a disorder is detected, parents face the difficult choice of whether to continue or terminate the pregnancy.

The purpose of pre-implantation genetic diagnosis (PGD) is to identify affected embryos at a very early stage and prevent them from implanting in the womb. The effect of such a procedure is to increase the probability that embryos that implant and form a pregnancy will be unaffected by the specific disease tested. Pre-implantation analysis is not yet considered to be a standard technique and consequently we strongly recommend that patients who become pregnant undergo prenatal testing using CVS or amniocentesis. Prenatal testing will reveal whether the pre-implantation genetic analysis was correct, and confirm whether or not the fetus has been affected by the genetic disease tested.

PROCEDURE

The procedure consists of five different steps, usually performed by different experts and laboratories. The first part is production of embryos by in vitro Fertilization (IVF) at Braverman IVF & Reproductive Immunology P.C.. The second part is embryo biopsy, by which one cell of the embryo is removed This is done by Braverman IVF & Reproductive Immunology P.C. The processing of the cell, in this case called cell fixation, is performed by Braverman Reproductive Immunology P.C. (iv) The analysis of the cell is performed by an Reprogenetics. (v) The final step, the transfer of the embryos to the female patient, is done by the physicians at Braverman IVF & Reproductive Immunology P.C.

BIOPSY OF BLASTOMERES

Patients having PGD will first undergo ovarian stimulation and in vitro fertilization, which usually results in the production of several embryos. When the embryos are approximately three days old, a single cell is removed from each of them (provided that they have at least 5 cells, embryos with fewer cells may not be biopsied). A blastomere is a cell from an embryo. To test the blastomere, the embryologist from Reprogenetics makes an opening in the covering of the embryo on the third day of development. A blastomere is removed via aspiration with a pipette. The embryo is returned to an incubator, while the cell is placed in a tube and sent to a reference laboratory for analysis. Please read and sign the consent form for embryo biopsy given to you by Braverman Reproductive Immunology P.C., which will explain the risks of this procedure.

CELL TRANSPORT

After the cells have been biopsied, washed and placed in a small test tube, Braverman IVF & Reproductive Immunology P.C. sends them to Reprogenetics for analysis using same-day or next-morning delivery couriers.

ANALYSIS

The biopsied cells are analyzed by Reprogenetics for the presence of specific changes in the genetic code that cause disease (mutations). Initially, the amount of DNA within the cell is too tiny to be detected and for this reason the DNA must be "amplified". DNA amplification is accomplished using a technique called PCR (polymerase chain reaction). Once the DNA has been amplified to a sufficient level, it may be tested to see if it contains the disease-causing mutation. Mutation testing may involve any one of several different methods. If the cell is found to be free of the disorder, then it is inferred that the embryo it was derived from is also clear of the disease. Embryos found to be unaffected are transferred to the mother or frozen for transfer in the future. Embryos that are predicted to be affected by the disease will not be transferred.

LIMITATIONS

Several embryos are generated during PGD to maximize the probability that at least one unaffected embryo will be found. However, it is possible that no unaffected embryos will be detected and consequently no embryos will be eligible for transfer to the womb. Additionally, embryos may be excluded from transfer because they are not developing normally.

At present, pre-implantation analysis detects about 95% of affected embryos. This means that misdiagnoses can occur, although they are uncommon. The probability of becoming pregnant with an affected fetus is much less after pre-implantation testing than it is after natural conception. For patients at risk of passing on a dominant disorder to their children, natural conception usually carries a 1 in 2 chance that the fetus will be affected by the disease. Couples where both parents are carriers of a recessive disorder generally face a 1 in 4 risk of having an affected child.

Currently, other PGD tests, such as those for advanced maternal age to prevent Down's syndrome and other chromosome abnormalities, cannot be simultaneously provided with a PGD test for gene disorders.

The pre-implantation genetic diagnosis that we perform for you will only provide information concerning the specific mutation(s) that we are made aware of via medical notes. Additional genetic disease mutations that might exist in an embryo will not be tested unless specifically requested by the patient and/or care provider and agreed in writing with the reference laboratory.

_____

Mutation to be diagnosed and name of disorder

Patient initials: _____ _____

Witness initials: _____

RISKS

THE RISK OF EMBRYO BIOPSY

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. More than 2000 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%). However, there have not yet been enough PGD cases performed to rule out any detrimental effect on embryo development. Thus, it is still strongly recommended that you have chorionic vil-

lus sampling or an amniocentesis performed, as well as a routine ultrasound examination. Regardless, IVF with PGD does not guarantee the birth of a normal baby.

THE RISKS OF CELL PREPARATION

After embryo biopsy, the biopsied cell is placed inside a tiny test tube and then burst, allowing the DNA to be released. After this process, the cells are no longer alive and can only be used for analysis. Not all cells can be analyzed after transfer to the test tube. A small fraction of cells will not be analyzable because they burst before they have been transferred to the test tube or are lost because of technical reasons beyond the control of the individual performing the preparation. Additionally, some cells do not have a nucleus and contain no analyzable DNA. Such cells will not yield a result. Less than 5% of embryos have cells that cannot be analyzed because they lack a nucleus. A further 3% of embryos cannot be analyzed for other technical reasons. Embryos without analysis can still be replaced, but ail the possible advantages of PGD will then not apply.

THE RISK OF TRANSPORT

Once the cells are fixed, a third party transports the cells to the reference laboratory. 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 are damaged during transport.

THE RISKS OF THE PGD ANALYSIS

The risk of a clinical misdiagnosis, that is the occurrence of a fetus or baby affected for the disease that was assessed using PGD, varies depending on the disease diagnosed, but is generally <5%. A more precise estimate of misdiagnosis is usually available after the PGD protocol has been tailored to the needs of the individual patient and preliminary testing has been completed. PGD laboratories may have different misdiagnosis rates. Due to the chance of misdiagnosis, as well as the presence of other genetic abnormalities for which we do not test (for example the risk of Down's syndrome for mothers over 35), we recommend prenatal testing by CVS or amniocentesis. CVS and amniocentesis offer higher accuracy and lower misdiagnosis rates than PGD because there are many more cells available for testing. 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. If most of the embryos tested are found to be abnormal, there may only be a few embryos suitable for transfer, and none left for freezing. It is possible that none of your embryos is found to be normal. Embryo replacement will then not be performed. Due to technical problems, or because the cell chosen for biopsy lacked a nucleus, about 7% of embryos will not have a diagnosis. Embryos without analysis can still be replaced, but all the possible advantages of PGD will not apply. It is essential that the cell biopsied from an embryo is the only source of DNA analyzed. If any other cells or DNA enter the test tube containing the biopsied cell, then the results of the analysis will be unreliable. We make a great effort to ensure that contamination of the sample with extra cells or DNA does not occur. However, even the most careful procedures cannot entirely eliminate this possibility. Contamination usually affects less than 5% of cells tested during PGD. The reference laboratory will perform a number of additional tests to assess whether or not contamination is present in each sample, allowing most cases of contamination to be detected. If a cell is affected by contamination, the embryo from which it is derived cannot be recommended for transfer.

BENEFITS

A benefit of PGD includes improving the chances of avoiding a specific genetic disease or specific chromosome abnormality in the fetus, thus reducing the chance that you will have to face a decision concerning pregnancy termination. However, neither becoming pregnant nor avoidance of a genetic disease or chromosomal abnormality in any fetus or offspring can be assured as a result of these procedures. No guarantee is made regarding the out- come of PGD.

ALTERNATIVES

Alternatives to pre-implantation genetic diagnosis include standard prenatal testing for abnormalities once preg- nant (chorionic villous sampling, amniocentesis, ultrasound examination). You are not obligated to undergo PGD even if your physician recommends it. You should undergo recommended prenatal testing that is based on your age and medical history. 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 in your area, please inform us. Although these tests may serve as alternatives to PGD, PGD is not a substitute for prenatal testing.

You are strongly recommended to seek prenatal diagnosis if you become pregnant. Prenatal testing using first trimester CVS or second trimester amniocentesis can confirm whether or not the pre-implantation genetic analysis was accurate and reveal whether the fetus is free from the genetic abnormalities for which the embryo was tested. Refusal to undergo CVS or amniocentesis may leave you in the same position as if you had conceived a child naturally, with the same risks of producing a child who has a genetic or chromosome

CONFIDENTIALITY

Confidentiality of the records will be kept at all times. Only personnel of the reference laboratory and Braverman Reproductive Immunology P.C. will have access to your records. Also the Department of Health of your state 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 specialized in PGD before undergoing PGD. This can be arranged by Braverman Reproductive Immunology P.C., 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.

INFORMING INVESTIGATORS REGARDING HEALTH OF OFFSPRING

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 locally. If prenatal diagnostic testing is not performed, genetic analyses should be performed on cord blood at the time of delivery. If a pregnancy loss occurs, we request that genetic studies be performed on the loss. We request that all results from genetic testing of the pregnancy or the child up to the age of one year be forwarded to the PGD Program Coordinator at the reference laboratory. This information will remain confidential and will be used to monitor outcomes of the PGD program.

COSTS

Fees for PGD are in addition to the cost of the IVF cycle. 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 pre-implantation genetic diagnosis. 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.

DECLARATION

We hereby attest that we have read the entire consent form, or that it has been read to us, so that we understand it completely. We further attest that we have been given an opportunity to ask questions about the PGD procedure and the contents of this consent form, and that any and all questions of mine/ours regarding this form or this study have been answered to my/our complete satisfaction. We understand that PGD has benefits and risks, some of which may be unknown at this time. We also understand that PGD may fail to yield a result and that misdiagnosis is possible. We want to proceed with PGD for the single gene disorder stated above.

We understand that undergoing PGD does not eliminate the need for standard prenatal testing such as chorionic villous sampling or amniocentesis. The need for these tests remains the same whether or not PGD 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.

If we think of additional questions, we may contact our physician, genetic counselor or nurse.

Patient's Name	Signature	Date
Partner's Name	Signature	Date
Witness's Name and Title	Signature	Date

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