

Overview of Preimplantation Genetic Diagnosis and Prenatal Screening.

- ◆ Bill Tillier
- ◆ Calgary, Alberta
 - ◆ July 6, 2002.

- ◆ Screening methods are designed to detect genetic defects very early in development.
- ◆ Screening yields a likelihood or risk of a defect. If problems are found, parents are counseled to make an informed decision about what to do.
- ◆ Three techniques are central to this screening:
 - *In Vitro* Fertilization (IVF).
 - Preimplantation Genetic Diagnosis (PGD) (or just Preimplantation Screening).
 - Prenatal screening.
- ◆ This presentation will give an overview of these techniques & will also synopsise stem cells.

- ◆ An egg is fertilized by a sperm in the oviduct.
- ◆ Once fertilized, it is called a zygote.
- ◆ The zygote first divides into 2 cells at 36 hours.
- ◆ Divides again at 60 hours (4 cells) & 3 days (8).
- ◆ The zygote takes about 3 - 4 days to travel down the Fallopian tube and into the uterus.
- ◆ Zygote enters uterus & sits there for 4 - 5 days.
- ◆ Around 7 - 9 days after fertilization, the 100 cell blastocyst specializes into an outer layer of cells and an inner cell mass (ICM) of about 20 to 30 undifferentiated cells.

Implantation.

- ◆ The blastocyst now implants itself into the wall of the uterus - now properly called an embryo, this is considered the start of the pregnancy.
- ◆ Over the next week, ICM cells differentiate into 3 layers that will go on to become the embryo.
- ◆ Two weeks after implanting: ~ 2000 cells.
- ◆ Gastrulation starts - major cell specialization.
- ◆ As time passes, cells become more specialized.
- ◆ Third week: major organs start to form.
- ◆ Third month, embryo now called a fetus.

In Vitro Fertilization (IVF). ♦ 5

- ♦ *In vitro*: “in a glass tube” or “outside the body.”
- ♦ Several eggs are removed from the female.
- ♦ Sperm is added to the eggs in a “test tube.”
- ♦ Ideally, a number of “embryos” result.
- ♦ Several of the “best looking” “embryos” are put back into the female (or into a surrogate).
- ♦ If all goes well, a normal pregnancy and healthy child will result.
- ♦ Success rate is low, the chance of pregnancy with each IVF treatment: about 20 to 30%.

- ◆ IVF is associated with:
 - An increased multiple pregnancy rate (twins account for about 20% of the pregnancies).
 - About 5.5% of IVF pregnancies are ectopic.
- ◆ IVF uses hormones to stimulate the ovaries to yield a number of eggs at one time:
 - In some cases, a serious complication called ovarian hyperstimulation syndrome (OHSS) can develop.
- ◆ Few improvements have taken place in IVF:
 - Success rate not improved “in past 20 years.”

- ◆ As methods for microscopically handling cells developed, it became possible to extract a single cell from a very early embryo. Combined with advances in genetic methods, this now allows for the testing of a number of genetic disorders before implantation takes place.
- ◆ PGD utilizes *In Vitro* Fertilization (IVF).
- ◆ PGD is considered “a highly specialized, largely experimental technique still under development”
 - Mueller, R. F., & Young I. D. (2001) (11th Ed.) Emery's Elements of Medical Genetics. Edinburgh: Churchill Livingstone.

Preimplantation Screening. ♦ 8

- ♦ IVF is used to create several “embryos.”
- ♦ At the 8 cell stage, 1 cell is removed from each:
 - This does not harm the remaining cells.
 - These cells are totipotent - the remaining 7 cells can go on to form a complete, implanted embryo.
- ♦ The cell’s DNA is cloned to allow for testing.
- ♦ This DNA is searched for genetic defects.
- ♦ If a defect is found, that “embryo” is discarded.
- ♦ Healthy looking “embryos” are selected and are inserted into the female (usually up to 4).

- ◆ Several technical problems (micro-contamination, mosaicism) can lead to a failure of the procedure or to a misdiagnosis (we think the embryo is OK when it is not).
- ◆ The overall success rate of PGD is also limited by the success rate of IVF (about 20 to 30%).
- ◆ Screening finds defects that we usually can not repair, only alternative is to discard “embryo.”
- ◆ May not be a total screen - may not be able to rule out all possible co-incidental defects.

- ◆ Today, several diseases can be screened for:
 - Duchenne muscular dystrophy
 - Spinal muscular atrophy.
 - Charcot-Marie-Tooth 1A.
 - Cystic fibrosis.
 - Myotonic dystrophy.
 - Huntington's Disease.
 - Fragile X syndrome.
 - Marfan's syndrome (to name a few examples).
- ◆ PGD holds great promise for the future as lab techniques & genetic tests are perfected.

- ◆ In this method, normal implantation takes place.
- ◆ Several different methods are used to examine the developing fetus while inside the female:
 - Cells can be removed for genetic study.
 - Ultrasound studies can be done to look for major physical defects (getting better & better over time).
 - A scope can be inserted to examine the fetus (high rate [up to 5%] of miscarriage - used less and less).
 - Blood tests are done - may reveal problems.
- ◆ If defects are suspected, the parents have the option of aborting the fetus.

- ◆ **Amniocentesis (amnio) {AM-KNEE-oh-cent-tee-sis}:**
 - Amniotic fluid from around the fetus is tested. This fluid contains fetal cells.
 - Usually done between the 14th and 18th week.
 - A needle is inserted into the uterus & about one ounce of fluid is taken out for testing.

- ◆ **Chorionic villi {CORE-ree-on-ick Vill-I} (CVS):**
 - A sample of tissue from the placenta (the chorionic layer) is removed and tested.
 - CVS is usually carried out between the 10th and 12th week.

◆ Ultrasound:

- Sound waves create a “picture” of the fetus.
- Can detect serious structural problems, example: blockage of the small intestine or heart defects.

◆ Blood tests:

- There are several blood tests that are used:
 - Example: Alpha-fetoprotein testing (AFP):
 - AFP testing is a term used to describe a group of tests done during pregnancy.
 - Cells from the fetus produce chemicals that are measured in the blood of the mother.

- ◆ Birth defects increase with maternal age:
 - Often used in pregnant women over age 35.
- ◆ History of family genetic disease (examples):
 - Down's syndrome.
 - Sickle cell disease.
 - Cystic fibrosis.
 - Phenylketonuria (PKU).
 - Down Syndrome.
- ◆ History of children with neural tube defects.
- ◆ History of still births.

- ◆ There is a risk to the fetus in many cases.
- ◆ Many people feel that aborting a fetus is wrong.
- ◆ Open to abuse (example, may screen for and select the sex of an otherwise healthy fetus).
- ◆ Line between disease and normalcy is unclear:
 - What “diseases” or conditions justify screening and possible abortion?
 - Questions of treatment versus enhancement.
- ◆ Some object that the fetus has rights and has not consented to the testing.

- ◆ Carrier Identification: genetic techniques are used to determine if a person carries a genetic defect (tested before a pregnancy).
- ◆ Individuals can be screened to see if they will eventually develop late-onset disorders, for example, Huntington's Disease.
- ◆ Mass testing of a particular ethnic group that shows a high rate of a specific genetic disorder.
- ◆ Testing done for identification of individuals.
- ◆ As methods develop and become cheaper, more screening will become possible.