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Oocyte Cryopreservation

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Abstract
Anti-mitotic therapies are a form of therapy used to treat cancer patients. The use of these treatments on females can result in fertility complications. Therefore, prior to treatment, women must seek ways to preserve their ability to conceive children after receiving treatment. This study analyzes the outcomes of oocyte cryopreservation and its many variables. Three important variables that can affect the outcome of oocyte cryopreservation are age, cryopreservation method and cryoprotectants. Evidence indicates that human oocyte cryopreservation can enable a woman to preserve her ability to give birth to a healthy child, following anti-mitotic therapies. Hundreds of babies have been born as a result of oocyte cryopreservation. Oocyte cryopreservation can even enable a woman with ovarian cancer to have a healthy offspring, post treatment.

Introduction

Early detection of cancer along with modern medicine has led to a rise in the survival rates of young cancer patients. This results in many cancer survivors who are capable of childbearing. However, since chemotherapy and radiation given during the cancer curing process can result in various fertility issues, patients must find a method to preserve their ability to give birth to children.

One method of preservation is oocyte cryopreservation. Human oocyte cryopreservation is a procedure in which a woman's oocytes are extracted, frozen and then stored. When the woman desires to become pregnant the eggs are thawed, fertilized and transferred in to the uterus.

This type of preservation is preferred by many for various reasons. Many single cancer patients prefer freezing unfertilized eggs, as opposed to fertilized ones, as they don't need any male donors at the time. Another reason women may want to freeze eggs is due to the fact that oocyte quality and quantity diminishes with age. This can cause a lack of healthy eggs to allow for pregnancy. Considering this, many women may prefer to freeze their healthy young and vital oocytes, which are more likely to produce pregnancies.

Furthermore, people may consider oocyte cryopreservation due to ethical, legal and religious hindrances that prevent them from doing embryo cryopreservation. Couples may not want to cryopreserve embryos as the embryos may have to be disposed if the cancer patient dies. (Noyes, et. al. 2010)

The goal of this study is to determine if oocyte cryopreservation is a means that enables women to have healthy offspring, post anti-mitotic therapy.

Methods

Pub med.gov, google scholar and Touro databases such as, EBSCO host, were used to research relevant studies and reviews for the background, process and results of oocyte cryopreservation. The review paper's references were used to find additional original papers that were relevant to the question proposed above. Key words such as oocyte cryopreservation, oocyte cryopreservation in cancer patients, slow freezing and vitrification were used in order to find articles.

Discussion

Various studies were done on oocyte cryopreservation. In one experiment, twenty-two cancer patients, between ages 21 and 38, underwent cycles of oocyte cryopreservation. After drug stimulation, oocytes were harvested from sixteen of the twenty-two infertile women, subsequently fertilized and implanted in them. The other six infertile patients received donor eggs. Only mature oocytes were preserved. The eggs were preserved by two methods, slow cooling method and vitrification. A total of 295/355 oocytes were recovered with a 92% survival rate.

At the time of publication of the study, fourteen of the patients had become pregnant, one had miscarried, and three pregnancies were still ongoing. A total of thirteen babies were born to the other expectant ten patients. Eleven of these babies were completely healthy, however a set of twins were born prematurely due to premature dilatation of an incompetent cervix. These twins suffered some complications of prematurity, but upon reaching two years of age, the twins were thriving within the average norms. Besides for two cases of gestational diabetes, no other complications were reported (Grifo, Noyes, 2010). Gestational diabetes is common in women during pregnancy. According to the CDC, the ratio of women with gestational diabetes ranges between one in every twenty to one in every fifty of expectant women.

Additionally, Dr. Nicole Noyas and other researchers pooled together data to see how many oocyte cryopreservation's resulted in normal babies. Any incomplete data was left out. A total of six hundred and nine births were reported between the years 1986-2008. All the babies born were a result of oocyte cryopreservation. However, the oocytes in those six hundred and nine births were preserved using different methods of cryopreservation. Three hundred and eight went through the process of slow freezing, two hundred eighty nine were preserved using vitrification and twelve had a combination of slow freezing and vitrification. A total of eight anomalies were reported. There were also three hundred twenty seven cryopreserved oocyte births published, totaling nine hundred thirty

six births. Out of the nine hundred thirty six babies, twelve babies were born with birth defects. Overall the anomaly rate is 1.3%. According to the CDC, three percent of babies are born with major structural or genetic defects. The twelve defects and the total incidents statistically occurring in natural conception babies compared to oocyte cryopreservation babies are listed in table 1. (Noyes, et. al. 2009)

Table1

Birth Anomaly	Approximate incidence in natural conception births	Incidence in total of 936 oocyte cryopreservation births (n)
All	One in 33	12 (one in 78)
Skin hemangioma	One in 50–225	1
Cardiac defects	One in 125	3
Neural tube defects	One in 385	0
Cleft lip and palate	One in 710	1
Clubfoot	One in 735	3
Arnold-Chiari syndrome	One in 1200	1
Choanal atresia	One in 7000	1
Biliary atresia	One in 10,000–15,000	1
Rubinstein-Taybi syndrome	One in 100,000–125,000	1

Birth anomalies in natural conception versus oocyte cryopreservation, listed most common to most rare.
Adapted from N. Noyes, E. Porcu & A. Borini, 2009

From the table one can assess that there were no neural tube defects and that the defect of skin hemangioma is the same range as babies born from natural conception. Additionally, cleft lip and palate as well as cardiac defects occurred less in the babies born as a result of oocyte cryopreservation.

Researchers have tried to improve the process of oocyte cryopreservation. One issue that arose from freezing the eggs was that extensive intracellular ice formed during freezing. Extensive intracellular ice can cause cellular disruption in the oocyte during the oocyte cryopreservation process. This can possibly be improved by using cryoprotectants such as, propanediol and sucrose to increase the extent of the dehydration process. The aim of the study done by researchers in Infertility and IVF Center of Buda was to introduce their preliminary clinical results with oocyte cryopreservation. They used slow cooling as the procedure to freeze the eggs. They specifically used propanediol (1.5M) and sucrose (0.3 M) as the cryoprotectants. After incubating the oocytes for 4-6 hours, the oocytes were thawed, fertilized and embryos were transferred into twenty-nine patients. Out of one hundred ten cryopreserved eggs, eighty-four survived. This is a 76% survival rate, which is high but not optimal. From fifty-two embryo transfers, seven resulted in clinical pregnancies, which is 7.3% implantation rate per egg thawed. Chorion biopsies that were performed indicated that there were no chromosomal abnormalities. Out of the seven pregnancies, five of them resulted in four singletons and one set of twins. One was still ongoing at the time of the study and the seventh spontaneously aborted in the tenth week. No abnormalities were indicated in the study. Additionally, there was only a small difference in the pregnancy rate, 33% versus 24%, between those pregnancies that resulted from frozen oocytes and those that resulted from fresh oocytes. As indicated from published literature at that time of the research, fifteen to thirty oocytes were needed in order to achieve one pregnancy. Previously, one hundred to one hundred fifty were needed to achieve one pregnancy. (Konc, et. al. 2008) The results show that oocyte cryopreservation is improving over time.

Vitrification is also known as ultra-rapid cooling. In recent years, vitrification has proven the superior method. Compared to slow freezing, vitrification results in higher oocyte survival and fertilization. (Cil, et. al. 2013) In a study done to compare the outcome of the two methods, the survival, fertilization, pregnancy and implantation rates were 57.9% versus 78.9%, 64.6% versus 72.8%, 7.6% versus 18.2% and 4.3% versus 9.3% correspondingly. The rates were higher in all steps for the vitrification method. (Fadini, et al., 2009)

The duration of cryostorage doesn't undesirably affect the thawing of frozen oocytes. A study was done to see if there is any influence on the outcome of thawing cryopreserved oocytes. There were three groups in the experiment. Group A's eggs were cryostored for one to three months, group B's eggs were cryostored for four to six months and group C's were cryostored for seven to forty eight months. Group C was further divided into three subgroups. Group C1, was cryostored for seven to nine months, group C2 was cryostored for ten to twelve months and group C3 was cryostored for a total of thirteen to forty eight months. The researchers found no significant difference, from groups A, B and C, in the main outcome measurements, which were oocyte survival after thawing, fertilization, implantation, embryo development and quality and birth. Oocytes can be cryopreserved for numerous years without having an effect on the oocytes quality and performance after thawing. (Parmegiani, et. al. 2009)

One factor that may affect the outcome of oocyte cryopreservation is the age. The value of freezing an older woman's oocytes is controversial. (Zhang, et. al. 2015) The rate of implantation of the fertilized egg that resulted from the slow freezing and vitrification methods declines with age. A study was done to collect data on the probability of live birth as of function of age. The

researchers found that live births occur from the slow freezing method until age forty-two, and until age forty-four from the vitrification method. They limited their results to the age range of twenty five to forty two years old, as there were only few cycles that were above or below the twenty-five through forty-two year old range. This study's data was on patients that were infertile. The study was not specifically performed on post cancer patients. (Cil, et. al. 2013)

Furthermore, a study was implemented in order to report the oocyte cryopreservation experience in women aged forty and older. One hundred fifty eight women, aged forty to forty-nine, underwent minimal ovarian stimulation to retrieve their eggs. A total of five hundred thirty two eggs were retrieved and frozen. Four of the women did not have any oocytes retrieved. A total of four hundred eighty five embryos were formed. Out of the four hundred eighty five embryos, only fifty-seven were relatively healthy. Six clinical pregnancies were achieved. Only three resulted in live births. There was a 5.3 % live birth rate per embryo transfer. The other three pregnancies were spontaneously aborted. As per the data, a woman aged forty and older can give birth to a baby after undergoing the process of freezing her eggs. However, there is a low chance that it will indeed happen, as there is a 5.3% chance that the woman will give birth. (Zhang, et. al. 2015)

A woman who has ovarian cancer may risk surgical menopause. Oocyte cryopreservation can be an option for woman facing ovarian cancer. It could also help patients that need to have a one or both ovaries removed. A twenty six year old woman with borderline ovarian tumors had her oocytes cryopreserved after a right adnexectomy. Seven mature eggs were retrieved and frozen. Thirty-nine months later, the woman underwent a left ovariectomy. Three embryos were transferred into the woman's uterus. Endometrial growth was achieved with the help of hormonal replacement treatment. The woman gave birth to healthy twin babies. (Porcu, et al., 2008)

Oocyte cryopreservation can help women have healthy babies even when they don't have their own healthy eggs. Remaining eggs from oocyte cryopreservation cycles can be saved and donated to another couple that are experiencing fertility complications. A study was done in which twenty-eight infertile women froze their oocytes. Twelve of the twenty-eight women had their frozen oocytes thawed. Three of the women used their own eggs in IVF treatment and the other twelve donated their eggs to other women. Premature ovarian failure, physiological menopause, abnormal karyotype and poor ovarian reserve are the reasons that the twelve women needed to receive oocytes from other women. Seven women became pregnant. Six of the seven used donated oocytes. A total of 6 healthy babies were born including a set of twins. The other 2 pregnancies were aborted due to a blighted ovum. (Li, et al., 2005)

Oocyte cryopreservation may not be for everyone. Women with cancers that need to be treated immediately after diagnosis, may not be a candidate for oocyte cryopreservation. This is because oocyte cryopreservation requires ovarian stimulation and retrieval. This can take an average of twelve days. (Noyes, et al., 2011) Additionally, some women that have breast cancer might run into issues with preserving their eggs. This is because estrogen levels rise during ovarian stimulation. High levels of estrogen might not be safe for women with breast cancer. (Rodriguez-Wallberg, Oktay, 2010)

Furthermore, some women may not want to undergo oocyte cryopreservation as it can cause a woman to have a risk having of intra-abdominal bleeding and ovarian hyper stimulation syndrome. However, there is a very low percentage rate of this risk. (Noyes, et al., 2011) Additionally, women with cancers may not be able to cryopreserve their eggs due to economic issues. It is a very expensive procedure. According to NYU Langone Medical Center's website, oocyte cryopreservation can cost about $16,000- $20,000. This includes initial office consultation, egg cryopreservation cycle, prerequisite blood testing and screening medication. As of 2010, cancer patients are generally not offered insurance coverage for oocyte cryopreservation. (Noyes, et al., 2011) Consequently, cryopreservation may not be an option for people that are struggling financially.

Conclusion

Oocyte cryopreservation is a viable method that enables women post mitotic therapies to have healthy offspring. As per the research discussed above, many women were able to have a healthy baby because they froze their oocytes. Even when abnormalities were reported, they were basically within normal range. Oocyte cryopreservation has even enabled a woman with borderline ovarian cancer to have a healthy offspring. Even though the value of freezing an older woman's oocytes is controversial and the rate of implantation of the fertilized egg declines with age, data has shown that oocyte cryopreservation can enable older women to have healthy babies.

There are different variables that may increase the outcome of oocyte cryopreservation. The vitrification method has shown to be the efficient and more reliable method. Cryoprotectants such as, propanediol and sucrose can increase the extent of the dehydration process and thereby prevent the oocytes from disrupting. Furthermore, the duration of cryostorage doesn't undesirably affect the outcome of oocyte cryopreservation.

Oocyte cryopreservation may not be for everyone due to economic reasons and timing of the anti-mitotic therapies. However,

it is a means that enable women to have healthy children even after their oocyte quality and quantity diminish as result of the cancer treatment.

References

Cil A, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. Fertility and Sterility. 2013; 100(2):492-499.e3. doi:10.1016/j.fertnstert.2013.04.023.

Diabetes And Pregnancy Gestational Diabetes. 1st ed. CDC; 2016. Available at: http://www.cdc.gov/pregnancy/documents/Diabetes_and_Pregnancy508.pdf. Accessed January 21, 2016.

Fadini R, Brambillasca F, Renzini M et al. Human oocyte cryopreservation: comparison between slow and ultrarapid methods. Reproductive BioMedicine Online. 2009; 19(2):171-180. doi:10.1016/s1472-6483(10)60069-7.

Grifo J, Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. Fertility and Sterility. 2010; 93(2):391-396. doi:10.1016/j.fertnstert.2009.02.067.

Konc J, Kanyo K, Varga E, Kriston R, Cseh S. Births Resulting from Oocyte Cryopreservation Using a Slow Freezing Protocol with Propanediol and Sucrose. Syst Biol Reprod Med. 2008;54(4-5):205-210. doi:10.1080/19396360802415778.

Li X, Chen S, Zhang X et al. Cryopreserved oocytes of infertile couples undergoing assisted reproductive technology could be an important source of oocyte donation: a clinical report of successful pregnancies. Human Reproduction. 2005;20(12):3390-3394. doi:10.1093/humrep/dei262.

Noyes N, Knopman J, Melzer K, Fino M, Friedman B, Westphal L. Oocyte cryopreservation as a fertility preservation measure for cancer patients. Reproductive BioMedicine Online. 2011;23(3):323-333. doi:10.1016/j.rbmo.2010.11.011.

Noyes N, Labella P, Grifo J, Knopman J. Oocyte cryopreservation: a feasible fertility preservation option for reproductive age cancer survivors. Journal of Assisted Reproduction and Genetics. 2010;27(8):495-499. doi:10.1007/s10815-010-9434-3.

Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reproductive BioMedicine Online. 2009;18(6):769-776. doi:10.1016/s1472-6483(10)60025-9.

Nyulangone.org. Financial Information. 2016. Available at: http://nyulangone.org/locations/fertility-center/financial-information. Accessed January 21, 2016.

Parmegiani L, Garello C, Granella F et al. Long-term cryostorage does not adversely affect the outcome of oocyte thawing cycles. Reproductive BioMedicine Online. 2009; 19(3):374-379. doi:10.1016/s1472-6483(10)60171-x.

Porcu E, Venturoli S, Damiano G et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reproductive BioMedicine Online. 2008;17(2):265-267. doi:10.1016/s1472-6483(10)60204-0.

Rodriguez-Wallberg K, Oktay K. Fertility Preservation in Women With Breast Cancer. Clinical Obstetrics and Gynecology. 2010;53(4):753-762. doi:10.1097/grf.0b013e3181f96e00.

Zhang J, Choo S, Yang M. Autologous oocyte cryopreservation in women aged 40 and older using minimal stimulation IVF. Reprod Biol Endocrinol. 2015;13(1). doi:10.1186/s12958-015-0110-4.