Does In-Vitro Fertilization Increase the Risk for Birth Defects?

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Abstract

Since 1978 when the first "petri dish" baby was born, In-Vitro Fertilization (IVF) has been used as a tool to give couples struggling with infertility the opportunity to have children. Using this method of Assisted Reproductive Technology (ART), the woman is given medication to stimulate her ovaries for the maturation of multiple eggs, which are then retrieved via needle aspiration, fertilized in a petri dish, and inserted in the uterus with the hopes of achieving a successful pregnancy. Many times IVF is completed with another technique known as Intracytoplasmic Sperm Injection (ICSI), where the sperm is injected straight into the egg increasing the chance of fertilization. In 2002, researchers discovered a clear association between an increased risk for birth defects with the use of In-Vitro Fertilization and Intracytoplasmic Sperm Injection. Since then, multiple studies were conducted to determine whether it is instigated by a mechanism of IVF itself, or influenced by the infertility problems of the couple (Hansen et al., 2002). There are various reasonable explanations for the findings of the surfeit occurrence of birth defects in pregnancies with use of IVF or ICSI. Firstly, the advanced age of couples undergoing infertility treatments could be the basis for the underlying increase in birth defects. Maternal factors such as obesity, metabolic disease, and chronic health issues are independent factors proven to increase the risk for birth defects as well (Davies MJ et al., 2012). Factors associated with the treatment such as, freezing and thawing of embryos, exposure of oocytes or embryos to a culture medium, or ICSI gamete manipulation, could also contribute Additional explanations point to the medications given to induce follicular numbers, or to speed the maturation of follicles into oocytes (Hansen et al., 2002). This paper reviews numerous studies that have been done to resolve the question at hand.

Introduction

Infertility

Intervention with medical assistance is required for one in ten couples who have difficulty conceiving naturally. Conception is a complex process that requires many factors to be working in synchrony to develop into a successful pregnancy. The problem can be attributed to female or male components. After one year without conceiving, couples are referred to a specialist to determine the root of the infertility. When the woman is over the age of 35, they are advised to seek medical advice after six months without conceiving. The most common causes of female infertility are irregular ovulation, obstructed fallopian tubes or, congenital anomalies of the uterus. Male infertility is most often caused by azoospermia, when no sperm is produced, or oligospermia, too few sperm. When faced with any of these factors, Assisted Reproductive Technology may be required.

In-Vitro Fertilization Process

The first step in the process of IVF is to produce ovarian hyperstimulation by giving medications to stimulate egg production. Injections of gonadotropins are given daily until multiple follicles develop into optimal size. Next, Human Chorionic Gonadotropin (HCG) is administered to speed the maturation of the follicles into oocytes. The eggs are then retrieved via needle aspiration using transvaginal ultrasonography and stored in a special culture medium until insemination. In a case with normal sperm, 50,000 to 100,000 motile sperm/ml are transferred into the petri dish with the mature eggs. When quality of the sperm is abnormal, such as poor motility or morphology, intracytoplasmic sperm injection (ICSI) is used to fertilize the egg. During ICSI, an embryologist uses a micro needle to inject one single sperm directly into the egg cytoplasm. After insemination, the embryo or embryos are placed in a catheter and injected into the endometrium in hopes of implanting onto the uterine wall (Wdowiak et. al. 2016). Cultured embryos often have difficulty exiting from the zona pellucida membrane. Artificial disruption using laser perforation may be required to aid in the process and increase the chance of implantation (Zakharchenko et al., 2015).

Methods

The research discussed in this paper was compiled from various published articles taken from Touro's database, including, Proquest Science, EBSCO, PubMed, and Google Scholar. All articles are original scientific papers that were analyzed and explored to obtain accurate data.

Discussion

IVF & Birth Defects

Researchers wondered whether the process of Assisted Reproductive Technologies, specifically IVF, can affect the risk of congenital birth defects, or developmental delays. Investigators used data from The Reproductive Technology Register in Western Australia, to analyze pregnancies between the years 1993 to1997, that were a product of IVF or ICSI. They surveyed all pregnancies that reached 20 weeks and were terminated because of fetal abnormalities. The Western Australian Birth Defects Registry listed all of the birth defects in pregnancies in Western Australia, from natural pregnancies and pregnancies that required the use of ART. With the data from these two institutions, researchers examined all pregnancies that were terminated, stillborn, or live births during these years, to determine whether birth defects were more common in infants conceived with use of IVF or ICSI. The presence of major birth defects diagnosed until the age of one year was examined.

There were a total of 168 out of 4000 infants conceived naturally, 75 out of 837 conceived via IVF, and 26 out of 301 from

ICSI, that were diagnosed with birth defects before the age of one year. The authors reported that the risk of birth defects was twofold in pregnancies that required Assisted Reproductive Technology. The results remained significant when only singleton births and full term births were taken into consideration. Other studies attribute the increase in risk of birth defects to the multiple births and preterm births that often are associated with use of ART. This research restricted the analysis to singleton and full term births so the results would not be explained by these factors. The overall risks remained the same when factors such as, maternal age and parity, sex of the infant, and association of siblings with birth defects, were taken into consideration. Furthermore, when analyzing the prevalence of birth defects in terminated pregnancies, the results remained similar to the original analyses. The prevalence of birth defects in terminated pregnancies was 4.5% in natural conception, 9.4% with use of IVF, and 8.6% in the ICSI category (Hansen et al., 2002).

After use of IVF the most commonly seen birth defects were cardiovascular, musculoskeletal, urogenital, gastrointestinal abnormalities and cerebral palsy. Also seen was an increased risk for multiple birth defects in singleton births specifically in the areas of cardiovascular defects, musculoskeletal, urogenital and cerebral palsy. The risk of respiratory disorders increased in cases of multiple births brought about by IVF. No association of increased risk in trisomy's, such as Down's, Edward's and Turner's was found (Davies et al., 2012).

Parental Factors

Factors related to maternal and paternal age and health were examined to find reliable information on the association of birth defects and parental issues. A study was done examining the occurrence of birth defects diagnosed before age five and including pregnancies that were terminated at any gestational age. The risks of birth defects were compared in pregnancies that were spontaneous versus assisted conception. Additional data was analyzed in women who reported infertility but eventually became pregnant without the use of ART. With this information it can be determined whether infertility is the major factor in the cause of birth defects or if the technology is to blame. A total of 308,974 births was used for analysis. The risk of birth defects increased significantly in pregnancies of women who experienced a history of infertility but were not treated with ART, versus spontaneous pregnancies without history of infertility. This indicates that the association of birth defects may be attributed to the patients' medical factors rather than the IVF. On the other hand, some patients use treatments such as clomiphene citrate which is given outside the clinic and data on who used this medication is not available for analyses. Clomiphene citrate is used for women experiencing anovulatory infertility to stimulate an increase in estrogen, a hormone that supports the growth of oocytes. This treatment could be the sole reason for increase in birth defects without use of IVF treatments, and may explain why women with a history of infertility had children with birth defects more commonly (Davies et al., 2012). Another study was done examining the mental health of children born to infertile women who conceived spontaneously. The study indicated that there was a significantly higher increase in mental disorders such as schizophrenia, mood disorders, and psychological development compared to children born to women without fertility problems (Svahn et al., 2015).

Another study was done to examine the degree at which maternal health issues were related to the increase in birth defects after IVF and ICSI. The South Australian Birth Defects Register contained all of the data on maternal medical conditions following various fertility treatments. The maternal factors that were considered were maternal age at delivery, parity, BMI, smoking habits, hypertension, diabetes, asthma, epilepsy, and gestational conditions such as, pre-eclampsia, impaired glucose tolerance, gestational diabetes, anemia, and UTI occurrences. With regard to health conditions, only smoking and obesity were linked to an increase in the risk for birth defects over the general population risk. With regard to ICSI, parity, anemia, and UTI occurrence, were also associated with an increase in birth defects. Additionally, the report indicated that the women with the greatest risk for an increase in birth defects with use of IVF were aged 29 and younger compared to fertile women of their age. The study suggests that the uterine environment of younger women is more likely to be able to sustain an embryo with birth defects or, the implantation success in older women is limited which helps to prevent developmentally compromised embryos from implanting. Women aged 40 and older were at a lesser risk for an increase in birth defects compared to fertile women of their age. A possible explanation may be the influence of the gonadotropins that may protect oocyte development (Davies MJ et al., 2012).

Paternal factors also add to the increased risk for birth defects with use of ART. According to one study, children born to fathers over the age of 40 are at an increased risk for childhood fatality due to congenital abnormalities and malignancies. When paternal age increased to over 45, the childhood fatality rate increased from 1.24% to 1.65% compared to fathers aged 30 to 34 (Urhoj et al., 2014). When the sperm of infertile men was analyzed under light microscopy, it was noticed that there was an excess of DNA damaged sperm. DNA damage limits the ability of apoptosis to occur. Typically, apoptosis removes the damaged sperm but with IVF, fertilization can take place with damaged sperm that would have been excluded in natural conception. This increases the risk for miscarriage and birth defects (Lewis & Kumar, 2015). Additionally, men with reproductive issues often require the use of ICSI because of the poor motility and morphology of their sperm. ICSI can be problematic when abnormal sperm is inadvertently injected, or the injection itself

could damage the chromosome spindle formation in the oocyte (Winston & Handyside, 1993).

Multiple studies imply that the increase in birth defects or mental disorders with use of IVF is likely associated with parental factors. One study pointed to alternative treatments that may be used in addition to IVF. Overall, parental issues play a large role in the increase in birth defects with use of ART, although there are other factors that are likely associated as well.

Cryopreservation

Cryopreservation involves preservation of an embryo or oocyte in liquid nitrogen after cooling the sample in a cryoprotectant to -30 degrees Celsius (Winston & Handyside, 1993). The two methods for cryopreservation are slow freezing and vitrification. Currently, vitrification is the preferred method as it instantly solidifies the samples preventing the formation of ice crystals causing less damage to the oocytes or embryos. Slow freezing involves the use of a less toxic concentration of cryoprotectants however, the limited ability to prevent ice crystals is thought to increase the risk for abnormalities.

There are severe problems involved in oocyte cryopreservation which is a common practice used for women approaching advanced maternal age. First, oocytes are temperature sensitive due to the high content of cytoplasmic liquid and, the arrangement of the chromosomes in the sensitive spindle formation. Disruptions during the freezing and thawing process lead to a threefold increase in aneuploidy when spindle formation is disturbed. The risk of polyploidy also increases, as frozen oocytes are more vulnerable to polyspermic fertilization when the cortical granules are unevenly distributed (Jiminez- Trigos et al., 2012). Caution must be taken with these results because most studies are done on mice and the effect of chromosomal segregation is different between species. Additionally, cryopreservation of oocytes reduces successful fertilization by inducing changes in the zona pellucida specifically, zona hardening, and, producing changes on the sperm receptors of the zona (Winston & Handyside, 1993). Data on the results of cryopreserved oocytes is limited as the number of births resulting from this technique is small. Further results on the health status of children born afterwards is not yet available, however reports do not indicate an increase in birth defects or developmental delays (Schattman, 2015). Some reports reveal that oocytes that developed in vitro have a decreased live births and pregnancy rates.

By analyzing the effect of vitrification on the oocyte, it can be determined if this technique causes adverse effects to oocyte functionality. The mitochondrial function of vitrified oocytes was observed by analyzing the condition of ATP synthase in the oocytes. ATP synthase in Metaphase II stage was analyzed by looking at the ratio of FAD to NAD(P)H. If the ratio is abnormally elevated, it insinuates a decrease in the ATP synthase function of the oocytes which results in abnormal spindle formation. Additionally, the stage at which the oocytes are vitrified effects the outcomes. Vitirification can be performed at the Metaphase II stage which contains sensitive spindle formation, or the germinal vesical stage, before the spindle is formed. The germinal vesicle stage has to go through maturation after thawing which may also effect the value of the oocyte. Live births have been seen from vitrification at both of these stages and it is not yet known which has a better success rate (Gao et al., 2017). Ultimately, the ideal method for freezing oocytes is not yet known, and it has been shown to increase the risk for aneuploidy or polyploidy, and decrease risk for fertilization. However, cryopreservation of oocytes is an opportunity for women who wish to preserve eggs for future use because of medical or age related issues. It is currently the only option to preserve fertility for women undergoing treatments such as radiation or chemotherapy which may affect their ability to conceive.

The transfer of frozen embryos has been used more frequently in the past few decades as it has shown several advantages. Multiple studies show that using frozen-embryo transfers increases the rate of live births compared to fresh-embryo transfers. Most reports point to the non-stimulated menstrual cycle that is associated with frozen transfers. When fresh-embryos are transferred, the artificial hormone induced menstrual cycle adversely effects the endometrial receptivity leading to implantation failure (Aflatoonian et al., 2016). Studies have been done to determine differences noted between fresh-embryo and frozen-embryo transfers. A study of, 1508 infertile women diagnosed with Polycystic Ovarian Syndrome and were undergoing their first IVF treatment, were randomized in two groups. They received either fresh-embryo or frozen-embryo transfers. The women were all between the ages 20 to 34 and were in a healthy weight range. All patients went through the standard IVF procedure and subsequently a transfer of up to 2, day-3 embryos. The frequency of live births was considerably higher after the frozen-embryo transfers. The rates showed a 49.3% versus 42% difference. It was proposed that when frozen-embryos are transferred, it allows time for the reproductive system to recover from the induced ovulation by hormones. The exposed endometrial lining has time to shed, increasing the chance that the embryo will implant. The results may not be pertinent to the overall population undergoing IVF since these subjects were PCOS patients. Another study was done to assess whether infertile women without Polycystic Ovarian Syndrome who were undergoing IVF showed the same results. The same method was used and in this case, the transfer of frozen embryos did not increase the chances for a higher live birth rate. Reasons for the different results may be due to the method of cryopreservation or the timing of the freezing (Vuong et al., 2018). In both studies no increase in the risk for congenital malformations was noticed (Zi-Jiang et al., 2016). Other studies note, that when comparing the risk of birth defects in the fresh-embryo and

frozen-embryo cycles, there was a significant increase in the risk of birth defects for the former. Plausible justifications may be related to the cryopreservation that would eliminate the developmentally compromised embryos, because they would be less likely to survive the freezing and thawing process. Additional explanations that would eliminate the inferior embryos would be the separation of the embryo from hormonal stimulation drugs (Davies et al., 2012).

Various researchers have attempted to observe the effects of the cryopreservation process and the health status of the resulting children. Most studies were done involving results from single-center analyses. A multi-center study between the period of 1995 to 2013 was done to analyze the miscarriage rates, birth weight, pregnancy complications and congenital malformations in IVF centers worldwide. It was determined that the suboptimal results were more likely caused by parental factors such as advanced age, concurrent metabolic, genetic and epigenetic alterations, which affects the health of gametes (Keshishian, 2014). After much research into the matter, the consensus appears to be that there is an increase in live birth rates after the use of frozen-embryo transfers although the reason is still unknown. It is most likely from the natural exclusion of unfit embryos during the freezing process, or the separation of the embryo from hormonal drugs giving the uterus time to readjust for the implantation process. The presence of birth defects does not seem be affected by the freezing process and is more likely associated with parental issues. This interpretation is consistent with the majority of studies done to analyze the effects of embryo cryopreservation.

Although cryopreservation of embryos is associated with an increase of pregnancy rates and a decrease in preterm labor, it is important to determine that there are no long term unforeseen consequences with regard to this technique. National registries in Denmark were used to examine the intellectual abilities of children aged 15 to 16 born from cryopreserved embryos. A standardized test was given to all children ages 15 to 16 and overall test scores were evaluated. No apparent difference in the test scores between children conceived via IVF, fresh or frozen, and natural conception, was noticed. The study was limited as they did not observe the children that did not enter the school system due to intellectual disabilities (Spangmose et al., 2019)

Culture Medium

Fertilization normally takes place in a protected well-controlled setting in the oviduct. During IVF, the male and female gametes are brought together in a medium that is intended to provide conditions for the sperm to go through the process of capacitation and produce acrosome reactions, in order for sperm penetration, fertilization, and cleavage to occur (Bavister, 1981). Studies done on mouse embryos show that different conditions in the culture can lead to changes in gene expression. Good quality human day 4 cryopreserved embryos were donated to observe the effect of culture media on transcription. The embryos were randomly selected to be cultured in one of two media (HTF or G5) and one of two oxygen levels. The two media used were Human Tubal Fluid mixed with glucose and phosphate, and the second, a more enriched version of the medium containing additives such as additional amino acids (G5). The two HTF cultures and two G5 cultures contained either 5% or 20% oxygen levels. The embryos were also classified for maternal age and developmental stage at the time of transfer. After culturing, 89 embryos were transferred to PCR and further analyzed. Microarray data analysis was used to observe any correlation between differentially expressed genes (DEG's), the upregulation or downregulation of genes, and whether they were caused by different culture conditions, or whether biological factors such as maternal age and developmental stage played a larger role. The number of differentially expressed genes was significantly higher with regard to biological factors when comparing it with the differentially expressed genes from different culture conditions. Notwithstanding the conviction that maternal age only effects oocytes, this data indicates that maternal age and developmental stage has a much greater effect on transcription. Although the correlation between transcription errors and culture conditions was minimal, it was noted that human embryos developed best in the G5 5% oxygen level culture medium. G5 medium caused an upregulation in genes involved in regulation of phosphorylation and mitosis, and the lower oxygen level led to an upregulation of genes involved in cell morphogenesis which aids in embryo development (Mantikou et al., 2016).

Intravaginal culture (IVC), also known as INVO, is an ART technique where oocytes and early embryos are cultured in a gas permeable air-free plastic device placed in the vaginal cavity for incubation. The advantages are that INVO mimics the environment of the uterus and excludes of use of a culture medium to sustain the fertilization and early growth of the embryo. IVF involves the use of a culture medium which influences embryo quality with changes in oxygen and carbon dioxide concentrations, and, PH or temperature changes. If any of these factors become unproportional, embryo fragmentation can occur. Oxygen in the uterine cavity is less than 5%. The INVO device is able to offer an environment similar in that way. The almost anaerobic oxygen concentration level guarantees a safe atmosphere for the energetic metabolism required for successful gamete viability, fertilization and embryo development. Carbon dioxide is another important factor involved in embryo development as it directly effects PH levels (Lucena et al., 2012). The INVO device is absorbent to gas in the uterus and allows for a balanced equilibrium of CO2 to uphold the PH level of 7.2 to 7.4 (Garcia-Ferreyra et al., 2015). On the other hand, in traditional IVF, the concentration of carbon dioxide can be altered when the large gas-filled incubators are opened. This effects the PH equilibrium and temperature of the culture medium, decreasing

embryo quality. A study was done to assess the outcomes of INVO and compare the pregnancy results to common existing IVF techniques (Lucena et al., 2012). Embryos were cultured in the INVO device and then transferred to the uterus on day 3 or day 5 after fertilization. The implantation rates, pregnancy rates, and miscarriage rates were considered. The results showed that the INVO-ICSI procedure had similar outcomes to the traditional IVF-ICSI procedure. Pregnancies were evaluated 14 days after embryo transfer by measuring hCG-beta subunits in the blood, and ultrasounds were utilized to reveal gestational sacs, and heartbeats 21 to 28 days after the transfer. INVO-ICSI was concluded to be alternative option for couples struggling with infertility, with advantages in cost effectiveness, and psychological benefits, allowing a more direct involvement in fertilization which was shown to reduce stress levels in patients (Garcia-Ferreyra et al., 2015).

Another study was done to assess the effect of culture conditions on Imprinting Disorders. Syndromes, such as, Angelman Syndrome, Beckwith- Wiedmann Syndrome, and Silver-Russel Syndrome, were found to be more prevalent after IVF. These syndromes are referred to as genomic imprinting disorders and are an epigenetic phenomenon that restricts the expression of one parental allele leading to activation of only one copy of a chromosome. Imprinting genes are controlled by the Imprinting Control Region (ICR) where abnormal cytosine methylation occurs on various genes causing them to deactivate. A study was done that observed the methylation levels of ART produced human embryos at day 3 of cleavage and the blastocyst stage. The specific ICRs analyzed were KCNQ1OT1, SNRPN, and H19, which are the ICR regions where most maternal methylation occurs in the syndromes studied. In the Beckwith-Wiedmann Syndrome children conceived with ART, there were 90% observed methylation errors at KCNQ1OT1 as compared with 50% in the general population of cases with Beckwith-Wiedmann Syndrome. SNRPN methylations occurred in 46% of the Angelman Syndrome ART children versus 5% in the general population. The ART children with Silver-Russel Syndrome were observed to have 92% of the H19 hypomethylations while only 40% of the general population had these defects (White et al., 2015). Some researchers ponder whether the prolonged exposure to a culture medium plays a role in development of these imprinting methylation errors (Davies et al., 2012). Day 3 embryos as well as blastocyst embryos were studied to determine if time spent in the media culture relates to an increase in methylation errors. It was noted that 76% of the day 3 embryos, and 50% of the blastocysts, exhibited defects in imprinting methylations (White et al., 2015). This report demonstrated that the extent of time spent in the culture does not pose a greater risk for the imprinting errors to occur. Multiple studies show that media culture does not significantly affect the outcome of IVF, and therefore does not play a role in the increased risk for birth defects.

The absence of natural reproductive fluids in early embryonic development has shown to influence the outcomes of gene expression in the embryo. Downregulation of embryonic nutritional elements and upregulation of apoptosis factors in the oviduct, have been seen with the absence of seminal fluid (Bromfeild et al., 2014) In mice studies, seminal fluid has been shown to influence fetal development by inducing immune responses from the female reproductive tract. The production of T-regulatory cells which act as a protection to the embryo is activated by seminal fluid. T-regulatory cells are programmed to recognize the male antigens present and to suppress inflammation that would normally occur with an unidentified antigen. This aids in the adaptation of the uterus required for implantation and placental development. Mice studies have shown that with the absence of seminal fluid, fetal development, phenotype, and metabolic function are altered (Schjenken & Robertson, 2015). Follicular fluids have also been shown to influence embryo development. A study was done to detect methylation levels in pig blastocysts to show differences between fluids present in IVF and natural embryos. Whole-genome DNA sequencing was performed for methylation analysis. The addition of reproductive fluids into the culture for IVF produced embryos of higher quality that were similar to embryos produced in vivo. The methylation patterns were closer to the methylation of naturally produced embryos. Additionally, fewer irregularities in genes involved in imprinting, development, and reprogramming, were noticed in the IVF culture that included reproductive fluids (Canovas et al., 2017).

Globally it has been proven through multiple studies that the culture medium does not play a role in the increased risk for birth defects. Reports on the amount of time spent in the culture and the culture conditions were analyzed and no increase in congenital anomalies was seen. There is a slight association between improved gene expression and addition of natural reproductive fluids to the culture.

Alternative Treatments

For couples who are having difficulty with conception, especially at advanced maternal age, the ideal approach is uncertain. Infertile couples have a 2 to 12% chance per year of becoming pregnant spontaneously. Alternative treatments include but are not limited to intrauterine insemination and ovulation induction. These treatments are less costly than IVF however the success rates are well below those of IVF. During intrauterine insemination, semen is condensed in a laboratory and then injected past the cervix into the uterus (Van Vorhis & Bradley, 2007). Ovulation induction involves use of Clomiphene Citrate to stimulate follicles and hence egg growth. Clomiphene citrate works to increase estrogen levels which then signals the anterior pituitary gland to release Luteinizing Hormone which stimulates ovulation. Ovulation induction is most often used in women with Polycystic Ovarian Syndrome which is the most

common cause of anovulatory infertility. Multiple studies found links between use of ovulation induction medications and an increase in birth defects such as neural tube and cardiac defects. This was reportedly due to the fact that these medications are given to PCOS patients who often struggle with obesity (Balen & Rutherford, 2007). One study suggests an association between use of clomiphene citrate and craniosynostosis (Reefhuis et al., 2003). This is likely due to the multiple births that are expected with ovulation induction. Multiples are at increased risk for mortality and long term consequences such as congenital anomalies and developmental delays (Corchia et al., 1996).

The use of prefertilization and preimplantation genetic diagnoses combined with IVF significantly increases the rates of successful pregnancies. With advanced maternal age, egg quality is reduced resulting from abnormalities in the spindle formation of the chromosomes. Eggs enter prophase 1 in the first meiotic division during the fetal period, and remain in that phase until ovulation. When meiosis resumes many years later, the spindle formation can be disturbed, leading to a failure to fertilize, abnormal embryo development, and fetal loss (Van Vorhis & Bradley, 2007). Genetic diagnosis of oocytes, also known as polar body analyses, is useful to differentiate between mutations in genetic material of the oocyte. Each polar body contains complementary genetic material to the oocyte. This can reveal any genetic alterations of the oocyte which would then be excluded from use in IVF. The procedure incorporates, laser microdissection of the zona pellucida with a UV-A laser, and extraction of the polar body with a micropipette (Clement-Sengewald et al., 2000). After genetically normal oocytes are recognized by polar body analyses, they are fertilized and cultured until either day 3 embryos or blastocyst stage when they can then be transferred into the uterus. Polar body analyses are only useful to detect problems with maternal genes. Therefore, another technique known as preimplantation genetic diagnosis in commonly used to select embryos for transfer using genetic analysis that is performed on cells biopsied from embryos. The procedure normally does not affect embryo development because the cells at this stage are totipotent. The practice allows for a choice of embryos that are unaffected by the heritable condition or chromosomal mutations prior to pregnancy and thus avoiding termination of pregnancy (SenGupta & Delhanty, 2012).

Conclusion

Multiple studies show a clear association between the use of IVF and an increase in birth defects. The research discussed above was done to determine whether certain techniques involved in IVF are related to the risk. In multiple studies, cryopreservation of oocytes and embryos was not seen to increase the risk for birth defects or intellectual disabilities. It was noted however, to increase the live birth rate. The various culture conditions were examined and they were noted to have slightly different effects on transcription but no overall effect on the risk for birth defects. Many reports are limited due to the ethical and practical difficulties that are involved while studying topics such as human embryonic development. Birth defects are rare and thus the observational results were done on small sample sizes. Larger studies are required to give a definite answer to the underlying cause of the association. A number of studies indicated that the infertility problems of the couples undergoing IVF are a likely answer for the increase in congenital anomalies. ICSI has also been thought to increase birth defects because of the increase in chromosomal abnormalities in men with low sperm counts. There is an association between IVF and Imprinting Disorders, however the underlying cause is not known. The generally older age of patients undergoing IVF adds to the plausible complications such as implantation failure, miscarriage, congenital anomalies, and fetal death. Some of these problems can be addressed with Preimplantation Genetic Screening (PGS) which screens for embryos with chromosomal abnormalities or Preimplantation Genetic Diagnosis (PGD) to search for a specific genetic disease. Overall, the comprehensive data related to children born from IVF shows that majority are not born with birth defects. The risk is greatly reduced when IVF is used together with PGD and PGS. Couples considering IVF should discuss genetic testing options with their doctor to determine if this service is appropriate for their situation.

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