Intracytoplasmic Sperm Injection: A Bioethical Analysis

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ABSTRACT

Assisted reproductive techniques have been a great blessing for the infertile couple. Some have questioned their use, citing the unknown risk to the unborn child. The emergence of one of the newest techniques, intracytoplasmic sperm injection, has again sparked debate on the ethics of assisted reproductive techniques. Those who oppose intracytoplasmic sperm injections use are primarily concerned with risk to the future child. Alternatively, others believe that once born, a person will almost always choose life over not being born at all. The former group espouses parental responsibility, while the latter invokes procreative liberty. Only until more data accumulates on current and future "intracytoplasmic sperm injection children" will the question of risk be more accurately assessed. Until that time, intracytoplasmic sperm injection should only be employed after a thorough medical review of each case, following fully informed consent, and as long as the malformation rate does not show a statistically significant increase from the normal population.

INTRODUCTION

The distress of infertility and its medical treatments profoundly affects those it afflicts. Its legacies, both painful and enduring, often remain unspoken. Aided by the rapid progression of medical innovations, couples once told they could not bear children are now conceiving. Yet, several ethical questions surrounding these new techniques remain to be answered. Although a discussion on the bioethical considerations of all of these techniques is beyond the scope of this paper, a thorough examination of one of the most advanced assisted reproductive techniques (ARTs), intracytoplasmic sperm injection (ICSI), can serve as an ethical framework for others.

INTRACYTOPLASMIC SPERM INJECTION

Recently, developments in the micromanipulation of sperm have made it possible for men with extremely low sperm counts to join with their partners in establishing a clinical pregnancy. The procedure involves the injection of a single sperm directly into the egg (oocyte). Once fertilization is achieved, the resulting embryo is introduced into the hormone-primed uterus for implantation and subsequent gestation. The first clinical pregnancies following ICSI were reported in 1992 (Palermo, 1992), ushering in what is widely regarded as a new era in infertility treatment. However, questions are being raised (Ericson and Kallen, 2001) about whether ICSI, in fact, causes serious illness and malformations in a small but significant proportion of children. Other commentators argue that it is nevertheless better to be alive, even with serious illness and disease than not to have existed at all. To help sort out this difficult question, both perspectives must be carefully analyzed and a risk-benefit analysis must be explored.

INTRACYTOPLASMIC SPERM INJECTION DEPENDENT PROBLEMS

ICSI dependent problems arise from the materials and methods used in the procedure. The technique involves the injection of a sperm cell into an egg. However, are there consequences to achieving fertilization in this manner?

Breach of Natural Barriers

There is a biological assumption (Lee et al., 1996) that the anatomic and physiological obstacles to normal fertilization are a means of preventing insemination of an egg with chromosomally abnormal sperm. In essence, there are intrinsic selection barriers to achieving normal human fertilization designed to eliminate germ cells destined for abnormal development. This complex quality control mechanism begins with germ cell atresia in the testis, then in the epididymis, female reproductive tract (e.g., the cervical mucus barrier and the relatively long traveling distance), and finally, the sperm-oocyte interface. Ordinarily, the surviving sperm will attempt to penetrate the initial barriers surrounding the egg: the granulosa cells of the corona radiata and the zona pellucida. These barriers (aside from the sperm-oocyte interface selection) are also bypassed in other reproductive techniques, including in vitro fertilization (IVF), which is widely accepted as a safe procedure. With ICSI, these selective barriers are circumvented by the direct injection of a spermatozoon (mature sperm cell) into the egg. Some have postulated (Prasad et al., 2000; Van Dyk et al., 2000) that the zona pellucida plays a critical role in the selection against sperm cells with genetic defects. With ICSI, there is an artificial breach of the zona pellucida. Spontaneous abortion remains the only natural prevention of major genetic anomalies. In fact, 50% of spontaneous abortions are due to genetic anomalies.

Compression in the Injection Needle

An additional concern is the compression of sperm cells
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and the possible damage incurred in the microinjection needle lumen. With normal fertilization, the successful sperm is relatively unencumbered in its trip up the female reproductive tract. When morphologically abnormal, leukocytic cells found in the semen may remove them, which prevents them from reaching their destination (Tomlinson et al., 1992). This may be a physiologic method of excluding structurally damaged sperm. Compression in the needle lumen might mimic morphological changes without surveillance from the seminal leukocytes.

Genetic Contaminants

Another concern is that foreign DNA might be transported into the egg by the sperm. Lavitrano et al. (1989) has demonstrated that homologous and heterologous macromolecules may be incorporated into mouse epididymal spermatozoa, eventually being transferred into the eggs to produce transgenic mice at a rate of 30%. Although this concern may produce horrid results, successful transfer of foreign DNA into human sperm has not been reported. In recent experiments, researchers have reported that spermatozoa from certain mammalian species have the ability to bind exogenous DNA. Human spermatozoa, however, did not bind the foreign DNA. These results indicate that certain factors may be protecting spermatozoa from accidental transfection by foreign from bacterial or viral sources (Camaioni et al., 1992). This data should alleviate fears of infectious gene products penetrating the sperm cell during the procedure.

Biochemical Contaminants

Some have also worried about the accidental injection of biochemical contaminants from the procedure medium. However, such findings have not been reported and perhaps the human spermatozoon shields itself from the foreign medium in the same fashion it wards off infection and other possible contaminants. Other biochemical contaminants that must be considered when evaluating the safety of the procedure are the exposure of the oocyte to hyaluronidase, intense light, and fluctuations in temperature. There is no data available on whether this is pure speculation, or is in fact a blatant warning sign that enough is not yet known about the procedure to permit its use. Associated with this anxiety is the injection of the spermatozoon in a 10% concentration of polyvinylpyrrolidone (PVP). There are concerns about the potential carcinogenic capability of this compound. However, sister-chromatid-exchange-analysis has demonstrated that neither PVP nor methylcellulose causes chromosomal aberrations under in vitro conditions (Ray et al, 1995).

Parthenogenesis

Another ICSI dependent problem is mechanical oocyte activation (parthenogenesis). This includes abnormal fertilization leading to the formation of abnormal embryos and the induction of parthenogenesis. Researchers have shown (Kola and Wilton, 1991) that an embryologist may eradicate such concerns after careful microscopic observation, which can detect induction of parthenogenesis by the presence of pronuclei in the zygote. These zygotes can then be disposed of before cleavage. Although some voice ethical concern about the disposal of zygotes, a discussion of this topic is beyond the scope of this paper.

Use of Spermatids in Intracytoplasmic Sperm Injection

Another potential chromosomal concern is the use of ICSI on spermatids (although most ICSI procedures do not use spermatids). Spermatids normally undergo spermatogenesis resulting in mature sperm (spermatozoa). Some males have sperm maturational arrest with their sperm consisting of these immature forms. Recent investigations have shown that in humans, the mature sperm cell provides the centrosome, the microtubule organizer, which directs the accurate union of sperm and egg. During interphase, the centrosome divides to form two spindle poles, which provides the framework for ensuing mitosis. In the spermatid, however, there is no centrosome. Nevertheless, healthy births have been reported with the use of spermatids. Several theories have been proposed (Navara et al., 1994) to explain the microtubule organizing function in these cases. Yet, there is great concern over using spermatids (Zech et al., 2000). Will there be abnormal cleavage and aberrant growth of the embryo? The early data appears encouraging (Al-Hasani et al., 1999). Still, some feel it is too early to declare ICSI safe on spermatids, because children born with the aid of ICSI have not fully matured.

Mitochondrial DNA

It is now known that mitochondrial DNA (mtDNA) is maternally inherited. Will the procedure result in mitochondrial DNA being paternally inherited (St. John et al., 2000)? If so, will the shift of inheritance have adverse effects? The direct injection of spermatid mtDNA into the center of the egg might be circumventing the normal mechanisms of destruction of paternal mtDNA. mtDNA is highly susceptible to point mutations and deletions being that mtDNA lacks an effective repair mechanism. Inclusion of paternal mtDNA might incorporate damaged DNA, or more importantly, may disrupt the electron transport chain or affect other oxidative cell functions; this could lead to the untimely accumulation of free radicals facilitating premature cell aging (Patrizio, 1995). While this prospect is daunting, it is impossible to verify until the passage of many more years of data collection. Furthermore, the possibility that some causes of male infertility may be caused by defective maternal inheritance of mtDNA then the incorporation of paternal
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DNA could have a corrective medical value (Cummins et al., 1994).

**INTRACYTOPLASMIC SPERM INJECTION: THE EARLY RESULTS**

Do these factors lead to an increase in congenital defects? Although case study dependent, 2.3% of children born with the aid of ICSI have a severe congenital disorder (Bonduelle et al., 1999). The expected rate of such disorders among the general population is somewhere between one and two percent (Bonduelle et al., 1996). In fact, more than 20 million Americans have a diagnosed genetic disease. One percent of all newborns have a recognizable Mendelian disorder, a half percent have a chromosomal syndrome, and two percent have a polygenic, multifactorial disorder (Ward, 1999). Thus, there may be a slight increase in severe disorders when using ICSI. Is such an increase statistically significant? Opponents of ICSI say, yes. That one more child is born with severe abnormalities is not fair to that child. On the other hand, while proponents of ICSI acknowledge that both morphologically and motility defective sperm are eliminated in the female genital tract, there seems to be no significant increase in the frequency of disorders. If the lack of physiological selection were truly a problem, one would expect the rate of abnormalities to be higher than it is. Moreover, the congenital anomalies that have occurred are similar to the ones affecting the general population. In essence, there are no peculiar deformities or anomalies being created.

Nevertheless, is this information sufficient to withhold ICSI from clinical use? Some critics contend (De Jonge and Pierce, 1995) that while ICSI may be well understood as a technical procedure, it may be somewhat premature to implement it as a clinical tool, particularly since the biological mechanisms of ICSI are not well understood. They point to the lack of knowledge on the mechanism for egg activation and the removal of the acrosome with its overlying membranes. Furthermore, animal research data is incomplete that might clarify the long-term effects of ICSI.

The foremost response given by those who support ICSI is that the risks are speculative in nature. They point to the early results from the children of ICSI, which at this juncture seem to reassure that an increase in major malformations, defined as those causing functional impairment or requiring surgical correction, are not caused by ICSI. Consider the data from a large infertility program in New York (Palermo et al., 1996): 9 ICSI children of 578 (1.6%) had major malformations compared with 3.6% of babies overall in the state. Furthermore, some male infertility specialists (Van Steirteghem et al., 1994) have reported on the genetic analysis of 823 offspring and detected only one abnormal karyotype and ten major congenital malformations (rate of 1.2%). It should be noted, however, that there is no consensus on this matter. When two groups of investigators examined malformations in children born with the aid of ICSI in a Belgian program, the results were conflicting! One team (Bonduelle et al., 1996) reported no increase, but the other observers (Kurinczuk and Bower, 1997) found a possible doubling of malformations. This discrepancy might be explained by the different clinical criteria used to diagnose “malformations.” The latter claim the Belgian team compared their data to in vitro fertilization births from the Australian National Perinatal Statistics Unit. This system has a much broader definition of what constitutes a major defect than does the Belgian group, thereby underestimating the comparative prevalence of major birth defects in their cohort of infants. For example, congenital anomalies such as atrial septal defect type II, renal duplication, and patent ductus arteriosus, were considered only minor malformations by the Belgian group but major by the aforementioned registry. Nevertheless, the above illustrates the controversy surrounding the use of ICSI. Finally, defenders of ICSI maintain that further animal research would be of no aid in evaluating the long term safety of ICSI in that animals do not live nearly as long as humans. Clearly, there is no consensus on the safety of ICSI.

**INTRACYTOPLASMIC SPERM INJECTION INDEPENDENT PROBLEMS**

ICSI independent problems result from the potential passage of genetically abnormal sperm to the future offspring independent of ICSI as a technique.

**Immotile Cilia Syndrome**

The most prominent ICSI independent issue is the male gamete carrying genetic anomalies. For example, researchers (Olmedo et al., 1997) have recently reported a successful fertilization with immotile spermatozoa from a young man with a combination of dysplasia of the fibrous sheath and dynein deficiency, a recently described variant of the immotile cilia syndrome, which is a rare autosomal recessive condition. These patients which is apart from immotile sperm cells, suffer from medical disorders, such as situs inversus and severe pulmonary disease. When such gametes are used, the resulting offspring is usually heterozygous for the gene, and will usually contain motile spermatozoa and be medically asymptomatic. With thorough genetic screening of a future partner, albeit quite costly, the syndrome can be prevented from being passed on from father to son.

**Cystic Fibrosis and Congenital Bilateral Absence of the Vas Deferens**

The condition of congenital bilateral absence of the vas
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deferens (CBAVD) is, in the majority of patients, related to defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Lissens et al., 1996). With the advent of ICSI, most men with CBAVD can father their own children. In men with CBAVD linked to mutations in CFTR with no history of cystic fibrosis (CF) reported for relatives of the female partner, the risk of having a child with CF is two percent (Engel et al., 1996). To date, over 500 different mutations have been reported (Mickle et al., 1995) in the CFTR gene the most common (about 70%) being the delta 508 mutation. Genetic analysis can now detect 80% to 90% of all mutations. Genetic counseling with proper screening tests could determine the presence of mutations on the CFTR gene. Furthermore, a blastomere biopsy can be performed on the resulting preembryo, which can ascertain whether the CFTR mutation has been inherited. Finally, technicians can now screen for CF in embryos and first trimester fetuses (McIntosh et al., 1989), but this increases the technological interventions and raises the added dilemma of selective termination of pregnancy.

Y Chromosome Microdeletions

Scientists (Ma et al., 1993) have recently reported that some forms of incomplete sperm maturational arrest presenting as azoospermia are due to microdeletions present on the long arm of the Y chromosome. Currently, a worldwide study (The Simmy Protocol) to monitor father/son pairs by Y chromosome PCR analysis is underway to test this possibility. Only after the completion of such a trial can more be said on this possibility. However, the cost of such screening would be extremely high. Moreover, genetic experts do not completely understand the specific genetic control mechanisms that are present on the Y chromosome. Although speculative, might it be possible that the gene for male infertility is associated with an oncogene on the chromosome (Tho and McDonough, 1987)? It might be conjecture at best, but what if the ICSI children begin to develop certain malignancies at a very young age?

Testicular Aging

The association between advanced paternal age and several genetic disorders in humans has been recognized for some time (Auroux et al., 1993). These include achondroplasia, myositis ossificans, Apert’s syndrome, Marfan’s syndrome, Duchenne’s muscular dystrophy, hemophilia A, and the sex-linked recessive disorder bilateral retinoblastoma. This possibility is supported by reports (Cummins and Jequier, 1994) of an association between unexplained male infertility and accelerated testicular aging, which reveals itself in mtDNA deletions, disordered oxidative phosphorylation, and uncontrollable free-radical production. Therefore, certain disorders normally associated with increased paternal age may be associated with male infertility. Nonetheless, the incidence of these conditions is so low that it would take many years of data collection to substantiate these concerns.

RISKS OF INTRACYTOPLASMIC SPERM INJECTION:
ETHICAL CONSIDERATIONS

Many questions, whether “ICSI dependent” or “ICSI independent,” surround the biological prudence of using ICSI. With the rapid proliferation of ICSI, many of these questions will no doubt be answered when researchers examine the children of ICSI as they develop.

Assessing the morality of ICSI is difficult, since many of its risks are speculative. To date, children born with the aid of ICSI are too young to assess whether or not the concerns with the procedure will be realized. Furthermore, patients treated with ICSI accept risks not for themselves, but for their future children. Nevertheless, the rapid proliferation of ICSI demands that its use and inherent risks be discussed in a morally meaningful way.

Some authorities assert that at the heart of the ethical battle are the “right to reproduce” and the limitations that may be imposed on this right. Ethicists have actually distinguished between a positive right to reproduce and a negative one. A negative right is a basic tenet of society that allows individuals to procreate without interference on any level. A positive right states that men and women have not only the freedom to reproduce without obstruction, but also the right to the available assistance to accomplish their goal. Perhaps the ethical questions can be formulated, as follows. Under what circumstance is there a moral obligation to refrain from reproducing? In particular, may assisted procreation be attempted in order to benefit the parents even though the future child is placed at risk? Of course, since the question hinges on the degree and nature of risk that couples, physicians, and society are willing to undertake for the future child, ethical boundaries of such risks must be outlined. Who draws this line and where is it drawn? How can we even begin to know how the future child will cope with his inherited condition? Of course, since the question hinges on the degree and nature of risk that couples, physicians, and society are willing to undertake for the future child, ethical boundaries of such risks must be outlined. Who draws this line and where is it drawn? How can we even begin to know how the future child will cope with his inherited condition? A devastating and debilitating illness to one is a welcomed challenge to the next. These difficulties are only magnified by the many unanswered questions in the biological section.

Some bioethicists (Steinbock and McClamrock, 1994) state that such births are unfair to the child. They invoke the principle of parental responsibility, which requires couples to refrain from having children unless certain minimal conditions are satisfied. These conditions include a fair start at life unencumbered by severe debilitation. Parents should not only be interested in fulfilling their deep-seated desire to reproduce. On the contrary, their primary interest should be the welfare of
Warren states: “There is no harm in non-existing. As Mary Anne not to have children, no harm is brought about. Simply binding the parents to have the child. If a couple decides brought into existence, there is no moral obligation Moreover, even if a child would have a happy life if not to have a child who is destined for a life of misery. In such a case, the responsible parent must put his/her own life branded with pain and overbearing restrictions. In create a child who has a distinct possibility of having a “what is best for my child?” Instead, it is whether to question confronting the would-be parents is no longer interest of the child. But when there is no child at all, the young, the responsible parent will have to consult with the physician and together determine what is in the best choice of the child. Of course, if the child is too of the child. But when there is no child at all, the question confronting the would-be parents is no longer “what is best for my child?” Instead, it is whether to create a child who has a distinct possibility of having a life branded with pain and overbearing restrictions. In such a case, the responsible parent must put his/her own desires aside. Parental responsibility obligates a parent not to have a child who is destined for a life of misery.

Moreover, even if a child would have a happy life if brought into existence, there is no moral obligation binding the parents to have the child. If a couple decides not to have children, no harm is brought about. Simply put, there is no harm in non-existing. As Mary Anne Warren states: Failing to have a child, even when you could have had a happy one, is neither right or wrong... But the same cannot be said of having a child, since in this case the action results in the existence of a new person whose interests must be taken into account. Having a child under conditions which should enable one to predict that it will be very unhappy is morally objectionable, not because it violates the rights of a presently existing person, but because it results in the frustration of interests of an actual person in the future (Warren, 1978).

When applied to the use of ICSI, the parental responsibility principle will hold that it should not be employed until further research unequivocally proves that its use does not bring about harm to children. This “harm” is neither substantial nor devastating. It is simply any ICSI dependent or independent impairment that will put the child at a clear disadvantage in life. While a physician can now counsel a patient and inform him/her, with a great deal of certainty via genetic screening, that there is no risk of passage of their condition to their offspring, there are still many questions, albeit speculative, about the procedure itself. Until additional animal research refutes these suspicions, a responsible couple should refrain from using ICSI.

Although the doctrine of parental responsibility is certainly quite persuasive, several points of objection must be broached. As cited above, people cope with illness and disability in different ways. How can one predict whether a person’s life will be one of misery if born with a certain medical condition? Furthermore, opponents of ICSI suggest (Hewiston et al., 2001) that responsible parents wait until further animal research proves that the myriad of manipulations in the ICSI procedure causes no damage to the offspring it helps produce. For many reasonable people, the current data, although limited, is sufficient evidence to declare ICSI a safe procedure. To engage in further animal research would be a waste, because it will not provide any more knowledge or certainty than what already exists. Animal studies cannot shed light on the long-term implications of ICSI, because animals do not live nearly as long as humans. Moreover, there is no guarantee of safety with any pregnancy. Some speculate (Andre, 1988) that the atmosphere of various urban centers is so saturated with toxic wastes that the children born in these cities might develop abnormally. Should responsible parents move to a safer environment when having their babies? In life, there are no guarantees. Both the fertile and infertile must accept the risks that come with achieving pregnancy through any method. A truly responsible parent is one that, regardless of with what condition the child is born, will never abandon that child and will continue to provide love and care to it for the duration of their lives.

There are many thinkers who think ICSI should be utilized to assist infertile couples. One of today’s foremost spokespersons of “procreative liberty” is John Robertson, who states, “whether one reproduces or not is central to personal identity, to dignity, and to the meaning of one’s life.” For Robertson, the right to reproduce belongs to both the fertile and infertile. Just as a blind person has the right to read, so does the infertile the right to procreate. Robertson writes, the higher incidence of birth defects in such offspring would not justify banning the technique in order to protect the offspring, because without these techniques these children would not have been born at all. Unless their lives are so full of suffering as to be worse than no life at all, a very unlikely supposition, the defective children of such a union have not been harmed if they would not have been born healthy (Robertson, 1994).
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For Robertson and like-minded thinkers, the doctrine of parental responsibility, which seeks to protect children from unnecessary harm, is fundamentally wrong by virtue of its deprivation of life that children born of these techniques receive. It is not at all pleasant to live with disease, but when considering the alternative of not living at all, it is no longer so terrible. This does not imply that procreative decisions need not be restricted. Indeed, procreation is more like a constitutional right that under “compelling” circumstances may be limited. Such instances may occur when reproduction would clearly cause the child to express the wish of not wanting to be born at all. For example, if ICSI would result in the birth of the inevitably fatal conjoined twins (Goldberg et al., 2000). Although there is no reported case law preventing parents from conceiving in such situations, a prudent couple, along with the infertility specialist and genetic counselor, would elect not to conceive.

Subscribers to the “procreative liberty” school would advocate the use of ICSI in almost all cases. But similar to the “parental responsibility” view, this assertion leaves the infertile couple and the treating physician without a clear recommendation. What are compelling reasons that might cause persons to state the wish they were never born? How can we even begin to contemplate what a future child would want? Are not judgments about the value of life too subjective to apply such rigid guidelines? For example, a child born with male infertility might be very happy that he exists and moreover, would be happy to employ ICSI as a means of reproduction. Alternatively, he might be unhappy with his parents who gave birth to him knowing he would have a distinct probability of having the disorder.

However, what about the more severe disorders? Would the ICSI child be satisfied living with the often-severe systemic manifestations of CF or the profound mental retardation and early death of trisomy 13? This is not meant to disparage those who are, or have been, afflicted with these diseases; many CF patients now live into their late thirties or mid-forties with the advent of newer medications and lung transplantation. It does, however, illustrate the complexity of the matter.

CONCLUSION

Only time will tell what whether ICSI is truly a safe and effective procedure. Until that moment, perhaps an intermediate stance is in order. This view places specific limits on the level of risk to be undertaken, and furthermore, on the nature of the risk as well. For instance, ICSI might be acceptable so long as risks do not exceed the rate normally expected in a natural pregnancy. This statement implies that natural risks and experimentally (ICSI dependent and independent) induced risks are interchangeable. While it might be feasible to set limits on the numerical level of risk (and even these values are disputed), it would be quite difficult to set standards for the nature of risk as well. Perhaps a morally pragmatic approach would be to review each case individually and render an ethically sound decision based on the most recent available evidence. Who actually determines if ICSI should be employed in borderline cases; the couple, physician, or both is another question that needs to be addressed and is beyond the scope of this article.

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