Donor insemination and infertility: what general urologists need to know

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SUMMARY

Therapeutic donor insemination (TDI), also known as artificial insemination by donor, is one of the oldest forms of male infertility treatment. With the advent of assisted reproductive technologies and *in vitro* fertilization techniques over the past few decades, the use of TDI in male infertility treatment has decreased dramatically. Knowledge of its use, indications, efficacy, and related psychosocial issues has also declined among urologists treating male infertility. Despite the change in popularity of the procedure, though, TDI remains an appropriate therapeutic option for certain cases of male infertility, particularly in patients who have failed multiple cycles of *in vitro* fertilization/intracytoplasmic sperm injection or in men with no available sperm even after attempted microdissection testicular sperm extraction. Further consideration and research should be focused on the potential uses and indications for TDI.

KEYWORDS artificial insemination by donor, cost analysis, donor insemination, infertility, therapeutic donor insemination

REVIEW CRITERIA

PubMed and OVID MEDLINE searches were conducted using the key words "artificial insemination by donor", "therapeutic donor insemination", "donor insemination", "cost-effectiveness", "psychosocial aspects" and "legal issues". Relevant articles were selected from these searches and references from the identified articles were checked for additional sources.

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INTRODUCTION

Therapeutic donor insemination (TDI), also known as artificial insemination by donor, is one of the oldest methods of infertility treatment, dating as far back as the 18th century.[1] Today TDI, by definition, refers to the noncoital placement of sperm into the vagina, uterus or oviduct of a female patient from a man other than her partner. Although TDI is occasionally used by some authors to describe the use of *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with donor sperm, in the strictest traditional sense, TDI refers to intrauterine insemination (IUI) or intracervical insemination (ICI) of donor sperm.

Roughly two decades ago, more than 170,000 women were treated every year with donor insemination, yielding nearly 20,000 births in the US during 1990.[2] While the Centers for Disease Control and Prevention (CDC) maintains a national database on the use of donor eggs in IVF, no national database or organization exists detailing the current prevalence of donor sperm or TDI use in the US. Since the advent of assisted reproductive technologies in the early 1980s, TDI has declined in popularity and use. This method does, however, remain a viable treatment for infertility. Data from the UK demonstrate a 2-year period (start of 1999 to end of 2000) when roughly 1,800 children were born as a result of insemination via TDI.[3] TDI thus continues to be a reasonable treatment option and should be included among the various therapies discussed with infertile patients.

INDICATIONS

The strongest indication for TDI is male infertility hampering conception. Even with conservative estimates, male infertility accounts for roughly 30% of all cases of infertility among couples in the US.[4] Within male infertility, perhaps the most common indication for TDI is azoospermia. The prevalence of obstructive azoospermia is estimated to be as high as 2–3%.[4] For men opting against microsurgical reconstruction of their

excurrent ductal system, attempts at epididymal or testicular sperm extraction for use in IVF/ICSI is also a viable therapeutic option. In the setting of nonobstructive azoospermia, sometimes no sperm can be retrieved. For other men insurance issues might preclude them from having sperm extraction procedures at all. In such instances, TDI serves as a highly efficacious option for treatment of infertility. Furthermore, many couples with azoospermia or other sperm-related, egg-related, or combined factors cannot become pregnant even after multiple cycles of IVF, with or without ICSI. For patients with such a clinical course, TDI should be presented as an alternative form of therapy.

While TDI remains an excellent option for patients with azoospermia and severe oligospermia, it should also be considered for male infertility due to many other causes. If a male partner has severe genetic defects or if couples have produced offspring with congenital diseases without known carrier status, TDI is an appropriate option. Roughly 10–15% of male infertility can be attributed to identified genetic causes.[5,6] Other indications for TDI include the male partner having a sexually transmissible disease that cannot be eliminated (which includes roughly 0.9% of infertile men)[5] or ejaculatory dysfunction.[7]

In addition to male factor infertility, TDI can be used in other situations: for Rhesus-negative women who are severely Rhesus-isoimmunized and have Rhesus-positive partners; for men or women who have high concentrations of sperm antibodies; or for women wishing to conceive but who lack a male partner.[7] Another indication for TDI exists among patients with monetary constraints precluding the use of IVF, an issue that will be discussed more in depth later.

CONTRAINDICATIONS

Careful screening of the donor is critical before TDI use. In addition to a complete history and physical examination, the FDA requires that all anonymous donors undergo thorough infectious disease screening that includes testing for HIV (types 1 and 2), hepatitis B and C, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, syphilis, cytomegalovirus, human T-cell lymphotropic virus (types I and II) and transmissible spongiform encephalopathies.[8] The FDA does not, however, require this evaluation for directed known donors. In their guidelines, the American Society for Reproductive Medicine strongly recommends screening for several other infectious diseases, in particular West Nile virus, smallpox virus, and severe acute respiratory syndrome, in addition to those required by the FDA.[7] The American Society for Reproductive Medicine also recommends evaluation for risks of infectious disease exposure, such as risky sexual behavior, previous blood transfusion or use of blood products, xenografts or allografts, past incarcerations, or previous intravenous drug use. Contraindications include any positive screening results for the aforementioned diseases. FDA screening protocol also demands that anonymous semen samples be quarantined for a minimum of 6 months and that the donor be rescreened to ensure that seroconversion has not occurred.

Genetic screening for common hereditary diseases, such as cystic fibrosis in white men, sickle cell disease in African Americans, and Tay–Sachs disease in donors of Jewish descent, should likewise be part of standard screening.[7] Any positive genetic test results for potential donors would constitute a contraindication to TDI.

Donor sperm should also be tested for minimum standards of normal sperm quality. Specifically, according to the WHO, sperm motility should be greater than 50%, normal sperm morphology better than 30%, and semen concentration higher than 20 million sperm/ml.[9] Donor sperm failing to meet these standards should not be used for TDI.

Another important feature of donor screening involves a thorough psychological evaluation of potential donors and recipients, especially in cases of directed, known donation. This evaluation should include counseling for potential donors and recipients, assessment of the impact of donation on relationships between the donor and recipient, as well as an evaluation to check for donor coercion (financial or emotional),[10] which would represent a contraindication to TDI.

Other contraindications to TDI relate to female factors of subfertility or infertility. Women with tubal factors, uterine malformations, active uterine infections, or anovulation should not undergo the procedure.

TECHNIQUES FOR INSEMINATION

For infertile couples undergoing treatment by TDI, several prognostic and technical factors should be taken into consideration. The characteristics of the sperm used for insemination, including the total motile sperm count and

sperm morphology, will influence the prognosis of treatment success. Typically, for donated sperm, these parameters are normal and robust, meeting the minimum WHO standards outlined above. Female factors should also be taken into consideration, including maternal age, ovulatory function, and uterine/tubal anatomic factors.

Artificial insemination can be performed via deposition of sperm into the cervical os (ICI) or by deposition of sperm directly into the uterus (IUI). ICI may be performed with either unwashed or washed sperm (i.e. devoid of seminal plasma), while only washed sperm is used in IUI.[11] For various reasons, but most importantly because of its notably better success rates, IUI is now the preferred method of artificial insemination.[12]

Several established methods may be used for preparation and washing of sperm, including conventional sperm washing, the so-called swim-up procedure, and density gradient centrifugation. Further details on these methods can be found in the descriptions by Speroff and Spitz.[12]

The issue of ovarian stimulation should also be addressed with couples undergoing TDI. Studies have shown that TDI with ovarian stimulation achieved by use of clomiphene citrate yields pregnancy rates similar to those with natural cycle TDI.[13] By contrast, TDI with ovarian stimulation achieved by gonadotropin hormones has been shown to result in a two-fold increase in pregnancy rates compared with those in women either receiving clomiphene citrate or no stimulation, although at the cost of a higher risk of complications.[13]

OUTCOMES AND EFFICACY

TDI has been proven to be an effective method of treatment for infertility. In a randomized study of fertile women undergoing either IUI or ICI with frozen donor sperm, the investigators found an overall pregnancy rate of 37%.[14] The study also demonstrated monthly fecundity rates of 15% and 9% with IUI and ICI, respectively. Other studies have shown similar outcomes with TDI. One randomized trial examining TDI with frozen donor sperm demonstrated a 19.4% clinical pregnancy rate per IUI cycle and a cumulative pregnancy rate of 75.4% after six cycles.[15] In another study of patients undergoing TDI with frozen donor sperm, a 22.3% clinical pregnancy rate was reported per cycle, with a 61.1% birth rate per couple after a mean of 3.2 treatment cycles.[16]

While TDI has good success rates, the number of couples infertile due to male factor infertility who achieve genetically related offspring has risen with the use of sperm retrieval techniques plus IVF/ICSI. Studies have demonstrated promising results with these methods in infertile couples, particularly in cases involving an azoospermic male. In a study examining microsurgical epididymal sperm aspiration, percutaneous epididymal sperm aspiration, and testicular sperm extraction with IVF/ICSI in obstructive azoospermic men, the investigators reported a combined 33% clinical pregnancy rate, and a success rate of 25.6% per treatment cycle.[17] Results of a study by Palermo *et al.*[18] are more impressive, with clinical pregnancy rates of 56.1% among obstructive azoospermic men and 49.1% among nonobstructive azoospermic men after using either microsurgical epididymal sperm aspiration or testicular sperm extraction plus IVF/ICSI.[18] In this study, the ongoing pregnancy and delivery rate was 50.6% in the obstructive azoospermic group and 39.6% in the nonobstructive azoospermic group. In general, other studies examining sperm retrieval techniques plus IVF/ICSI demonstrate a pregnancy success rate of around 30%, which compares favorably to the national results for IVF/ICSI published by the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology.[19–21]

Despite study results demonstrating that sperm retrieval plus IVF/ICSI is clearly an excellent treatment option for male infertility due to either obstructive or nonobstructive azoospermia, the success rate is not 100% even with repeated IVF/ICSI cycles. In a study of couples with initial fertilization failure after IVF/ICSI, repeat IVF/ICSI has demonstrated a clinical pregnancy rate of 45.4% and a delivery rate of 36.3%.[22] In another study of repeat IVF/ICSI cycles, Westlander *et al.*[23] reported ongoing pregnancy and delivery rates in the obstructive azoospermic group of 18.2% with the first cycle, 52.4% with the second, and 25.0% with the third. In the nonazoospermic group, ongoing pregnancy or delivery rates were 8.3% in the first cycle, 17.6% in the second, and 7.1% in the third. Despite the success rates for IVF/ICSI using a patient's own sperm, TDI has the potential to have a major role in the treatment of male factor infertility, as has been demonstrated by one study of couples with severe male factor infertility that failed to conceive with IVF/ICSI.[24] The authors found a

cumulative pregnancy rate of 84% within seven cycles using IUI with frozen donated sperm, with a pregnancy rate per cycle of 27.9% and a live birth rate of 24.6% per cycle.

For patients choosing to pursue TDI, IUI has been shown to be roughly twice as effective as ICI in fertile women, as discussed above.[14] IUI with ovarian stimulation by gonadotropins also results in higher pregnancy rates (23.9%) than the natural cycle (12.5%) and ovarian stimulation by clomiphene citrate (13.1%).[13] Studies have shown poorer outcomes with IUI for women older than 35 years than for younger women, both with and without ovarian stimulation.[25,26] Also, a recent article suggests that for women older than 37 years, natural cycle IUI may be more effective than IUI with ovarian stimulation.[27] Couples with an older female partner should, therefore, carefully consider the use of ovarian stimulation given its outcomes and associated risks, including ovarian hyperstimulation and multiple gestation.

COST ANALYSIS

While sperm retrieval techniques and ICSI technology have revolutionized the treatment of male infertility, these methods of therapy are not without disadvantages. Perhaps chief among them are issues of cost and lack of insurance coverage for the treatment.

IUI, with or without female hormonal stimulation, has reported costs ranging from US$7,800 to $10,300 per delivery.[28,29] Cost per delivery with sperm retrieval techniques and IVF/ICSI range from $63,357 to $81,685, with an average cost of $73,146 when accompanied by testicular sperm retrieval techniques, and an average of $71,896 when epididymal sperm retrieval is concurrently performed.[30] In a cost-effectiveness study of IVF/ICSI, Schlegel[31] found the average cost to be $89,091 per delivery, with a best-case scenario cost of $62,263 based on the highest published success rates for IVF/ICSI. In these cost analyses for IUI and IVF/ICSI, factors such as missed work, lost wages, and complications were included in the analysis. However, while the costs of IUI are well established, the end costs of donor sperm for use in IUI are difficult to estimate because of the wide variance in price per donated sperm sample and the absence of price regulation. Few published data exist on costs per vial of donor sperm. In general, retail costs range from $200 to $400, but can reach as much as several thousand dollars based on donor characteristics.[32] As such, the total cost for TDI is likely to range from several hundred to several thousand dollars more than the aforementioned costs per delivery for IUI with nondonor sperm.

While costs for TDI are not well established in the US, a Swedish study directly compared costs of donor insemination and IVF/ICSI. The total costs per delivery were SEK88,900 and SEK174,900 for donor insemination and IVF/ICSI, respectively.[33] At the time of the study, SEK100 converted to approximately US$15.[34] The saving for use of TDI is, therefore, around 50% when compared with the cost of IVF/ICSI.

In a related study examining the cost-effectiveness of IVF in general, the authors estimated that the costs per delivery typically ranged from US$66,667 for couples requiring one cycle to $114,286 for couples requiring six cycles.[35] The authors also calculated IVF costs for couples deemed to have a reduced chance of success, defined as couples with a diagnosis of male infertility and a female partner older than 40 years of age. For this subgroup, they determined costs ranging from $160,000 for the cumulative care through and including the first cycle to $800,000 for cumulative care through and including the sixth cycle. This study is unusual because the cost analysis included the probabilities of success per cycle and cost estimates for subsequent treatment cycles after a failed cycle, in addition to the usual economic costs of lost wages, missed work, multiple gestations, and complications. These issues of failed cycles, additive costs, and probabilities for subsequent success were not broached in the cost analyses mentioned above, in which pregnancy rates for each treatment cycle were independently computed. The estimated costs in that study were, however, determined using much lower probabilities of success per IVF cycle and should, therefore, be considered very outdated. Nonetheless, in couples in which multiple cycles of IVF/ICSI have failed, the sum total costs of treatment are probably greater than previously thought.

While calculated costs of TDI and IVF/ICSI differ substantially, monetary issues should also be considered in the context of insurance coverage. According to data published in 2002, only four US states at that time (IL, MA, NJ, and RI) had laws requiring Health Management Organizations and health insurance companies to provide complete coverage for the costs of infertility diagnosis and treatment.[36] Five states (AR, HI, MD, OH, and WV) had laws requiring

partial coverage, defined as maximum lifetime coverage up to $15,000, coverage of only a portion of the costs or, specifically, provision of coverage by a Health Management Organization. At the time, the remaining 42 states and districts provided no coverage, with some not offering infertility treatments at all.

Although some time has passed since the publication of that study, the current insurance climate is similar to the one described. As such, with roughly 10–15% of the population considered infertile, the vast majority of patients using infertility treatments today do so without insurance coverage. Most patients, therefore, obtain access to infertility treatments, including TDI, through the numerous privately owned and operated infertility clinics and sperm banks, and pay for these services personally. In this context, the cost difference between TDI and IVF/ICSI becomes even more notable. At the same time, the value of having genetically related offspring cannot be reasonably calculated for many couples, making the issue of monetary cost irrelevant to them.

LEGAL, ETHICAL AND PSYCHOSOCIAL CONCERNS

While TDI has been available for decades as a viable infertility treatment, a myriad of legal, ethical, and psychosocial concerns exist over its use. In the US, no national laws exist governing the practice of TDI. On the contrary, in the UK, a national regulatory body, the Human Fertilisation and Embryology Authority, regulates and governs the practice of TDI. Similar organizations exist in other European nations. In the US the FDA has produced guidelines establishing minimum standards for donor sperm screening and testing, but the practice of TDI is generally governed on a state-by-state and municipal basis.

Most states have laws that establish the rights of recipient parents of children born by artificial insemination and eliminate the parental rights of the donor. A handful of states, however, have yet to establish such laws. In most states, anonymous sperm donors have no legal rights or responsibilities regarding the TDI children and no legal rulings have yet signified otherwise. Known sperm donors might, however, be considered the legal parents of the TDI child and be subject to similar rights and responsibilities as a recipient parent. In two recent rulings in Pennsylvania, Ferguson versus McKiernan[37] and Shultz-Jacob versus Jacob and Frampton,[38] the courts determined that in cases of known donors, the sperm donor is subject to the same duties and responsibilities accorded to the recipient parents. In these two cases, the known sperm donor was held liable for payment of child support to his donated, biological child. Importantly, both courts' decisions first and foremost upheld the rights and wellbeing of the child. As such, patients undergoing donor insemination with a known donor should be advised to seek the counsel of a lawyer to gain specific information about the laws of their state.

In addition to the ongoing legal debate, concerns over secrecy, privacy, and disclosure remain prominent sources of controversy. In the past few years, the issues of donor anonymity and disclosure have risen to the forefront of this debate. Several European countries have passed legislation banning anonymous sperm donation. Countries such as the UK, Netherlands, Norway, Switzerland, and Austria have joined Sweden and Italy as European nations where anonymous sperm donation is prohibited.[39] Advocates for anonymous sperm donation have decried these changes and predicted substantial declines in sperm donations in these nations,[40] citing the 85% decrease in donations in Sweden after the introduction of a ban there in 1985.[41] On the other hand, preliminary data from the Human Fertilisation and Embryology Authority, although limited, do not substantiate these concerns in the UK.[42] Nonetheless, throughout Europe growth has been seen in the so-called medical tourism or fertility tourism industry. Large numbers of patients native to countries such as Sweden who require sperm have traveled to Denmark, France, and other countries where there is no shortage of anonymous sperm donors.[43]

Most parents of children born through artificial insemination do not disclose the donor conception to the child.[44] This secrecy and lack of disclosure has been cited as possibly being damaging to the child and to parent–child relationships.[45] Several studies have been conducted to examine the possible consequences of disclosure on the well-being of the child, the relationship between the child and parents, and the relationship between the parents themselves.

In one study, the authors discovered that mothers who disclosed donation status to their children self-reported less parent–child conflict, viewed themselves as more competent parents, and perceived fewer conduct issues with their children than mothers who did not disclose.[46] On

the other hand, there was no difference in these self-reported results for fathers who disclosed donor status or for the children's teachers to whom the children's status was disclosed. Overall, measures of child adjustment, marital relationships, and parent–child relationships were equal between disclosers and nondisclosers in the study. These results are supported by other studies examining disclosure. Authors of one study found that the decision regarding disclosure had no impact on the parental bonding or the child–parent relationship and concluded that disclosure or lack thereof would not be detrimental to relationships in families with TDI children.[47] In another study, the authors examined teenagers born through TDI who already knew about their conception status. The researchers found that many of youths (80%) reported feeling comfortable with the knowledge and stated that the disclosure had neutral or positive impacts on their family relationships.[48] In a related study assessing parents of children for whom the donor was willing to be known, nearly all parents had told their children early on about their conception circumstances and had experienced neutral to positive impact of the disclosure.[49]

Beyond questions of disclosure and its impact on families, studies have found that, in general, children born through donor insemination are well adjusted and have good relationships with their parents. In addition, these children display normal intellectual, psychomotor, and language development as compared with naturally conceived children.[50–53] In one study of 12-year-old children and their families, the authors found that TDI children and mothers displayed significantly increased feelings of warmth and closeness as well as decreased feelings of aggression and control during disciplinary interactions as compared with mothers and naturally conceived children.[54] In this study, child psychologists unaware of the conception method also evaluated the children independently, assessing their socio-emotional wellbeing. Children in the TDI group were found to exhibit fewer conduct problems than children in the natural conception group; no differences were found in school performance or peer relationships. The study also found no differences in marital relationships between parents in either group, which supports the findings of previous studies that examined couples who underwent TDI.[44]

Situations with known or related donor insemination present further ethical, legal and psychosocial dilemmas. Financial incentives, emotional coercion or unhealthy family dynamics might arise in such circumstances, compromising the integrity of donor insemination practice. In a study of related donors, Marshall[10] explores some of the various possible scenarios for intrafamilial sperm donation, including inter-generational and sibling-to-sibling donation. Some related donations arise out of a desire to prevent transmission of known parental genetic diseases or traits. The use of related donor sperm is not, however, always medically appropriate; comprehensive genetic counseling should still be conducted for relatives. In addition, the emotional risks involved in related donation, especially with regard to the potential impact on relationships between donor, recipient, and child, should be addressed through psychological screening and counseling. Furthermore, as discussed above, legal issues regarding disclosure and parental rights and responsibilities should also be explored with the aid of legal counsel. If any concerns arise alternative options, such as anonymous TDI, should be recommended.

Another area of ethical and legal concern over TDI surrounds the issue of maximum number of births per sperm donor. Several studies have examined this subject using mathematical probabilities to estimate the number of consanguineous pairings of TDI children. Estimates range from one mating per century to one per 19 years.[55,56] Similar mathematical models have been used to delineate maximum allowable limits of donor sperm use. On this basis, in the Netherlands 25 is the maximum number of offspring per sperm donor allowable by law; in the UK 10 is the legal limit.[57–60] By contrast, in the US no laws limit the number of donor sperm uses. A suggested number of 292 has been calculated[56] but no reported uses have led to a single donor exceeding 50 offspring.[56] Since the number of offspring remains a source of possible concern in the US, care should be taken by potential recipients to obtain donor sperm from reputable infertility clinics and sperm banks where complete records are maintained.

Related to the issue of maximum sperm donor use, concerns over transmission and heritability of genetic diseases also exist. Over the course of the past few decades, several cases have been reported of sperm donors who were found later in life to have inheritable diseases or who might have had transmissible genetic diseases masked by mosaicism.[61–64] Some of these case reports

were, however, published at a time when genetic screening was rarely done and many of these diseases are now included in thorough genetic screening. It is also important to note that IVF/ICSI, but not IUI, are associated with significantly higher risks of congenital malformations and birth defects than natural conception.[65–67] Thus, potential risks of any infertility treatment should be carefully discussed with and considered by patients.

CONCLUSIONS

Despite excellent outcomes with the use of TDI, favorable results seen with assisted reproductive technologies coupled with strong desires for genetically related offspring present an understandably clear choice to many infertile couples with male factor infertility. Regardless of the substantial differences in cost, many couples with even the most severe form of male factor infertility, nonobstructive azoospermia, will initially attempt to conceive through sperm retrieval and IVF/ICSI. Failure to achieve pregnancy with such methods does, however, remain a possibility for many couples. Although such a prognosis of treatment failure is distressing to both the couple and the urologist, urologists should remember to offer TDI as a possible option.

With a dearth of information on patients failing treatment with sperm retrieval and IVF/ICSI, further studies are needed to better elucidate their numbers and to examine their subsequent rates of success with TDI.

KEY POINTS

- Despite becoming an increasingly obscure form of infertility treatment, therapeutic donor insemination (TDI) has a role in the armamentarium for treating male infertility
- TDI is a potential treatment option for all couples with male factor infertility, including those who have failed multiple cycles of *in vitro* fertilization or intracytoplasmic sperm injection and/or who are unable to afford the high expense of these therapies
- While the risks associated with TDI should be discussed with patients, the prevailing evidence has shown that it is a safe treatment option for infertility
- Vast regulatory differences exist between countries and between states and provinces within countries; thus, relevant legal, safety, ethical, and psychosocial counseling must be provided to all patients considering TDI

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