# Therapeutic donor insemination for LGBTQ+ families: a systematic review

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**Importance:** Lesbian, gay, bisexual, transgender, and queer+ (LGBTQ+) families deserve evidence-based care within environments designed for their unique needs; however, care provided in fertility clinics has been reported to fall short, most notably for assigned female at birth recipients of therapeutic donor insemination (TDI).

**Objective:** To identify the aspects of routine infertility care that are clinically appropriate for this unique patient population, specifically those seeking pregnancy with donor sperm. The research question was posed, "What screening and treatment protocols are supported by the evidence regarding TDI care for LGBTQ+ families?"

**Evidence Review:** High quality, prospective studies specific to and/or inclusive of this patient population in assisted reproductive care contexts is limited, however evidence regarding age-informed prognosis, screening guidelines, treatment outcomes, insemination timing, number of inseminations per cycle, when to refer, and safety of the procedure were found.

**Findings:** Findings indicate that compared with routine infertility care protocols, a low-tech, low-intervention model of care for ovulatory LGBTQ+ individuals renders equal or higher success rates without increasing risk.

**Conclusion:** Given the current evidence, TDI for LGBTQ+ families can, with support and training, be provided appropriately in a variety of contexts, including community-based and primary care settings as well as in fertility clinics.

**Relevance:** This review establishes the current state of the evidence supporting TDI for LGBTQ+ families, expanding access to care for recipients as well as their care providers and outlining areas for further study. (Fertil Steril® 2024;■:■–■. ©2024 by American Society for Reproductive Medicine.)

**Key Words:** LGBTQ+, lesbian, same-sex, insemination, TDI

The definition of infertility established by American Society for Reproductive Medicine (ASRM) in 2023 is inclusive of a sexual history that demonstrates the need for donor gametes to achieve a pregnancy (1). Although infertility can occur in any population, it stands to reason that the physiological capacity to conceive and carry a pregnancy is not directly impacted by a social factor such as sexual orientation. As a scientific concept, sexual orientation consists of attraction, behavior, and self-identification (2). Although certain behaviors can impact the physical body, and population risks should inform clinical care, just because an individual experiences romantic or sexual feelings or opts to build their life with a person of the same-sex does not mean their body's reproductive system is inherently disabled.

The utilization of a social factor to establish a clinical indication for care may help broaden access for lesbian, gay, bisexual, transgender, and queer+ (LGBTQ+) families; however, the conflation of same-sex orientation to a diagnosis of pathological infertility is of questionable clinical utility in the absence of any actual indication of pathologic infertility in the individual. Notably, same-sex assigned female at birth (AFAB) couples receiving care in fertility clinics report being routinely treated for infertility regardless of indication, including invasive tests, costly procedures, and medications with adverse effects (3). Lesbian, gay, bisexual, transgender, and queer+ families report that the care they receive in fertility clinics largely feels unsupportive of and/or unable to address their specific health care needs (4), whereas, on the other hand, they convey a high level of satisfaction with community-based and primary care providers such as midwives, doulas, and public health nurses, as well as services centered on LGBTQ+ parents (5).

Those seeking pregnancy with donor sperm can inseminate on their own without accessing clinical care; however, cryopreserved sperm samples are more effective with the intrauterine insemination (IUI) procedure (6), which requires a clinician. The IUI procedure is also used to assist heterosexual couples with infertility; however, when

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The appropriate checklist of the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols for this study design was followed.
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donor sperm is used, the practice is known as therapeutic donor insemination (TDI). Therapeutic donor insemination is a low-tech, relatively noninvasive procedure that consists of placing a prepared sample of donor sperm into the uterus with a sterile catheter (7). Potential donors are screened, and sperm samples are quarantined to ensure negative sexually transmitted infection status before release from sperm banks. Samples can then be obtained from a sperm bank as "IUI-ready" so that no further processing is needed in the clinic before the IUI procedure. Aside from a simple thaw procedure, insemination requires similar procedural skills as a pap smear or intrauterine device placement. However, TDI is typically more straightforward and more easily tolerated than intrauterine device placement because the cervix is soft and the cervical os is open during ovulation when the procedure occurs. Worldwide, the TDI procedure is performed by a range of providers, including midwives, nurses, and physicians, and the success of the procedure has not been shown to be influenced by provider type (8).

With this basic background and to inform evidence-based TDI practice for LGBTQ+ families, a systematic review of the literature was performed with the research question, "What screening and treatment protocols are supported by the evidence regarding TDI care for LGBTQ+ families?"

Note to the reader: although terminology varies within the literature, this article uniformly utilizes the terms "AFAB" and "LGBTQ+" to encompass the broad range of sexual orientations and gender identities represented among nonheterosexual recipients of TDI, who are all AFAB individuals.

## MATERIALS AND METHODS

A PubMed search was conducted on July 18, 2024, using the search terms "therapeutic donor insemination" and included articles from January 1, 2000, to June 2024, in English, specific to biomedical research regarding TDI care for ovulatory AFAB individuals. Opinions, ethics statements, psychosocial studies, animal studies, and studies focusing on sperm donors or offspring, those limited to autologous sperm samples, and/or those with only clinically infertile subjects were excluded. To minimize the influence of data drawn from clinically infertile subjects, studies that were expressly limited to heterosexual couples were also excluded. One review was identified extraneously because it is referenced in multiple articles due to its specificity regarding lesbian conception; however, the title does not contain any of the search terms (9). Studies were excluded when they were reflective of practices that have become obsolete, such as the use of fresh anonymous sperm samples.

From the original 578 search results, an inclusion set of 45 articles was reviewed for methodological quality. To compile the entirety of available research regarding TDI care, most of the studies included in this review are retrospective in nature; however, conclusions drawn from randomized controlled trials and systematic reviews are emphasized in the results and discussion.

Data specifically linked to sexual orientation and gender identity is sparse but growing. Commonly in TDI research, same-sex female couples, single women, and heterosexual couples with male infertility are combined to increase the sample size and analytical power of the results. As noted above, research limited to only heterosexual couples was excluded. Studies were included when data from LGBTQ+ families was measured independently (7 studies) or in combination with other populations (25 studies), even when the inclusion of LGBTQ+ families was not specifically stated but could logically be presumed (13 additional studies).

## RESULTS AND DISCUSSION

### Overall, LGBTQ+ TDI recipients do not exhibit patterns of infertility

Up to 88.9% of AFAB couples are able to achieve a live birth (LB) through assisted conception, and among those who conceive via TDI, the average number of cycle attempts is 3 (10), which is far short of the 6–12 unsuccessful cycle attempts necessary for a diagnosis of clinical infertility in the heterosexual population. Assigned female at birth couples have even been shown to have a higher pregnancy rate in TDI than single women (11). As a group, AFAB couples do not exhibit specific causes of female infertility—except possibly polycystic ovary syndrome, but available studies are contradictory (12). Assigned female at birth couples have equivalent or higher LB rates (LBRs) than heterosexual female partners seen in fertility clinics (9, 13). Overall, pregnancy and LBRs are higher in TDI than IUI with sperm from a heterosexual male partner (14), although this benefit fades for TDI recipients aged >38 years who are treated with ovarian stimulation (15). In contrast to heterosexual couples experiencing unexplained infertility, in whom pregnancy rates decrease with each subsequent cycle attempt, LGBTQ+ TDI recipients demonstrate a consistent per cycle pregnancy rate up to at least six cycles (16).

### Among ovulatory TDI recipients, age is the most important factor in the potential for success

A basic menstrual history can detect the prevalence of ovulatory cycles 99.5% of the time, although occult anovulation can be present in those with hirsutism (male pattern hair growth on the face, lower abdomen, back, or chest, hair loss, and/or acne, without having received exogenous testosterone treatment). Ovulation can be confirmed with a serum progesterone level >3.0 ng/mL drawn on cycle day 22 or 1 week before expected menses (17). Female fecundity naturally declines with age (18), and thus far age is the only factor found to impact pregnancy rates in ovulatory recipients of TDI (19, 20). With advancing age, the cumulative TDI pregnancy rate decreases, and the steepest rate of decline occurs in patients aged ≥40 years (21). According to a large, multicentric cohort study that tracked single women and lesbian couples, at an age of good prognosis for assisted conception (aged ≤37 years), the per cycle LBR in TDI is approximately 17% (22). Chances of TDI success decline as recipients aged from 38–42 years (23). By age 43 years, TDI LBRs are <2%, regardless of medication protocol (24).

## Age may impact decision-making regarding route to pregnancy in LGBTQ+ families

Although families that consist of more than one partner with the capacity to contribute oocytes and/or carry a pregnancy may present for care specifically seeking TDI, there is evidence to inform the creation of an overall family building plan that considers various methods of conception in light of age and health of each of the partners. When more than one partner is willing and able to provide oocytes—even when one does not wish to gestate the pregnancy—there is a greater likelihood of LB because the partner who contributes oocytes can be selected on the basis of age and other factors that impact egg health. This advantage is seen in TDI pregnancy as well as in vitro fertilization (IVF) or reciprocal IVF (R-IVF), an option unique to AFAB couples in which one partner carries a pregnancy created with the other partner's oocyte (10). In vitro fertilization treatments and outcomes are similar whether embryos are created with donor sperm or partner sperm (25). Among single AFAB individuals and LGBTQ+ families, prognosis for LB is similar between IVF and TDI when adjusted for age (26). More work remains to be done as one retrospective treatment comparison shows a per cycle pregnancy rate of 18% in IUI, 50% in IVF, and 77% in R-IVF (27), and another prospective study demonstrated a per cycle pregnancy rate in R-IVF at 45.3% vs. 21.8% in TDI (28).

Given current comparate age-related success rates, at ages <38 years old, TDI may be preferable in terms of both cost and risk, given that TDI cycles are much less expensive ($1,500–$3,000 vs. $15,000–$30,000 for IVF) and many families conceive within just a few cycles. However, when the family is planning one or more pregnancies at age ≥38 years and the prognosis is good for at least one partner to create enough embryos for future pregnancies using IVF with subsequent frozen embryo transfer, they may find that IVF is the most secure and cost-effective method. The same may hold for ovulatory AFAB individuals who present for care at age 40–42 years, in whom one cycle of IVF with intracytoplasmic sperm injection demonstrates a cumulative delivery rate equivalent to six cycles of TDI (29). By age 43 years, ovarian stimulation generally ceases to be effective for increasing the LBR in IVF as well as TDI (24).

## Measures of ovarian reserve do not predict the likelihood of conception in TDI

It is well known in fertility medicine, but commonly misunderstood by the layperson, that ovarian reserve does not accurately determine the likelihood of pregnancy. Measures of ovarian reserve have only been shown to predict the likelihood of response to ovarian stimulation as part of medically assisted reproduction. Many fertility clinics perform ovarian reserve testing routinely for all patients establishing care, including LGBTQ+ people seeking TDI. However, neither serum nor ultrasound indicators of ovarian reserve have been shown to inform the clinical prognosis of TDI in those without indications of clinical or pathological infertility. Serum antimüllerian hormone level is not predictive of pregnancy in noninfertile recipients of TDI (30). Similarly, when adjusted for age, no difference has been shown in per cycle or cumulative pregnancy rates among those with very low, low, average, or high antral follicle counts, and antral follicle count has not been found to predict the rate of pregnancy or miscarriage in unstimulated TDI cycles (31).

## Those opting for donor conception who have no indication of infertility can expect the best treatment outcomes in natural, unmedicated TDI cycles

Regarding the type of procedure, IUI is superior to "intracervical" insemination (ICI), which is thought to be because of the deposit of sperm closer to the oocyte, which compensates for the diminished quality of sperm samples after freezing and thawing (32, 33). Earlier, retrospective studies failed to show a benefit to IUI over ICI (34); however, a recent randomized controlled trial demonstrated that the overall likelihood of LB within six cycle attempts was up to 63% higher for IUI recipients than for ICI recipients at age 30–38 years (6).

Regarding medication treatment in TDI, research has repeatedly demonstrated a sharp increase in the risk of multifetal pregnancy without any clinically significant benefit toward increasing the overall likelihood of pregnancy when ovarian stimulation is used in TDI recipients (16, 19). Stimulated TDI cycles result in a multifetal pregnancy rate of approximately 11% with clomiphene citrate and 8.7% with letrozole (35) whereas unstimulated cycles show multiple pregnancy rates equivalent to the general population (2.4%) (36). This represents a >400% increase in the likelihood of inducing a high-risk pregnancy when ovulation stimulation is used in TDI. Among TDI pregnancies, the risk for poor perinatal outcomes (low birth weight, preterm delivery, and congenital disorders) is only increased in multifetal pregnancies (37). One small retrospective study showed increased cumulative pregnancy rates in medicated TDI cycles for recipients aged >40 years or with antimüllerian hormone levels <1.2 ng/mL and after three unsuccessful natural cycle TDIs. However, the relative benefit must be on balance with the incidence of twins, which was even higher at 23% in the medicated group in this study (38). A much larger study demonstrated no significant benefit to ovarian stimulation at any age group in TDI, including those aged >40 years, nor was any benefit demonstrated up to at least six cycle attempts (16).

## TDI can be accurately timed with simple, at home urinary luteinizing hormone tests, which show equivalent or better success rates over ultrasound monitoring and human chorionic gonadotropin trigger

In TDI, routine practice is to perform IUI approximately 24 hours after detecting the onset of the luteinizing hormone (LH) surge (serum or urine) or 36–40 hours after human chorionic gonadotropin (hCG) injection is administered when a dominant follicle is identified on ultrasound at >16–17 mm (23, 24, 26, 28). The difference in cost between the two

methods is significant for many families, both in terms of direct expenses of at home LH test strips vs. out-of-pocket costs of ultrasound and injected medication, as well as other expenses associated with additional clinic visits (e.g., time away from work, childcare, transportation, and others).

The LH surge can be detected using clinical serum tests or at home with low-cost urine test strips. Timing insemination 1 day after the detection of an LH surge has resulted in a 19.7% clinical pregnancy rate (39). The LH surge begins most often around noon; however, for the individual, multiple urine tests can be used to identify the onset of the surge within a few hours. (40). When IUI is timed using the onset of the LH surge rather than an hCG trigger, the ongoing pregnancy rate is higher and the follicular phase longer, which may indicate that the hCG trigger interrupts the natural cadence of ovulation in a way that inhibits ample development of the oocyte and decreases the likelihood of a viable pregnancy (41). One prospective study showed comparable LBRs among timing approaches for normo-ovulatory women aged $\leq$40 years and recommended that a method of timing be chosen on the basis of the availability of clinical staff to perform inseminations on the weekend or recipient choice on the basis of cost or preference for self-monitoring vs. monitoring in the clinic (35).

Some studies have looked even more closely at the number and timing of TDI cycles, including Blasco et al. (14) whose retrospective study in 2014 showed a higher pregnancy rate when TDI was performed concurrently with ultrasound evidence of follicle rupture during a period of high uterine contractility, conveying that timing IUI on the day of ovulation is vital because of the attrition that occurs within a few hours for cryopreserved donor sperm (14). This, plus a paucity of data to demonstrate any benefit of more than one insemination per cycle (42, 43), especially in single and lesbian women (44), suggests that correct timing is a more critical parameter than the number of insemination procedures performed in the IUI cycle.

## TDI is a safe, low-risk procedure

As confirmed by a systematic review, the incidence of pelvic inflammatory disease after TDI is extremely low (0.0001%–0.0003%), even lower than IUI with partner sperm (0.021%) (45). Multiple systematic reviews and meta-analyses have confirmed that the primary risks associated with TDI are preeclampsia and hypertensive disorders of pregnancy (46–49). In spontaneous conception as well as in TDI, preeclampsia occurs at a higher rate when exposure to the sperm source is short, which is theorized to be because of immunologic factors present in the uterus and impacts on placental implantation, which may be decreased with repeated exposure to the sperm source, which is less likely with TDI. A lower incidence of gestational hypertension and preeclampsia is seen in TDI recipients exposed to three or more cycles of TDI (50).

## CONCLUSION

Currently, evidence-based clinical care for TDI recipients consists of screening for infertility, providing prepregnancy care, and performing the IUI procedure, all of which can be accomplished in primary and community-based care settings as well as fertility clinics. The ASRM fertility evaluation guidelines mirror those from all disciplines in which prepregnancy care is typically provided (American Academy of Family Physicians, American College of Nurse-Midwives, and American College of Obstetricians and Gynecologists), including a comprehensive medical, reproductive, and family history; physical examination; routine preventive health maintenance; screening for relevant genetic conditions; and basic prepregnancy care. The guidelines state that initial emphasis should be placed on the least invasive methods for the most common causes of infertility, which in most cases involves no more than a thorough menstrual history. Specifically regarding TDI recipients, ASRM guidelines state that tubal patency screening (an often painful and expensive procedure) and assessment of the uterine cavity should be tailored on the basis of medical history and risk assessment, not required as a routine aspect of TDI care.

ASRM guidelines also state that care should be expeditious and cost effective. However, the additional testing and cycle monitoring typically required by fertility clinics increase costs without improving TDI outcomes. In addition to the financial impact, limiting the provision of TDI treatment to fertility clinics decreases access to care because of long wait times and/or lack of proximity to a fertility clinic in many areas. The inequity in the provision of evidence-based care for recipients of TDI is exacerbated by the overall dearth of fertility clinics offering LGBTQ+ sensitive care environments (4). This general lack of responsiveness to the needs of LGBTQ+ families contributes to the overall inequity experienced by this marginalized population in the process of childbearing.

Although TDI care can be safely and appropriately performed in community-based and primary care settings, providers in these settings may falsely assume that they do not possess the knowledge and skills to perform TDI. However, screening of TDI recipients typically requires no more than a health history and basic physical examination, and those with signs or symptoms of infertility can and should be referred to a higher level of care. For those with regular menstrual cycles between 21 and 35 days, additional testing to confirm ovulation is not required unless patients demonstrate hirsutism. The evidence supports a good prognosis for TDI for individuals aged $<$38 years within six natural, unmedicated treatment cycles, which is well within the scope of any provider of basic pelvic care and requires no knowledge of medical infertility treatment. Furthermore, TDI is typically best timed approximately 24 hours after in-home detection of a spontaneous LH surge, which means care providers need not perform ultrasounds as part of TDI care.

Patient counseling regarding methods of conception and prognosis in relation to age can be provided by any community-based or primary care practitioner who puts their mind to it, which is a common practice among providers who opt to specialize in caring for populations that are marginalized in mainstream health care contexts, including LGBTQ+ care. Similarly, community-based providers who maintain availability for labor management and emergent concerns during

pregnancy may find that it is perfectly feasible to offer IUI procedures concurrent with spontaneous ovulation, especially given the 24-hour lead time and opportunity for maintaining continuity of care throughout the entire pregnancy process.

Care providers outside of fertility clinics may also worry that they are not able to provide the adjunct care recommended for recipients of donor gametes, including psychoeducation regarding donor-conceived family building and legal consultation. However, although fertility clinics typically require patients to consult with a mental health provider at their facility, TDI recipients who receive care in primary and community-based settings can access psychoeducation via referral to a qualified mental health professional, preferably one who specializes in serving LGBTQ+ families. Similarly, regardless of the type of clinical care provider they choose, families can review considerations for legal protection by referral to an attorney who specializes in LGBTQ+ family law.

Although the current ASRM definition of infertility supports access to care for LGBTQ+ people in fertility clinics, there remains a need for explicit, evidence-based guidelines for caring for same-sex individuals seeking TDI. Ultimately, access to care in fertility clinics should not prevent or supersede access to care for same-sex individuals in primary and community-based settings when indicated. So far, the available evidence points to a model of low-tech, minimal intervention care for this population that can and should be provided in primary and community-based settings. Future research should be designed to clarify evidence gleaned thus far from retrospective reviews, and sexual orientation and gender identity data should be collected and evaluated to hone and expand the evidence regarding TDI in LGBTQ+ populations.

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## CRediT Authorship Contribution Statement

Liam Kali: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

## Declaration of Interests

L.K. is the sole owner of Maia Midwifery & Fertility Services, Professional Limited Liability Company, Seattle, Washington, a community-based midwifery practice specializing in lesbian, gay, bisexual, transgender, and queer+ family building, education, and advocacy.

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