Does ovarian reserve predict egg quality in unstimulated therapeutic donor insemination cycles?

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Objective: To compare reproductive outcomes of patients with very low, low, normal, and high antral follicle counts undergoing unstimulated therapeutic donor insemination (TDI) cycles.
Design: Retrospective cohort study.
Setting: University-affiliated regional fertility clinic.
Patient(s): Four hundred fifty-nine patients who had 1,107 TDI treatment cycles from January 2006 to December 2013.
Intervention(s): Unstimulated therapeutic donor insemination.
Main Outcome Measure(s): Clinical pregnancy rates and miscarriage rates as surrogate markers for oocyte quality.
Result(s): The overall pregnancy rate per cycle start was 12.46% in the study population. There was no difference in per-cycle or cumulative pregnancy rates among patients with very low, low, average, or high antral follicle counts within each patient age group of $\leq$35, 36–39, and $\geq$40 years. The overall miscarriage rate per pregnancy was 13.61%. When stratified by patient age, there was no correlation between miscarriage rate and antral follicle count.
Conclusion(s): AFC is not a predictor of pregnancy or miscarriage rates in patients undergoing unstimulated TDI. (Fertil Steril® 2015;103:1170–5. ©2015 by American Society for Reproductive Medicine.)
Key Words: Diminished ovarian reserve, antral follicle count, therapeutic donor insemination, pregnancy rate, miscarriage rate

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Intrauterine insemination, with (SO-IUI) or without (IUI) superovulation, is a commonly used fertility treatment. In the presence of at least one patent fallopian tube, SO-IUI is indicated for mild and moderate male-factor infertility, mild endometriosis, cervical-factor infertility, and unexplained infertility. The pregnancy rate per cycle ranges from 8% to 26% depending on the patient population under study (1).

Several factors have been shown to be predictive of success in IUI cycles, including female age, the duration and cause of infertility, the number of previous treatment cycles, and sperm parameters (2, 3). There is no consensus regarding patient features to indicate that IUI with the male partner's sperm should be bypassed in favor of using donor sperm or in vitro fertilization techniques.

Cryopreserved donor sperm from commercial sperm banks is commonly used for IUI in cases of azoospermia or severe oligospermia in the male partner. Donor sperm is also used in women seeking pregnancy who don't have a male partner, such as same-sex female couples and single women. Although pregnancy rates are lower with the use of frozen versus fresh sperm (4), therapeutic donor insemination (TDI) with thawed cryopreserved specimens offers the advantages of anonymity and protection against transmission of disease through screening and quarantine protocols.

Fertility specialists use a variety of diagnostic tools to try to determine a patient's ovarian reserve. These tests aim to measure the quantity and quality of remaining oocytes. In the absence of histologic assessment, the best available surrogate for testing oocyte quantity is evaluation of the patient's response to ovarian stimulation. The available tests have shown a reasonable ability to predict response to ovarian stimulation (5).

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The most commonly used tests of ovarian reserve are basal FSH levels, antimüllerian hormone (AMH), and transvaginal ultrasound measurement of antral follicle count (AFC). Although these tests are almost universally assessed during initial fertility evaluations, they have only been demonstrated to correlate with ovarian response to fertility drugs as measured by oocyte quantity (6, 7).

There is no accepted definition of oocyte quality, but it is commonly accepted that it should equate to fecundity—the ability to achieve a live birth within one menstrual cycle. There is no evidence that the above-mentioned tests accurately predict oocyte quality or fertility potential, although they are still commonly interpreted as doing so. Diagnostic tools to measure oocyte quality before attempting assisted reproductive therapies remain elusive. Epidemiologic studies aimed to identify patient features that suggest high oocyte quality are difficult to undertake in the assisted reproductive technology (ART) population, owing to the many confounding factors that exist in these patients. These confounders include the potential effect of exogenous gonadotropin therapy on egg quality and the effects of sperm and lab conditions on embryo competence. Consequently, a more ideal population in which to study predictors of oocyte quality is women seeking fertility therapy because of absence of a male partner who are undergoing donor sperm insemination in a natural ovulatory cycle.

In the present study, we retrospectively reviewed all patients at our center who had no history of infertility and were undergoing unstimulated TDI for indications of azoospermia in the male partner or absence of a male partner. It is presumed that the sperm donors also lacked a history of infertility. In this select group of patients in whom confounding factors affecting the success of insemination are not present, pregnancy rates and miscarriage rates were used as surrogate markers of oocyte quality. Reproductive outcomes of patients undergoing TDI with low, normal, and high ovarian reserve, as assessed by AFC, were compared to determine whether a relationship exists between ovarian reserve and oocyte quality.

MATERIALS AND METHODS

Subjects

A total of 1,019 consecutive unstimulated TDI cycles in 469 patients at the Ottawa Fertility Centre between 2006 and 2012 were reviewed. Only the first three treatment cycles were analyzed for each individual patient. This study was approved by the Ottawa Health Science Network Research Ethics Board.

Patients desiring pregnancy who required TDI for the indications of same-sex relationship, single female, or an azoospermic male partner were evaluated with a detailed history and physical examination. A baseline hormonal profile including FSH, LH, E_2, PRL, and TSH was performed early in the follicular phase. Hystero-contrast sonography (HyCoSy) was performed to confirm tubal patency. A transvaginal ultrasound for both assessment of pelvic anatomy and AFC measurement was performed on menstrual cycle days 2–4. Antral follicles were defined as hypoechoic ovarian follicles with mean diameter 2–9 mm. AMH levels are not routinely measured during initial investigations at our center.

Study inclusion criteria were intrauterine insemination requiring the use of anonymous donor sperm, patency of at least one fallopian tube as demonstrated by HyCoSy, an AFC measured within 1 year before the start of TDI treatment, and regular menstrual cycles occurring every 21–35 days. Ovulatory cycles were confirmed by luteal-phase $P>10$ nmol/L. Patients were excluded if they had received ovarian stimulation with selective estrogen receptor modulators, aromatase inhibitors, or gonadotropins during their TDI cycle, or had abnormal TSH or PRL values. There was no upper limit of FSH that prompted exclusion from the study. At our center, patients starting TDI treatment do not receive ovarian stimulation for the first three cycles, regardless of their ovarian testing results. Patients with incomplete medical records were excluded from the analysis.

Patients who became pregnant were followed until 10 weeks' gestational age.

Monitoring and Insemination

Ovulation was detected with serial home urine LH testing or serum LH levels depending on patient preference. LH testing was initiated 3–4 days before the expected date of ovulation. A single TDI was performed 1 day after a positive urinary or serum LH test.

Thawed cryopreserved sperm was used for insemination following an unstimulated TDI protocol. The concentration and motility of all semen was checked to ensure a total motile count of $\geq 1–2 \times 10^6$ spermatozoa per specimen. Insemination was performed with the patient in a modified lithotomy position. The cervix was visualized with the use of a Pederson speculum, and the cervical os was cleaned with a cotton swab. A catheter was gently passed through the cervical canal. A 0.5-mL volume of sperm was injected into the uterine cavity. The patient remained in a supine position for 15 minutes after the procedure, and was assessed by the attending physician before discharge home. No luteal support was given.

Serum β-hCG levels were measured 17 days after insemination to detect pregnancy. If there was biochemical evidence of pregnancy, a confirmatory ultrasound was scheduled for the 6th–8th gestational week. Pregnancy was defined as the presence of a fetal heart beat at the first ultrasound. Miscarriage was defined as positive β-hCG and no fetal heart beat present at the first or subsequent ultrasound before 10 weeks.

Statistical Analysis

The study cohort represents all eligible consecutive TDI cycles performed at our center since ultrasound reports with AFC data were first stored electronically. Patients were divided into one of three age groups. Age group 1 included all women ≤ 35 years old. Women in age group 2 were 36–39 years old. All women ≥ 40 years old were in age group 3. Patients were also stratified based on AFC counts. Women in the low AFC group had 0–12 follicles, those in the medium AFC group had 13–23 follicles, and those in the high AFC group had