In vitro fertilization cycle and embryo transfer outcomes in oligoanovulatory patients with hypothalamic hypogonadism vs. polycystic ovary syndrome and compared with normo-ovulatory patients

Rebecca A. Heidenberg, B.S.,[a] Elizabeth S. Ginsburg, M.D.,[b] Catherine E. Gordon, M.D.,[b] and Andrea Lanes, Ph.D.[b]

[a] Department of Clinical Sciences, Florida State University College Medicine, Florida State University College, Tallahassee, Florida; and [b] Department of Obstetrics and Gynecology, Brigham and Women's Hospital Center for Infertility and Reproductive Surgery, Harvard Medical School, Boston, Massachusetts

Objective: To study the difference in the live birth rates between anovulatory women with hypothalamic hypogonadism (HH) and those with polycystic ovary syndrome (PCOS) and normo-ovulatory women undergoing fresh embryo transfer or frozen embryo transfer (FET).
Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): Patients with oligoanovulation (HH, n = 47; PCOS, n = 533) and normo-ovulation (tubal factor infertility, n = 399) undergoing in vitro fertilization and intracytoplasmic sperm injection cycles from January 1, 2012, to June 30, 2019.
Intervention(s): None.
Main Outcome Measure(s): Live birth rate.
Result(s): Patients with HH had longer stimulation durations than both patients with PCOS and tubal factor infertility. Patients with HH had fewer oocytes retrieved than patients with PCOS, but their numbers of blastocysts were similar. Patients with HH and tubal factor infertility had similar numbers of oocytes retrieved and blastocysts. In fresh embryo transfer cycles, the live birth rates were similar among patients with HH, PCOS, and tubal factor infertility (37.5% vs. 37.1% vs. 29.3%, respectively). When evaluating FET cycles, patients with HH had lower live birth rates than patients with PCOS (26.5% vs. 46.7%) and tubal factor infertility (42.6%).
Conclusion(s): Live birth rates are similar among patients with HH, PCOS, and normo-ovulation undergoing fresh embryo transfer but are significantly lower in women with HH undergoing FET. (Fertil Steril Rep® 2022;3:237–45. ©2022 by American Society for Reproductive Medicine.)
Key Words: Hypothalamic hypogonadism, polycystic ovary syndrome, PCOS, IVF, embryo transfer

Received December 31, 2021; revised June 12, 2022; accepted June 13, 2022.
R.A.H. has nothing to disclose. E.S.G. has nothing to disclose. C.E.G. has nothing to disclose. A.L. has nothing to disclose.
Reprint requests: Rebecca A. Heidenberg, B.S., Florida State University College Medicine, Florida State University College, 1115 W Call St, Tallahassee, Florida 32304 (E-mail: rah15e@med.fsu.edu).

Fertil Steril Rep® Vol. 3, No. 3, September 2022 2666-3341

https://doi.org/10.1016/j.xfre.2022.06.003

Chronic oligoanovulation is the most common cause of female infertility (1). Polycystic ovary syndrome (PCOS) accounts for approximately 85% of ovulation disorders in reproductive-age women (1). Dysregulation in the hypothalamic-pituitary-ovarian axis results in infrequent or absent ovulation. Although most women are normogonadotropic, approximately 10% of anovulatory women have hypothalamic hypogonadism (HH) (2). Polycystic ovary syndrome is diagnosed according to the modified Rotterdam criteria by having at least 2 of the following criteria: ovulatory dysfunction; polycystic-appearing ovaries on ultrasound; and hyperandrogenism (3, 4). Hypothalamic hypogonadism is characterized by low gonadotropin production and can be acquired or congenital (5). The estradiol (E_2) levels in women with PCOS are within the normal range, whereas these are low in women with HH (6, 7).

Factors other than anovulation may contribute to diminished fertility in women with PCOS, including poor oocyte quality, fertilization, and embryo development. Although patients with PCOS often have more oocytes retrieved than patients with tubal factor infertility, the fertilization rates in patients with PCOS are lower, and more patients have cancelled fresh embryo transfers (8–10). Lai et al. (11) demonstrated that women with PCOS undergoing in vitro fertilization (IVF) had significantly higher levels of reactive oxidative species produced by their granulosa cells and lower rates of fertilization and cleavage than those with tubal factor infertility. Although fertilization and embryo development appear to be impaired in patients with PCOS, the pregnancy and live birth rates per cycle are not affected, likely because of the large number of oocytes retrieved. A meta-analysis by Sha et al. (12) demonstrated similar pregnancy rates per embryo transfer for patients with PCOS vs. normo-ovulatory women but higher clinical pregnancy and live birth rates per cycle start for patients with PCOS. Patients with PCOS were found to be at higher risk of ovarian hyperstimulation syndrome, gestational diabetes, gestational hypertension, and preterm delivery.

There are fewer studies on IVF outcomes in women with HH. Several studies have demonstrated that women with HH required longer ovarian stimulation and higher total gonadotropin doses than women with tubal factor infertility but the live birth rates per cycle with completed egg retrieval were comparable between groups (13–15). However, other studies have demonstrated lower fertilization rates and fewer embryos with good morphological grades in women with HH than in women with tubal factor or unexplained infertility (16, 17).

There are no studies comparing blastocyst development and reproductive outcomes in women with chronic oligoanovulation because of HH vs. those with PCOS. Given data from previous studies comparing patients with PCOS and HH with patients with tubal factor infertility, we hypothesized that patients with HH would have fewer oocytes retrieved and fewer blastocysts available than patients with PCOS but similar clinical pregnancy and live birth rates with fresh embryo transfer and frozen embryo transfer (FET) cycles compared with patients with PCOS and tubal factor infertility. This study aimed to determine whether the blastocyst conversion, clinical pregnancy, and live birth rates differ among women with PCOS, HH, and tubal factor infertility.

MATERIALS AND METHODS

Autologous IVF and intracytoplasmic sperm injection cycles performed from January 1, 2012, to June 30, 2019, at the Center for Infertility and Reproductive Surgery at Brigham and Women's Hospital, Boston, Massachusetts, were evaluated for infertility diagnoses. The diagnosis of PCOS was based on the modified Rotterdam criteria requiring the presence of oligo-ovulation combined with either hyperandrogenism or polycystic ovaries on ultrasound (3). The diagnosis of HH was based on either primary or secondary amenorrhea and low serum gonadotropin and E_2 levels, with absent progestin withdrawal bleeding. All patients with HH had prior brain magnetic resonance imaging to rule out central processes. Women with tubal factor infertility were included as a comparison group. Tubal factor infertility was diagnosed by hysterosalpingography findings of either proximal or distal tubal occlusion in women with regular menstrual cycles and normal hormonal levels. Hydrosalpinges were removed or occluded proximally before IVF.

Cycles were excluded if the following were met: women were diagnosed with ovulatory dysfunction associated with thyroid disease, hyperprolactinemia, or congenital adrenal hyperplasia; women were diagnosed with uterine factor infertility; egg donation or in vitro maturation was used; the oocytes or embryos were imported from another institution; the oocytes were cryopreserved; the embryos were thawed and then biopsied and refrozen; and gestational carriers were used.

The primary outcome was live birth, defined as the birth of at least 1 live born infant per embryo transfer. The secondary outcomes were the total number of oocytes retrieved, number of mature oocytes (metaphase II) retrieved, fertilization rate (2 pronuclei [2PN]/metaphase II), number of cleavage- and blastocyst-stage embryos, embryo grade, number of embryos frozen, number of euploid embryos, implantation rate, clinical pregnancy rate, and miscarriage rate. Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion on ultrasound. Miscarriage was defined as the loss of pregnancy after confirmation of a gestational sac on imaging or the presence of villi on pathologic examination after office biopsy in cases of pregnancy of unknown location.

Clinical and Laboratory Protocols

Standard controlled ovarian hyperstimulation and monitoring protocols were used. Gonadotropin doses were determined on the basis of age, serum antimüllerian hormone (AMH) levels, antral follicle count, body mass index (BMI), and previous response to stimulation. Ovarian stimulation was performed using exogenous gonadotropins (Gonal-F [EMD Serono, Darmstadt, Germany], Follistim [Organon, Roseland, NJ], or Menopur [Ferring Pharmaceuticals, Saint-Prex, Switzerland]). Stimulation protocols for patients with HH included human menopausal gonadotropin (Menopur)

and did not include pituitary suppression. Pituitary suppression for patients with tubal factor infertility or PCOS was most often attained using a gonadotropin-releasing hormone (GnRH) antagonist (Cetrotide; EMD Serono) or GnRH agonist (leuprolide acetate; Abbott Laboratories, Chicago, IL). Gonadotropin dosage was adjusted according to each patient's response to stimulation, which was monitored using transvaginal ultrasound and serial E_2 levels. When at least 2 follicles reached a mean diameter of 18 mm, final oocyte maturation was triggered using a human chorionic gonadotropin (hCG) (Pregnyl [Organon] or Novarel [Ferring Pharmaceuticals]), GnRH agonist (leuprolide acetate; Abbott Laboratories), or both. Patients with HH were triggered with hCG. The dose of hCG (5,000 or 10,000 IU) was tailored on the basis of the serum E_2 levels on the day of trigger and number of follicles. Patients with PCOS or tubal factor infertility considered to be at high risk of ovarian hyperstimulation syndrome were given a GnRH agonist, 5,000 units of hCG, or a combination trigger (40 units of leuprolide acetate with 1,500 units of hCG). Ultrasound-guided oocyte retrieval was typically performed under intravenous general anesthesia 36 hours after trigger.

All gametes and embryos were cultured at 37 °C in a dry incubator under an atmosphere of carbon dioxide (5%–6%), oxygen (5%), and nitrogen (89%–90%). Box incubators were used from January 2012 to April 2014, and benchtop incubators were used after April 2014. In vitro fertilization or intracytoplasmic sperm injection was performed 4–6 or 3–5 hours after oocyte retrieval, respectively, followed by a fertilization check 16–18 hours after fertilization. Oocytes inseminated using conventional IVF were stripped of surrounding cumulus cell clumps at the time of fertilization check. Single-step medium (25-μL microdrops; global total, IVFOnLine, Guelph, Ontario, Canada; under mineral oil) was used to culture 2PN zygotes (1 zygote/drop). Embryos were evaluated on day 3 between 66 and 69 hours after insemination and transferred if the patient met criteria for day 3 transfer (<6 2PN zygotes for the age of <41 years or <8 2PN zygotes for the age of ≥41 years). Cleavage-stage embryos for patients aged >40 years or those planned for preimplantation genetic testing for aneuploidy (PGT-A) underwent assisted hatching using laser pulses (ZILOS-tk laser; Hamilton Thorne, Beverly, MA).

For patients planning culture to the blastocyst stage, the embryos were moved to a fresh drop of equilibrated global total medium for culture to day 5 or 6. Blastocyst morphology was evaluated on day 5 between 112 and 115 hours and scored according to the stage of development and quality of the inner cell mass (ICM) and trophectoderm (TE) (Supplemental Table 1, available online) (18). For patients undergoing fresh blastocyst transfer, embryo transfer was performed on day 5. For embryo cryopreservation, blastocysts with a score of <4A (good-quality early blastocyst, Gardner stage 1) (19) were considered ineligible for freeze. Embryos that were ineligible for freeze on day 5 were left in culture and re-evaluated on days 6 and 7. Embryos that met criteria for freeze on days 5–7 were vitrified.

In PGT-A cycles, embryos were biopsied on day 5 or 6 once biopsy criteria were met. Early blastocysts, expanding blastocysts, and any blastocyst with a "C" grade for both the ICM and TE or a "D" for either the ICM or TE were considered ineligible for biopsy. Embryos that were ineligible for biopsy or freeze on day 5 were left in culture and re-evaluated on day 6. Biopsies were performed using standard techniques by embryologists certified to perform the procedure. Briefly, the embryo was immobilized using a holding pipette, and 4–5 cells were aspirated using a biopsy pipette with an internal diameter of 20–30 μm. The biopsied specimens were exposed to wash buffer, and the cells were placed in 0.2-mL polymerase chain reaction tubes with 2–3-μL lysis buffer. The specimens were stored at either −20 °C or −80 °C (depending on the predetermined genetic testing laboratory) before being sent for analysis. The biopsied blastocysts were frozen using the standard vitrification technique. Embryos that were determined by PGT-A to be euploid were eligible for transfer.

Patients undergoing fresh embryo transfer started vaginal progesterone supplementation (Crinone; Allergan Pharmaceuticals, Dublin, Ireland) 2 days after egg retrieval. Those who received combination leuprolide acetate and hCG triggers were also started with twice daily oral estrogen supplementation (Estrace; Teva Pharmaceuticals, Petah Tikva, Israel) the day after trigger. Patients who underwent a freeze-all cycle had subsequent FET cycles. Patients with regular menstrual cycles were offered "natural" FET cycles. The luteinizing hormone (LH) levels were monitored during the follicular phase to identify the LH surge with urinary testing at home and serum LH confirmation on that day or serum progesterone levels 3 days later or with daily serum LH measurements starting on cycle day 10. Cleavage- and blastocyst-stage transfers were performed 4 and 6 days after LH surge, respectively. Most patients received vaginal progesterone supplementation (Crinone; Allergan Pharmaceuticals), which was initiated 3 days after LH surge. Anovulatory patients, and those desiring hormonally regulated cycles, underwent "programmed" cycles. Estradiol was supplemented with tablets (Estrace; Teva Pharmaceuticals) given orally or vaginally or using E_2 patches (Climara; Sandoz Pharmaceuticals [Basel, Switzerland] vs. Bayer Pharmaceuticals [Leverkusen, Germany]), 3 patches changed every other day. After at least 14 days of E_2 administration and once adequate endometrial thickness was achieved (7 mm), daily intramuscular progesterone (25 mg on the first day and then increased to 50 mg daily; AuroMedics Pharma LLC, East Windsor, NJ) was initiated. Embryos were transferred after 6 days of exposure to progesterone. The serum progesterone level was checked on the day of transfer for those using intramuscular progesterone, and if it was <20 ng/mL, dosing was increased to reach a level of ≥20 ng/mL. All embryos were graded at the time of fresh transfer or embryo cryopreservation (embryo quality classification system in Supplemental Table 2, available online).

Statistical Analysis

The means and SDs were generated for continuous variables, and frequencies and proportions were generated for categorical variables. To test for significance, the Wilcoxon's rank sum test was used for continuous variables, and the χ^2 test

TABLE 1

Demographic and cycle characteristics among patients with anovulatory infertility and normo-ovulatory patients.

	Oligoanovulatory		Normo-ovulatory
	HH	PCOS	Tubal factor
	N = 47	N = 533	N = 399
Demographic and cycle characteristics			
Woman's age (y)	34.9 (3.5)	34.0 (4.3)	36.9 (4.0)
Woman's age (y)			
<35	24 (51.1)	324 (60.8)	124 (31.1)
35–37	11 (23.4)	116 (21.8)	103 (25.8)
38–40	10 (21.3)	52 (9.8)	103 (25.8)
41–42	2 (4.3)	31 (5.8)	50 (12.5)
>42	0 (0)	10 (1.9)	19 (4.8)
BMI (kg/m^2)	21.1 (2.5)	28.8 (7.6)	26.9 (6.7)
BMI (kg/m^2)	10 (20.8)	4 (0.7)	8 (2.0)
<18.5	36 (75.0)	216 (39.1)	181 (45.4)
18.5–24.9	2 (4.2)	139 (25.2)	107 (26.8)
25–29.9	0 (0)	76 (13.8)	60 (15.0)
30–34.9	0 (0)	59 (10.7)	18 (4.5)
35–39.9	0 (0)	37 (6.7)	17 (4.3)
40–44.9	0 (0)	21 (3.8)	8 (2.0)
>45			
Day 3 FSH (IU/L)	4.1 (3.4)	6.2 (1.9)	7.5 (2.2)
Day 3 E_2 (pg/mL)	23.2 (40.0)	39.3 (24.9)	39.1 (20.6)
AMH (ng/mL)	3.7 (3.7)	7.6 (6.0)	2.8 (2.4)
Cycle day number at times of trigger	15.2 (3.3)	12.4 (2.7)	11.8 (1.9)
Type of trigger used:			
hCG 5,000 IU	7 (14.9)	12 (2.3)	1 (0.3)
hCG 10,000 IU	29 (61.7)	230 (43.2)	201(50.4)
hCG 1,500 IU/Lupron 40 units	4 (8.5)	166 (31.1)	72 (18.1)
Lupron 40 units	0 (0)	53 (9.9)	18 (4.5)
Ovidrel 250 μg	7 (14.9)	46 (8.6)	71 (17.8)
Ovidrel 500 μg	0 (0)	26 (4.9)	36 (9.0)
ICSI	16 (34.0)	216 (40.5)	156 (39.1)
Stimulation protocol:			
Poor responder	5 (10.6)	35 (6.6)	80 (20.1)
Good responder	42 (89.4)	498 (93.4)	319 (80.0)
Starting daily FSH dose (IU)	4.9 (2.6)	3.3 (1.7)	5.0 (2.1)
Total FSH dose received (IU)	67.0 (43.4)	34.9 (22.0)	50.6 (26.3)
Estradiol level on the day of trigger (ng/mL)	2,298.4 (983.7)	2,193.8 (1270.6)	2,054.4 (920.6)
Freeze-all cycle	7 (14.9)	127 (23.8)	65 (16.5)
FET endometrial stimulation protocol			
Natural—LH testing with luteal progesterone	0 (0)	11 (2.6)	23 (10.0)
Modified natural—OI with hCG trigger and luteal progesterone	1 (2.9)	13 (3.1)	11 (4.8)
Programmed	33 (97.1)	398 (94.3)	196 (85.2)
Number of embryos transferred:			
Fresh	1.70 (0.88)	1.65 (0.90)	2.10 (1.21)
Frozen	1.18 (0.39)	1.33 (0.53)	1.37 (0.61)
Day of transfer:			
Day 3	25 (33.8)	206 (25.3)	219 (40.0)
Day 5	49 (66.2)	607 (74.7)	328 (60.0)
Transferred embryo quality:			
Excellent	19 (25.7)	232 (28.5)	152 (27.8)
Good	22 (29.7)	283 (34.8)	181 (33.1)
Fair	25 (33.8)	205 (25.2)	151 (27.6)
Poor	8 (10.8)	93 (11.4)	63 (11.5)
Endometrial thickness (mm):			
Fresh embryo transfer	9.2 (2.4)	11.0 (2.9)	11.3 (3.0)
FET	7.1 (1.5)	9.2 (2.6)	10.1 (2.6)

Note: Values represent mean (standard deviation) for continuous variables or n (%) for categorical variables. AMH = antimüllerian hormone; BMI = body mass index; E_2 = estradiol; FET = frozen embryo transfer; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HH = hypothalamic hypogonadism; ICSI = intracytoplasmic sperm injection; LH = luteinizing hormone; OI = ovulation induction; PCOS = polycystic ovary syndrome.

Heidenberg. IVF outcomes in patients with HH. Fertil Steril Rep 2022.

was used for categorical variables. Relative risks (RRs) and 95% confidence intervals (CIs) were generated using the Poisson regression for counts and Poisson regression with an offset for rates. These models were adjusted for age, BMI, AMH, and stimulation protocol. Relative risks and 95% CIs were generated using log binomial regression for dichotomous outcomes and were adjusted for age, BMI, AMH, stimulation protocol, number of embryos transferred, day of embryo transfer, endometrial stripe thickness, and embryo quality and PGT-A-tested embryos (FETs only). Point biserial correlation, a type of Pearson's correlation, was used to assess the correlation between the live birth rate and endometrial stripe thickness. This was used to determine the relationship between dichotomous and continuous variables. Generalized estimating equations were used to account for patients contributing >1 cycle. An α of 0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.4 (Cary, NC). Approval for this study was obtained from the Partners HealthCare institutional review board (protocol number 2020P002177).

RESULTS

A total of 979 egg retrieval cycles from 691 patients were analyzed. The demographic characteristics for patients with HH (n = 47), PCOS (n = 533), and tubal factor infertility (n = 399) are shown in Table 1. The mean ages of patients with HH and PCOS were lower than that of patients with tubal factor infertility (all $P<.01$). A higher proportion of patients in the HH group were underweight and normal weight compared with patients in the tubal factor infertility and PCOS groups (all $P<.01$). As expected, patients with HH had lower mean day 3 follicle-stimulating hormone and E_2 levels than patients with PCOS (all $P<.01$) and tubal factor infertility (all $P<.01$). Patients with HH had similar mean AMH levels compared with patients with tubal factor infertility ($P=.62$) but lower AMH levels than patients with PCOS ($P<.01$). Patients with HH received higher total doses of gonadotropins than patients with PCOS ($P<.01$) but similar total doses compared with patients with tubal factor infertility ($P=.05$). Patients with HH had longer stimulation durations than both patients with tubal factor infertility and PCOS (all $P<.01$). A larger proportion of patients with PCOS had a freeze-all cycle compared with patients with tubal factor infertility (23.8% vs. 16.5%, $P<.01$). There was no statistically significant difference in the number of freeze-all cycles between patients with PCOS and those with HH ($P=.16$). Patients with HH had a similar number of good-quality embryos compared with patients with PCOS ($P=.38$) and patients with tubal factor infertility ($P=.56$). The mean endometrial stripe thickness was lower in fresh embryo transfer and FET cycles for patients with HH (fresh, 9.2 [2.4]; frozen. 7.1 [1.5]) than in those for patients with PCOS (fresh, 11.0 [2.9]; frozen, 9.2 [2.6]; $P<.01$) and patients with tubal factor infertility (fresh, 11.3 [2.9]; frozen, 10.1 [2.6]; $P<.01$).

Stimulation cycle outcome data by diagnosis are shown in Table 2. Patients with HH had similar numbers of oocytes

TABLE 2

In vitro fertilization cycle outcomes for patients with HH vs. patients with PCOS and normo-ovulatory patients.

Cycle outcomes	HH N = 47	RR (95% CI)	PCOS N = 533	RR (95% CI)	aRR (95% CI)	Tubal factor infertility N = 399	RR (95% CI)	aRR (95% CI)
No. of oocytes retrieved	13.8 (8.6)	Ref	19.1 (11.7)	1.38 (1.11–1.73)	1.28 (1.01–1.63)	13.6 (8.0)	0.98 (0.79–1.23)	1.08 (0.85–1.37)
No. of mature oocytes	10.5 (6.2)	Ref	14.8 (9.6)	1.41 (1.14–1.76)	1.40 (1.10–1.79)	10.1 (6.4)	0.97 (0.78–1.21)	1.10 (0.87–1.39)
Fertilization rate (No. of 2PN/No. of mature)	8.4/10.5 (80.1)	Ref	11.3/14.8 (76.4)	0.96 (0.89–1.03)	0.96 (0.87–1.06)	7.5/10.1 (74.3)	0.93 (0.86–1.00)	0.94 (0.86–1.03)
Blastocysts	4.3 (4.5)	Ref	6.8 (6.9)	1.59 (1.03–2.46)	1.46 (0.98–2.18)	3.8 (4.6)	0.88 (0.56–1.38)	1.07 (0.72–1.60)
No. of blastocysts/2PN	4.3/8.4 (51.2)	Ref	6.8/11.3 (60.2)	1.18 (0.92–1.51)	1.07 (0.85–1.35)	3.8/7.5 (50.7)	0.98 (0.75–1.26)	1.02 (0.81–1.28)
No. of frozen embryos	2.7 (2.9)	Ref	4.5 (5.4)	1.67 (1.09–2.57)	1.54 (1.03–2.31)	2.6 (3.5)	0.96 (0.62–1.50)	1.23 (0.82–1.84)
No. of euploid embryos[a]	2.3 (2.1)	Ref	3.5 (4.0)	1.56 (1.00–2.43)	0.65 (0.34–1.23)	2.0 (2.0)	0.87 (0.55–1.37)	0.80 (0.54–1.19)
Euploid embryos per embryos biopsied[a]	2.3/5.8 (39.1)	Ref	3.5/7.6 (46.3)	1.18 (0.97–1.44)	0.73 (0.54–0.99)	2.0/4.1 (47.5)	1.21 (0.98–1.51)	1.01 (0.82–1.24)

Note: Values represent mean (standard deviation) or n/n (%).The denominator is the cycle except for the fertilization rate, blastocyst conversion rate, and euploid embryos per embryos biopsied. Relative risks adjusted for age, body mass index, antimüllerian hormone, and stimulation protocol. aRR = adjusted relative risk; CI = confidence interval; HH = hypothalamic hypogonadism; PCOS = polycystic ovary syndrome; RR = relative risk; 2PN = 2 pronuclei.

[a] Where preimplantation genetic testing for aneuploidy was performed (tubal factor infertility, N = 24; HH, N = 4; PCOS, N = 33).

Heidenberg. IVF outcomes in patients with HH. Fertil Steril Rep 2022.

TABLE 3

Transfer outcomes for patients with HH vs. patients with PCOS and normo-ovulatory patients undergoing fresh embryo transfer.

	HH N = 40	RR (95% CI)	PCOS N = 391	RR (95% CI)	aRR (95% CI)	Tubal factor infertility N = 317	RR (95% CI)	aRR (95% CI)
Fresh embryo transfer outcomes								
Chemical pregnancy rate	6 (15.0)	Ref	47 (12.0)	0.80 (0.38–1.67)	0.68 (0.32–1.46)	37 (11.7)	0.78 (0.37–1.64)	0.62 (0.30–1.30)
Ectopic pregnancy rate	2 (5.0)	Ref	8 (2.1)	0.41 (0.92–1.82)	N/A	4 (1.3)	0.25 (0.49–1.30)	N/A
Implantation rate	21/68 (30.9)	Ref	223/645 (34.6)	1.12 (0.77–1.62)	N/A[a]	146/665 (22.0)	0.71 (0.48–1.04)	N/A[a]
Clinical pregnancy rate	19 (47.5)	Ref	168 (43.0)	0.90 (0.59–1.39)	0.69 (0.52–0.90)	113 (35.7)	0.75 (0.48–1.16)	0.64 (0.48–0.84)
Clinical SAB rate	2 (5.0)	Ref	32 (8.2)	1.64 (0.39–6.92)	N/A	20 (6.3)	1.26 (0.29–5.43)	N/A
Live birth rate	15 (37.5)	Ref	145 (37.1)	0.99 (0.62–1.59)	0.83 (0.55–1.26)	93 (29.3)	0.78 (0.48–1.27)	0.74 (0.48–1.12)

Note: The denominator is the fresh transfer except for the implantation rate, which is defined as the number of sacs/number of embryos. Relative risks adjusted for age, body mass index, stimulation protocol, number of embryos transferred, endometrial stripe thickness, day of embryo transferred, and embryo quality. aRR = adjusted relative risk; CI = confidence interval; HH = hypothalamic hypogonadism; N/A = not available, could not be calculated because of the small number in 1 or more groups; PCOS = polycystic ovary syndrome; RR = relative risk; SAB = spontaneous abortion.

[a] Implantation rate calculated as a pooled effect and cannot generate adjusted RR.

Heidenberg. IVF outcomes in patients with HH. Fertil Steril Rep 2022.

TABLE 4

Transfer outcomes for patients with HH vs. patients with PCOS and normo-ovulatory patients undergoing frozen embryo transfer.

	HH N = 34	RR (95% CI)	PCOS N = 422	RR (95% CI)	aRR (95% CI)	Tubal factor infertility N = 230	RR (95% CI)	aRR (95% CI)
Frozen embryo transfer outcomes								
Chemical pregnancy rate	9 (26.5)	Ref	49 (11.6)	0.44 (0.24–0.80)	N/A	30 (13.0)	0.49 (0.26–0.92)	N/A
Ectopic pregnancy rate	0 (0)	Ref	1 (0.2)	N/A	N/A	1 (0.4)	n/a	N/A
Implantation rate	19/40 (47.5)	Ref	290/560 (51.8)	1.09 (0.78–1.52)	N/A[a]	145/316 (45.9)	0.97 (0.68–1.37)	N/A[a]
Clinical pregnancy rate	15 (44.1)	Ref	238 (56.4)	1.28 (0.84–1.96)	1.34 (0.87–2.07)[b]	115 (50.0)	1.13 (0.73–1.76)	1.30 (0.83–2.03)[b]
Clinical SAB rate	6 (17.7)	Ref	43 (10.2)	0.58 (0.30–1.10)	N/A	15 (6.5)	0.37 (0.17–0.79)	N/A
Live birth rate	9 (26.5)	Ref	197 (46.7)	1.81 (1.13–2.89)	1.83 (1.13–2.96)	98 (42.6)	1.61 (0.98–2.65)	1.83 (1.14–2.94)

Note: The denominator is the cycle except for the implantation rate, which is defined as the number of sacs/number of embryos. Relative risks adjusted for age, body mass index, stimulation protocol, number of embryos transferred, endometrial stripe thickness, day of embryo transferred, embryo quality, and euploid embryo transfer. aRR = adjusted relative risk; CI = confidence interval; HH = hypothalamic hypogonadism; N/A = not available, could not be calculated because of the small number in 1 or more groups; PCOS = polycystic ovary syndrome; RR = relative risk; SAB = spontaneous abortion.

[a] Implantation rate calculated as a pooled effect and cannot generate adjusted RR.

[b] Relative risk adjusted for all aforementioned factors except euploid embryo transferred to allow the model to run.

Heidenberg. IVF outcomes in patients with HH. Fertil Steril Rep 2022.

retrieved and blastocysts compared with patients with tubal factor infertility (13.8 vs. 13.6 and 4.3 vs. 3.8; adjusted RR [aRR], 1.08; 95% CI, 0.85–1.37, and aRR, 1.07; 95% CI, 0.72–1.60, respectively). Patients with HH had significantly fewer oocytes retrieved and mature oocytes than patients with PCOS (13.8 vs. 19.1 and 10.5 vs. 14.8; aRR, 1.28; 95% CI, 1.01–1.63, and aRR, 1.40; 95% CI, 1.10–1.79, respectively), but there was no statistically significant difference in the number of blastocysts (4.3 vs. 6.8; aRR, 1.46; 95% CI, 0.98–2.18). The blastocyst conversion rates were similar when comparing patients with HH with patients with tubal factor infertility (51.2% vs. 50.7%; aRR, 1.02; 95% CI, 0.81–1.28) and patients with PCOS (51.2% vs. 60.2%; aRR, 1.07; 95% CI, 0.85–1.35). Patients with PCOS had a higher euploidy rate than patients with HH in the unadjusted model (46.3% vs. 39.1%; RR, 1.18; 95% CI, 0.97–1.44), whereas patients with HH had a significantly higher euploidy rate when adjusting for confounders (aRR, 0.73; 95% CI, 0.54–0.99). The euploidy rates were similar between patients with HH and those with tubal factor infertility in the unadjusted and adjusted models (39.1% vs. 47.5%; aRR, 1.01; 95% CI, 0.82–1.24).

A total of 1,434 transfers from 655 unique patients were included in the analysis of embryo transfer outcomes. Fresh embryo transfer cycle outcome data for a total of 748 transfers from 554 patients are shown in Table 3. Despite no difference in the unadjusted model, patients with HH had significantly higher clinical pregnancy rates than patients with tubal factor infertility (47.5% vs. 35.7%; aRR, 0.64; 95% CI, 0.48–0.84) and patients with PCOS (47.5% vs. 43.0%; aRR, 0.69; 95% CI, 0.52–0.90) in the adjusted model. The live birth rates were similar for patients with HH compared with those for patients with PCOS and tubal factor infertility (37.5% vs. 37.1% vs. 29.3%; aRR, 0.83; 95% CI, 0.55–1.26, and aRR, 0.74; 95% CI, 0.48–1.12, respectively).

The FET cycle outcomes for 686 transfers in 393 patients are shown in Table 4. Patients with HH had higher chemical pregnancy and miscarriage rates than patients with tubal factor infertility (26.5% vs. 13.0%; RR, 0.49; 95% CI, 0.26–0.92, and 17.7% vs. 6.5%; RR, 0.37; 95% CI, 0.17–0.79, respectively). The aRR could not be calculated because of the small numbers in the HH group. Patients with HH also had lower live birth rates than patients with tubal factor infertility (26.5% vs. 42.6%; aRR, 1.83; 95% CI, 1.14–2.94) and patients with PCOS (26.5% vs. 46.7%; aRR, 1.83; 95% CI, 1.13–2.96). Point biserial correlation showed no significant correlation between the live birth rate and endometrial stripe thickness in patients with HH undergoing FET ($r = 0.028$; $P=.876$).

The live birth rates by day of embryo transfer and embryo testing status are shown in Supplemental Table 3 (available online). For day 3 fresh transfer, there was no difference in the live birth rates for patients with HH compared with those for patients with PCOS (32% vs. 33.5%; aRR, 0.86; 95% CI, 0.48–1.54) or patients with tubal factor infertility (24.5%; aRR, 0.77; 95% CI, 0.43–1.37). The same was true for day 5 fresh transfer (46.7% vs. 40.2% and 36.8%, respectively; RR, 0.86; 95% CI, 0.47–1.56, and RR, 0.79; 95% CI, 0.43–1.46, respectively). The aRR could not be calculated because of the small numbers in the HH group. For untested day 5 FETs, the live birth rate was significantly higher for patients with PCOS than for those with HH (47.9% vs. 26.7%; aRR, 1.77; 95% CI, 1.04–3.01). The same was true for patients with tubal factor infertility compared with patients with HH (42.6% vs. 26.7%; aRR, 1.74; 95% CI, 1.02–3.00). The live birth rate for patients with HH undergoing euploid embryo transfers was 25%; however, there was only 1 live birth of 4 euploid embryo transfers in patients with HH; therefore, limited conclusions can be drawn.

DISCUSSION

In this study, we investigated IVF cycle and embryo transfer outcomes among anovulatory patients with HH and PCOS and compared them with those of ovulatory patients with tubal factor infertility. We found that patients with HH required more days of stimulation and higher total gonadotropin doses than patients with PCOS. Patients with PCOS had more mature oocytes retrieved, whereas patients with HH had a similar number of blastocysts. Patients with HH had lower live birth rates with FET than patients with PCOS and tubal factor infertility.

There are limited data in the literature describing ovarian stimulation response in patients with HH. Pandurangi et al. (20) described 7 patients with HH who underwent ovarian hyperstimulation, 6 of whom required >12 days of stimulation. Cecchino et al. (13) evaluated 33 patients with HH, and Yildirim et al. (15) evaluated 13 patients with HH. In both studies, women with HH required longer stimulation and higher total gonadotropin doses than patients with tubal factor infertility. Our study evaluated a larger cohort of patients with HH and found that patients with HH required longer stimulation duration than patients with tubal factor infertility despite similar AMH levels but a similar total dose of gonadotropins. Patients with HH required more total gonadotropins than patients with PCOS, likely because of lower AMH levels. The long stimulation durations required for patients with HH may infer that patients with HH are less sensitive to gonadotropins compared with patients with tubal factor infertility and PCOS, possibly because of the less sensitive gonadotropin receptors on the follicles. Despite a more robust response to stimulation, we found lower euploidy rates in women with PCOS than in women with HH. Limited conclusions can be drawn given the low number of patients with HH who underwent euploid embryo transfer; however, this finding is consistent with other studies. The blastocyst aneuploidy rates have been reportedly higher in patients with PCOS in several, but not all, studies (5, 6, 11). Although the mechanism for greater aneuploidy is not fully understood, some studies suggest that oocyte metabolism and steroidogenesis are impaired in patients with PCOS, leading to deoxyribonucleic acid instability (11).

When evaluating fresh embryo transfer cycles, patients with HH had significantly higher clinical pregnancy rates than both patients with PCOS and tubal factor infertility; however, the live birth rates were similar between all groups. This is consistent with the findings of previous studies evaluating fresh embryo transfer cycles in patients with HH compared with patients with tubal factor infertility

(13, 15, 16). To our knowledge, this is the first study to compare patients with HH with patients with PCOS. When stratified by day of embryo transfer, there was no difference in the live birth rates between groups for day 3 or 5 transfer.

When evaluating FET cycles, patients with HH had significantly higher biochemical pregnancy and miscarriage rates than patients with tubal factor infertility. The live birth rate was also significantly lower in patients with HH undergoing FET than in patients with tubal factor infertility or PCOS. Kuroda et al. (21) reported good clinical pregnancy and live birth rates (65.1% and 50.5%) after FET in patients with HH; however, they did not compare these outcomes with a control population or with fresh embryo transfer cycle outcomes. Our results suggest that patients with HH have lower pregnancy rates with FET than those with fresh transfer when controlling for confounders and those with PCOS or tubal factor infertility. To our knowledge, this is the first study to compare FET outcomes in anovulatory patients with HH vs. patients with PCOS. Additionally, this study was performed at a single institution using the same cohort of patients, which allowed for a direct comparison of embryo transfer outcomes between groups.

The Society for Assisted Reproductive Technology (SART) groups women with ovulatory dysfunction under the category of anovulation. However, the hormonal environment and pathophysiology of women with PCOS differ significantly from those of women with HH. Additionally, the IVF cycle response to ovarian hyperstimulation and embryo transfer outcomes differ for patients with HH and PCOS. Patients with HH may have lower live birth rates than patients with PCOS in FET cycles; therefore, the cumulative live birth rate per cycle may be lower in patients with HH than in patients with PCOS. The IVF success predictor model from the SART combines patients with HH and PCOS under the same category of ovulatory dysfunction; therefore, the live birth rate reported for patients with HH may be artificially inflated in this model. It is important to differentiate between these forms of ovulatory dysfunction when selecting stimulation protocols and in counseling patients on anticipated outcomes.

When evaluating the lower live birth rates for patients with HH undergoing FET, endometrial stripe thickness and embryo quality must be considered. The mean endometrial stripe thickness was lower in FET cycles for patients with HH than for patients with tubal factor infertility and patients with PCOS (7.1 vs. 10.1 and 9.2 mm, respectively); however, there was no significant correlation between the live birth rate and endometrial stripe thickness ($P=.876$). Although the HH group had lower quality embryos, the live birth rate remained lower even when we adjusted for embryo quality and euploid embryo transfer (compared with PCOS, aRR, 1.81; 95% CI, 1.13–2.89; compared with tubal factor infertility, aRR, 1.83; 95% CI, 1.14–2.94). These poorer outcomes may be because of inadequate endometrial receptivity associated with insufficient endometrial gonadotropin receptor stimulation. Molecular studies have identified gonadotropin receptors within the endometrium, which are up-regulated in the secretory phase (22–24). Other studies have indicated that these receptors may mediate several cellular functions, including increasing intracellular cyclic adenosine monophosphate and activation of steroidogenic enzymes and production of cytokines, promoting a favorable endometrial cellular environment for embryo implantation (25, 26). In our study, 33 of 34 patients with HH underwent programmed FET endometrial preparation. Because women with HH do not produce significant autologous gonadotropins, they may have impaired endometrial receptivity during programmed FET cycles.

Lower circulating gonadotropin levels and possibly less sensitive receptors may result in higher miscarriage and lower live birth rates in patients with HH undergoing programmed FET. Long-term reduced gonadotropin signaling on endometrial receptors in hypothalamic patients may impact implantation. Modified natural stimulation with gonadotropins may lead to improved clinical outcomes for FET in patients with HH. Additional studies are needed to evaluate the role of adding low-dose gonadotropins to the standard programmed protocol or using a modified natural endometrial preparation with gonadotropins in FET cycles for women with HH.

Our study is limited in its retrospective nature and the limited, although relatively large compared with that of prior studies, sample size of patients with HH. Because this is a retrospective cohort study, sampling bias may have occurred. A larger retrospective or prospective cohort study would provide further insight into IVF outcomes among patients with HH. Additionally, patients with PCOS were not categorized by PCOS phenotype (hyperandrogenic vs. nonhyperandrogenic); therefore, conclusions cannot be drawn when comparing patients with HH with to one or the other phenotype on the basis of our data. Because some patients underwent fresh embryo transfer with subsequent FET, the FET cycles may have used poorer-quality embryos. The study controlled for embryo quality and used generalized estimating equation modeling to account for patients contributing multiple cycles.

CONCLUSION

In conclusion, research regarding blastocyst development and reproductive outcomes in women with chronic anovulation associated with HH in comparison with those with PCOS is limited. The results of our study demonstrate that patients with HH require more days of stimulation and higher gonadotropin doses than patients with PCOS to achieve similar numbers of blastocysts. Women with HH have a higher euploidy rate than women with PCOS. Women with HH have equivalent live birth rates with fresh embryo transfer cycles compared with women with PCOS and tubal factor infertility but significantly lower live birth rates with FET cycles. The SART currently reports outcomes for patients with PCOS and HH under the category of anovulation; however, these 2 groups respond differently to ovarian hyperstimulation and have different embryo transfer outcomes. It is important for providers to identify anovulatory patients as HH vs. PCOS and counsel patients on anticipated outcomes on the basis of their specific diagnosis. The findings from this study can be used in counseling patients from these 2 distinct patient groups.

REFERENCES

1. Mikhael S, Punjala-Patel A, Gavrilova-Jordan L. Hypothalamic-pituitary-ovarian axis disorders impacting female fertility. Biomedicines 2019;7:5.
2. National Collaborating Centre for Women's and Children's Health (UK). Fertility: assessment and treatment for people with fertility problems. London, UK: Royal College of Obstetricians and Gynaecologists; 2004.
3. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2016;31:2841–55.
4. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
5. Skałba P, Guz M. Hypogonadotropic hypogonadism in women. Endokrynol Pol 2011;62:560–7.
6. Chang RJ, Kazer RR. Polycystic ovary syndrome. Glob Libr Women's Med 2014;10:1756–2228.
7. Silveira LFG, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2013;98:1781–8.
8. Dor J, Shulman A, Levran D, Ben-Rafael Z, Rudak E, Mashiach S. The treatment of patients with polycystic ovarian syndrome by in-vitro fertilization and embryo transfer: a comparison of results with those of patients with tubal infertility. Hum Reprod 1990;5:816–8.
9. Kodama H, Fukuda J, Karube H, Matsui T, Shimizu Y, Tanaka T. High incidence of embryo transfer cancellations in patients with polycystic ovarian syndrome. Hum Reprod 1995;10:1962–7.
10. Okohue JE, Onuh SO, Ikimalo JI. Comparison of IVF/ICSI outcome in patients with polycystic ovarian syndrome or tubal factor infertility. Niger J Clin Pract 2013;16:207–10.
11. Lai Q, Xiang W, Li Q, Zhang H, Li Y, Zhu G, et al. Oxidative stress in granulosa cells contributes to poor oocyte quality and IVF-ET outcomes in women with polycystic ovary syndrome. Front Med 2018;12:518–24.
12. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. Reprod Biomed Online 2019;39:281–93.
13. Cecchino GN, Canillas GM, Cruz M, García-Velasco JA. Impact of hypogonadotropic hypogonadism on ovarian reserve and response. J Assist Reprod Genet 2019;36:2379–84.
14. Ulug U, Ben-Shlomo I, Tosun S, Erden HF, Akman MA, Bahceci M. The reproductive performance of women with hypogonadotropic hypogonadism in an in vitro fertilization and embryo transfer program. J Assist Reprod Genet 2005;22:167–71.
15. Yildirim G, Ficicioglu C, Attar R, Akcin O, Tecellioglu N. Comparision of reproductive outcome of the women with hypogonadotropic hypogonadism and tubal factor infertility. Clin Exp Obstet Gynecol 2010;37:120–2.
16. Ghaffari F, Arabipoor A, Lankarani NB, Etminan Z, Tehraninejad ES. Assisted reproductive technique outcomes in hypogonadotropic hypogonadism women. Ann Saudi Med 2013;33:235–40.
17. Kumbak B, Kahraman S. Women with hypogonadotropic hypogonadism: cycle characteristics and results of assisted reproductive techniques. Acta Obstet Gynecol Scand 2006;85:1453–7.
18. Bakkensen JB, Brady P, Carusi D, Romanski P, Thomas AM, Racowsky C. Association between blastocyst morphology and pregnancy and perinatal outcomes following fresh and cryopreserved embryo transfer. J Assist Reprod Genet 2019;36:2315–24.
19. Gardner DK, Schoolcraft WB, Wagley L, Schlenker T, Stevens J, Hesla J. A prospective randomized trial of blastocyst culture and transfer in in-vitro fertilization. Hum Reprod 1998;13:3434–40.
20. Pandurangi M, Tamizharasi M, Reddy NS. Pregnancy outcome of assisted reproductive technology cycle in patients with hypogonadotropic hypogonadism. J Hum Reprod Sci 2015;8:146–50.
21. Kuroda K, Ezoe K, Kato K, Yabuuchi A, Segawa T, Kobayashi T, et al. Infertility treatment strategy involving combined freeze-all embryos and single vitrified-warmed embryo transfer during hormonal replacement cycle for in vitro fertilization of women with hypogonadotropic hypogonadism. J Obstet Gynaecol Res 2018;44:922–8.
22. Reshef E, Lei ZM, Rao CV, Pridham DD, Chegini N, Luborsky JL. The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. J Clin Endocrinol Metab 1990;70:421–30.
23. Licht P, Von Wolff M, Berkholz A, Wildt L. Evidence for cycle-dependent expression of full-length human chorionic gonadotropin/luteinizing hormone receptor mRNA in human endometrium and decidua. Fertil Steril 2003;79(Suppl 1):718–23.
24. La Marca A, Artenisio AC, Stabile G, Rivasi F, Volpe A. Evidence for cycle-dependent expression of follicle-stimulating hormone receptor in human endometrium. Gynecol Endocrinol 2005;21:303–6.
25. Sacchi S, Sena P, Degli Esposti C, Lui J, La Marca A. Evidence for expression and functionality of FSH and LH/hCG receptors in human endometrium. J Assist Reprod Genet 2018;35:1703–12.
26. Licht P, Russu V, Wildt L. On the role of human chorionic gonadotropin (hCG) in the embryo-endometrial microenvironment: implications for differentiation and implantation. Semin Reprod Med 2001;19:37–47.