ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Impact of the levonorgestrel-releasing intrauterine device on controlled ovarian stimulation outcomes

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Objective: To report differences in ovarian stimulation outcomes in women using a levonorgestrel-releasing intrauterine device (LNG-IUD).
Design: Retrospective cohort study.
Setting: University-based infertility practice.
Patient(s): Female patients pursuing either social oocyte cryopreservation or oocyte donation.
Intervention(s): Chart review of all female patients presenting from January 1, 2012, to June 30, 2017, for social oocyte cryopreservation or oocyte donation. Demographic data, cycle performance data, and the presence or absence of an LNG-IUD at the time of ovarian stimulation were compared.
Main Outcome Measure(s): Total oocyte yield and total mature oocyte yield. Secondary measures included clinical pregnancy rate and live birth rate in recipients of donor oocytes.
Result(s): Univariate analysis of predicted oocyte yield and mature oocyte yield showed no significant difference between subjects with and without an LNG. When controlling for history of recent hormonal contraceptive use, initial antral follicle count (AFC), age, body mass index (BMI), gonadotropin dose, and stimulation day/protocol, no significant differences were seen in total oocyte yield or mature oocyte yield in the presence or absence of an LNG-IUD. Univariate analysis of the effect of LNG-IUDs on the predicted clinical pregnancy rate and live birth rate did not significantly differ for oocyte recipients. Controlling for history of recent hormonal contraceptive use, initial AFC, age, BMI, gonadotropin dose, and stimulation day/protocol also showed no significant differences in the predicted clinical pregnancy rate and live birth rate.
Conclusion(s): LNG-IUDs do not affect cycle performance in women undergoing ovarian stimulation cycles. (Fertil Steril® 2018;■: ■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Levonorgestrel, intrauterine device, oocyte stimulation, oocyte donation

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Levonorgestrel (LNG)–releasing intrauterine devices (IUDs) are an effective form of long-acting reversible contraception (1). Because the popularity of intrauterine devices has increased in recent years, a growing proportion of women presenting for either social oocyte cryopreservation or oocyte donation may have an LNG-IUD in place during controlled ovarian stimulation (2).

These devices contain up to 52 mg LNG and function by releasing 20 μg local LNG to the endometrial cavity daily. In a retrospective study of 110 women, serum LNG levels were collected in women who had an LNG-IUD placed from 20 days to 11 years before sampling. At 1 year after LNG-IUD placement, the mean serum level of LNG was 191 $\pm$ 71 pg/m,L whereas after 3 years of use, the mean LNG level was 134 $\pm$ 41 pg/mL and decreased progressively over the subsequent years of sampling. The authors demonstrated a strong negative correlation between time of LNG-IUD placement and serum LNG levels (3). There has been some concern that either the local effects of LNG-IUDs may extend to the ovaries and have a direct impact on follicular maturation or that systemic levels may be high enough to affect ovarian stimulation (4). However, the general belief is that the mechanism of action of the LNG IUD is confined to the endometrium and cervical mucous.

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Limited data exist about the fertility potential of oocytes collected in the presence of an LNG-IUD. In 1997, Söderström-Anttila et al. reviewed seven ovarian stimulation cycles in the presences of an LNG-IUD matched with 16 cycles without the device and found no difference in stimulation. Recent matched retrospective cohort studies have reported similar findings wherein there appears to be no impact of the LNG-IUD on ovarian stimulation outcomes (5, 6). The first case report of two successful pregnancies with the use of oocytes donated from a woman who had an LNG-IUD during stimulation was described in 2004 (7).

Women pursing social oocyte cryopreservation typically do not intend to conceive in the near future. Furthermore, oocyte donors tend to be young women at the height of their reproductive potential. Both groups of women undergo similar treatment regimens of ovarian stimulation and during this time are known to be at risk for unintended pregnancy if they do not abstain from intercourse or use a barrier contraceptive method. It is important to understand if effective contraception, such as the LNG-IUD, commonly used by such individuals, impairs controlled ovarian stimulation and cycle performance. These data should assist providers in counseling patients regarding whether or not to remove their LNG-IUD before treatment.

In the present study, we evaluated any potential impact that an LNG-IUD may have on controlled ovarian stimulation and/or pregnancy outcomes from donated oocytes.

MATERIALS AND METHODS

Study Population

All patients who sought oocyte cryopreservation or who donated oocytes at the Center for Reproductive Health at the University of California San Francisco (UCSF) from January 1, 2012, to June 30, 2017, were eligible for this retrospective cohort study. Potential subjects who pursued fertility preservation for a diagnosis of malignancy or who had previously demonstrated infertility as documented in the patient chart were excluded. All eligible cycles were included for evaluation. Eligibility determination and data collection were performed by means of electronic chart review. Patient protocols included both agonist and antagonist protocols, which were categorized and accounted for in analysis. The UCSF Committee on Human Research, approved this study (IRB 17-22176).

Assessment of Antral Follicle Count

We assessed antral follicle count (AFC) by measuring follicles 2–10 mm in mean diameter with the use of a GE Voluson S6 transvaginal ultrasound. An initial AFC was determined to be either the AFC assessed at initial consultation or, for patients who pursued multiple cycles, the last documented AFC unrelated to controlled ovarian stimulation collected within the year before the planned cycle. If an adequate initial AFC was not described, we used a baseline AFC obtained at the start of the controlled ovarian stimulation cycle.

Protocols

The majority of patients, 79.5%, were stimulated with the use of a GnRH antagonist protocol. Antagonists included cetrorelix or ganirelex acetate and were started between cycle days 6 and 8 when the lead follicle was ≥ 12 mm. A minority of patients were treated with a leuprolide acetate (Lupron)–based protocol. In such cases, subjects were treated with 10 U Lupron daily beginning in the midluteal phase and then decreased to 5 U or discontinued at the commencement of gonadotropins. Criteria for hCG trigger included two follicles ≥ 17–18 mm with consideration of the cycle day and E_2 level. A small number of patients (8.06%) underwent clomiphene citrate or letrozole flare protocols (Table 1).

Outcome Measures

Primary outcome measures included the total oocyte yield and mature oocyte yield. Because conventional IVF was used in a large proportion of donated oocytes, the number of mature oocytes could be determined only in subjects who completed ovarian stimulation for the purposes of oocyte cryopreservation or intracytoplasmic sperm injection with the use of donated oocytes. Secondary outcome measures included predicted fertilization rate, blastocyst progression rate, blastocyst transfer rate, clinical pregnancy rate, and live birth rate from donated oocytes collected in the presence or absence of an LNG-IUD. In a given cycle, pregnancies may have occurred after either a fresh or frozen-thawed embryo transfer.

TABLE 1

Characteristics of patients undergoing ovarian stimulation in the presence or absence of a levonorgestrel-releasing intrauterine device (LNG-IUD).

Subject characteristic	LNG-IUD absent (n = 1,028)	LNG-IUD present (n = 45)	*P* value
Age, y	32.77 ± 5.92	33.14 ± 4.54	.60
BMI, kg/m^2	23.04 ± 3.58	22.79 ± 2.69	.60
Initial AFC	18.39 ± 9.70	19.15 ± 8.76	.60
No. of stimulation days	9.82 ± 1.52	10.30 ± 3.66	.39
Total FSH dose	1,863.31 ± 761.96	2,091.86 ± 773.03	<.05
Peak E_2	3,289.0 ± 1,589.14	2,600.69 ± 1,266.18	<.01
Peak E_2 per oocyte collected	194.41 ± 108.40	150.42 ± 51.50	<.01

Note: Values are reported as mean ± standard deviation. AFC = antral follicle count; BMI = body mass index; FSH = follicle stimulating hormone.

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