The role of elagolix in ovulation suppression during controlled ovarian stimulation: a retrospective cohort study

David Soliman, M.Sc.,[a] Rita Naoom, B.Sc.,[a] Mohamed Zaied, B.Sc.,[a] and Samuel Soliman, M.D.[a,b,c]

[a] Department of Embryology, Newlife Fertility Centre, Mississauga, Ontario, Canada; [b] Department of Obstetrics and Gynaecology, Brampton Civic Hospital, William Osler Health System, Brampton, Ontario, Canada; and [c] Department of Obstetrics and Gynaecology, University of Toronto, Toronto, Ontario, Canada

Objective: To compare in vitro fertilization treatment outcomes for the oral gonadotropin-releasing hormone (GnRH) antagonist elagolix (E) to the conventionally used injectable GnRH antagonist ganirelix (G) for achieving pituitary gonadotropin suppression during a controlled ovarian stimulation (COS) cycle.
Design: Retrospective cohort study.
Setting: Private university-affiliated fertility center.
Patient(s): One hundred and ninety-four infertility patients receiving either E or G for pituitary suppression during the COS cycle.
Exposure: Use of E for ovulation suppression during the COS cycle.
Main Outcome Measure(s): Biochemical pregnancy, sustained implantation, and cycle cancellation rates were the primary outcome measures. Secondary outcomes included miscarriage, fertilization, and blastulation rates.
Result(s): The groups did not differ in their baseline demographic characteristics (age, body mass index, hormone profiles, total dosage of gonadotropins, number of oocytes retrieved, and number of embryos transferred). The overall cycle cancellation rates were 7.0% and 4.9% for e and G, respectively, and the difference was not statistically significant. For the frozen embryo transfers, the biochemical pregnancy, sustained implantation, and miscarriage rates for E were 74.5%, 51.0%, and 31.6%, respectively. For G, these were 55.9%, 39.8%, and 28.8%. Out of these outcomes, only the biochemical pregnancy rates were significantly different. For the fresh embryo transfers, biochemical pregnancy, sustained implantation, and miscarriage rates for E were 33.3%, 33.3%, and 0.0%, and for G, they were 37.5%, 25.0%, and 33.3%. None of the differences reached significance.
Conclusion(s): The oral GnRH antagonist, E, may be as effective as the injected antagonist, G, regarding embryological and clinical outcomes and could offer a less invasive, more cost-effective, and "patient-friendly" approach to pituitary suppression for in vitro fertilization treatment. (F S Rep® 2024;5:356–62. ©2024 by American Society for Reproductive Medicine.)
Key Words: Ovulation suppression, GnRH antagonist, elagolix, ganirelix

Controlled ovarian stimulation (COS) for in vitro fertilization (IVF) treatment has proved to be one of the major advances in assisted reproductive technology. (1) During a COS cycle for IVF treatment, it is necessary to suppress the pituitary secretion of luteinizing hormone (LH) to prevent a premature LH surge, triggering ovulation before planned oocyte retrieval (2). Such pituitary suppression is achieved with gonadotropin-releasing hormone (GnRH) analogues, including agonists and antagonists. Gonadotropin-releasing hormone agonist protocols take advantage of the hypothalamic-pituitary-ovarian axis' natural feedback inhibition to prevent the premature ovulatory LH surge wherein the pituitary GnRH receptors are at first stimulated by the agonist and then subsequently desensitized and down-regulated, leading to a reversible inhibition of pituitary gonadotropin secretion (1). Agonist protocols have proved efficacious in this respect but have several drawbacks, including the time required to achieve pituitary desensitization and suppression (usually several weeks) because of the initial gonadotropin flare on receptor activation (1).

Received February 29, 2024; revised June 27, 2024; accepted June 28, 2024.
Correspondence: David Soliman, M.Sc., Department of Embryology, Newlife Fertility Centre, 4250 Sherwoodtowne Blvd., Mississauga, Ontario, L4Z 2G6, Canada (E-mail: davidsoliman@newlifefertility.com).

F S Rep® Vol. 5, No. 4, December 2024 2666-3341

https://doi.org/10.1016/j.xfre.2024.06.006

Moreover, agonist protocols are more costly overall because of the increased frequency of drug injections.

Conversely, GnRH antagonists can inhibit gonadotropin secretion immediately and reversibly through a dose-dependent competitive inhibition of the pituitary GnRH receptors (3). Thus, GnRH antagonists can limit pituitary suppression to only the days during which a premature LH surge is most likely to occur, precluding the need for the long down-regulation protocol of the agonists (1, 4). Elagolix (E) is an orally bioavailable GnRH receptor antagonist approved by the US Food and Drug Administration for the treatment of endometriosis-induced pain (4, 5). It inhibits endogenous GnRH stimulation of pituitary gonadotrophs by binding competitively and reversibly to the GnRH receptor in the anterior pituitary. This achieves rapid suppression of LH levels and follicle-stimulating hormone (FSH) release, which in turn decreases the production of ovarian estradiol (E2) and progesterone (P4) (4, 6). Endometriosis-induced pelvic pain is thought to be exacerbated by estrogen's promotion of the inflammatory implantation of endometrial-like tissue outside the uterus, causing dysmenorrhea, dyspareunia, and infertility (7). Despite its oral bioavailability, E retains a high affinity for the GnRH receptor and was found to significantly reduce pelvic pain associated with endometriosis in two double-blind, randomized, placebo-controlled clinical trials (8, 9). Elagolix was found to achieve rapid and reversible pituitary suppression, as noted by a maximum inhibition of LH secretion at doses of 200 mg twice per day and above with suppression increasing in a dose-dependent manner and gonadotropin levels returning to baseline 24–48 hours after the last dose (6). Currently, the only GnRH antagonists approved for pituitary suppression in COS for IVF treatment are the injectable types, such as ganirelix (G). Protocols using this medication require the patient to undergo multiple injections, which increases the cost of an already expensive IVF treatment cycle (10). The use of an orally bioavailable GnRH antagonist, therefore, would reduce the cost incurred by the patient while offering a less invasive and more "patient-friendly" option while still achieving acceptable ovulation suppression during COS (11). Elagolix has not yet been approved for pituitary suppression in the context of IVF treatment. Although previous studies have shown that E is not inferior to G in preventing premature ovulation, no well-controlled, randomized clinical trials have been conducted (10, 11). Thus, the goal of this retrospective cohort study was to assess the efficacy of E for pituitary suppression compared with G, with the aim of using the retrospective outcome data to establish a basis for a future randomized clinical trial. The primary outcomes were cycle cancellation, biochemical pregnancy, and sustained implantation rates, whereas the secondary outcomes were miscarriage, fertilization, and blastulation rates.

MATERIALS AND METHODS

Subjects

This retrospective cohort study was conducted at a private IVF treatment center in Mississauga, Canada, and was approved by the local research ethics board. The data on clinical and embryological outcomes and usage of E were gathered from patients' electronic medical records and the IVF treatment center dataset from January 4, 2022, until September 25, 2022. Included patients were those who had pituitary suppression achieved with E during the COS cycle and cases that used G as a comparator. Data on baseline demographic characteristics such as age, body mass index (BMI), number of embryos transferred, gonadotropin dose and stimulation duration, and infertility diagnosis were compared between the study and control groups. Clinical and embryological outcome data were analyzed retrospectively and compared between the study and control groups. The final sample comprised 194 patients with infertility aged 23–50 years with a BMI ranging from 15–42 kg/m^2 who had received E or G for pituitary suppression. The E group comprised 71 patients, whereas the G (control) group comprised 123 patients.

- Inclusion criteria: patients with infertility, aged 23–50 years with a BMI ranging from 15–42 kg/m^2 having received either E alone or G alone for pituitary suppression during the COS cycle.
- Exclusion criteria: patients outside the age range defined in the inclusion criteria. Patients who received neither or both E or G. Patients who were receiving either drug for a reason other than COS.

Pituitary Down-Regulation and COS

On cycle day 3, patients began oral clomiphene citrate (Clomid. Ferring Inc., Toronto, Ontario, Canada; 100 mg orally) daily for 5 days as well as daily injections of recombinant FSH (Puregon; Organon Canada Inc., Kirkland, Quebec, Canada), with the initial dose ranging from 200–325 IU/d on the basis of age, FSH level, antimüllerian hormone (AMH) level, and antral follicular count. On day 7 and then at 3–4-day intervals, serum E2 level testing and ultrasound monitoring were performed to guide recombinant FSH dosing. When a lead follicle of 14 mm or greater was observed on ultrasound, pituitary suppression was initiated. The study group received E (Orilissa, AbbVie Inc., Saint-Laurent, Quebec, Canada; 200 mg orally, two times per day); the control group received G (Cetrotide, Merck Canada Inc., Kirkland, Quebec, Canada; 250 μg, subcutaneously [SC], every night at bedtime). Elagolix, or G, was discontinued 24 hours before the GnRH agonist and human chorionic gonadotropin (hCG) trigger. Once follicular maturity was reached, as indicated by the E2 levels and follicular number and size, a GnRH agonist (Decapeptyl, Ferring Inc., Toronto, Ontario, Canada; 0.2 mg, SC/Suprefact, Xediton Pharmaceuticals Inc., Oakville, Ontario, Canada; 0.5 mg SC) and an hCG trigger (Pregnyl, Organon Canada Inc., Kirkland, Quebec, Canada; 10,000 IU SC) was used to induce ovulation. Oocyte retrieval was performed 36 hours after the trigger injection.

Endometrial Preparation for Embryo Transfer

Hormone replacement therapy was adopted for endometrial preparation. The protocol was initiated with oral E2 (Estrace, Trimel Pharmaceuticals Inc., Mississauga, Ontario, Canada; 4

mg three times daily) beginning on cycle days 2–5 after the transvaginal ultrasound scan. After a second ultrasound scan was performed and serum E2 and P4 levels were checked, the dose of E2 was adjusted accordingly. Luteal support was initiated when endometrial thickness reached ≥8 mm, and serum E2 and P4 levels were optimal. Luteal phase support was achieved via oral P4 (Prometrium, Merck Canada Inc., Kirkland, Quebec, Canada; 200 mg three times) daily and intravaginal micronized P4 suppositories (200 mg, three times daily). Progestin supplementation continued until pregnancy was confirmed at 10 weeks.

Embryo Vitrification, Thawing, and Transfer

Embryo vitrification and thawing followed the Kitazato (Kitazato Corp., Fuji, Shizuoka, Japan) protocol. Embryos were thawed the morning of the transfer and moved into organ culture dishes containing 1 mL of culture media (Life GlobalTotal, Cooper Surgical Inc., Toronto, Ontario, Canada) to be cultured for 3–4 hours, awaiting the transfer. The embryo transfer (ET) procedure was performed as described previously (12).

Preimplantation Genetic Testing for Aneuploidy

Embryos were hatched using a Reproductive Instruments Saturn diode laser (Cooper Surgical Inc., Toronto, Ontario, Canada) on day 3 of culture to allow trophectoderm herniation by day 5 or 6, after which biopsy was performed according to previously described methods (13). Biopsied samples were processed for deoxyribonucleic acid amplification, which was performed using a polymerase chain reaction. Chromosomal copy number analysis was performed using next-generation sequencing using the Illumina MiSeq platform (Illumina Canada Inc., Victoria, British Columbia, Canada) performed at the in-house genetic laboratory.

Reproductive Outcomes

A positive serum β-hCG level test confirmed biochemical pregnancy 2 weeks after the transfer. Sustained implantation was defined as the presence of a fetal heartbeat observed using ultrasonography 7–9 weeks post-ET. The sustained implantation rate per transfer was defined as the number of sustained implantations divided by the total number of ETs. Miscarriage was defined as a positive biochemical pregnancy test followed by the absence of a fetal heartbeat on the 7–9-week ultrasound. The miscarriage rate per biochemical pregnancy was defined as the proportion of patients who had a positive biochemical pregnancy test but did not show a fetal heartbeat on a 7–9-week ultrasound. The fertilization rate was defined as the number of fertilized oocytes divided by the total number of mature oocytes inseminated. The blastulation rate was defined as the number of blastocysts generated divided by the total number of fertilized oocytes.

Statistical Analysis

Continuous variables were presented as means. As appropriate, differences between groups were assessed using Student's or Welch's *t*-test and Mann-Whitney *U* tests. Categorical variables were expressed as frequencies and percentages within groups and were compared using Pearson's χ^2 and Fisher's exact tests as appropriate, with a *P* value of $<.05$ considered statistically significant. Relative risks (RRs) with 95% confidence intervals were calculated.

RESULTS

Group Demographic and Cycle Characteristics

A total of 194 cycles were included in this study: 71 cycles were included in the study group receiving E, and the control group comprised 123 patients receiving G. The G group had a significantly higher mean peak E2 level (11,352.3 vs. 7,505.6 pg/mL; *P*=.03) than the E group. Other than this, the baseline traits between groups were similar; there were no statistically significant differences in age or BMI between groups, with the mean age being approximately 35.4 years old in the E group and 36.1 years old in the control group (*P*=.304). There were no significant differences between groups regarding the proportion of patients in each age group (<35, 35-37, 38-40, >40). (Table 1) The mean BMI was 26.9 in the E group and 26.2 in the control group (*P*=.368). The groups were similar regarding the mean levels of basal FSH (E: 7.00 vs. G: 7.60 IU/L; *P*=.186), AMH (E: 36.7 vs. G: 21.6 pmol/L; *P*=.456), or P4 at the time of trigger (E: 1.40 vs. G 1.20 ng/mL; *P*=.142). The groups were similar regarding the mean number of retrieved (E: 12.7 vs. G: 12.4; *P*=.879), mature (E: 10.2 vs. G: 10.1; *P*=.679), and fertilized oocytes (E: 8.6 vs. G: 8.2; *P*=.90). The mean number of blastocysts generated (E: 5.2 vs. G: 5.2; *P*=.569) and embryos frozen (E: 4.9 vs. G: 4.5; *P*=.467) were similar between groups (Table 1).

Regarding the primary cause of infertility, the E group showed a significantly higher incidence of polycystic ovarian syndrome (11.3% vs. 0.0%; *P*=.02; RR 29.28 [1.72, 499.81]) and tubal factor infertility (9.9% vs. 2.4%; *P*=.038; RR 4.042 [1.079, 15.141]) compared with the G group. The incidences of all other primary causes of infertility were similar between groups. (Supplemental Table 1, available online). The groups did not differ regarding the proportions of transfer types performed, including single ET, double ET, and >2 ET, with most of the cycles being single ETs. (Supplemental Table 2). The gravidity and parity of each group were similar; most patients had no prior pregnancies (g0) and no prior deliveries (P0) (Table 1).

Embryology Outcomes

The intracytoplasmic sperm injection utilization rate was 75.8% and 76.1% for E and G, respectively (*P*=.962). Out of 671 mature oocytes inseminated by either intracytoplasmic sperm injection or conventional IVF treatment in the E group, 566 oocytes were fertilized, achieving a fertilization rate of 84.4%. In the control group, 955 oocytes were fertilized out of 1,178 mature oocytes to obtain a fertilization rate of 81.1%, and the difference was not statistically significant (*P*=.069; RR 1.041 [0.997, 1.086]). A total of 340 blastocysts were generated from fertilized oocytes of the E group, with a blastulation rate of 60.1%. In the control group, 610

TABLE 1

Group demographics and cycle characteristics: fresh and frozen cycles combined.

Characteristics	Elagolix	Ganirelix	*P* value	RR (95% CI)
No. cycles	71	123	n/a	n/a
overall cancellation rate	5/71 (7.0%)	6/123 (4.9%)	.499[a]	1.4855 (0.4705–4.6898)
Mean gonadotropin dose (IU)	3207.8	3422.0	.215[b]	n/a
Mean FSH (IU/L)	7.60	7.00	.186[b]	n/a
Mean P4 at hCG trigger (ng/mL)	1.40	1.20	.142[c]	n/a
Mean AMH level (ng/mL)	5.138	3.024	.456[d]	n/a
Mean peak E2 (pmol/L) (pg/mL)	1,050,784	1,589,322	.03[d]	n/a
Mean peak LH (IU/L)	7.1	7.2	.281[d]	n/a
Mean BMI (kg/m^2)	26.9	26.2	.368[b]	n/a
Grav 0	41/71 (57.7%)	83/123 (67.5%)	.192[e]	0.856 (0.677–1.081)
Para 0	57/71 (80.3%)	102/123 (82.9%)	.651[e]	0.968 (0.841–1.114)
Mean age (y)	35.4	36.1	.304[b]	n/a
<35	32/71 (45.1%)	45/123 (36.6%)	0.238[e]	1.2319 (0.8711–1.7421)
35–37	17/71 (23.9%)	32/123 (26.1%)	750[e]	0.9203 (0.5523–1.5335)
38–40	10/71 (14.1%)	27/123 (22.0%)	.190[e]	0.6416 (0.3303–1.2466)
>40	12/71 (16.9%)	19/123 (15.5%)	.790	1.0941 (0.5649–2.1192)

Note: AMH = antimüllerian hormone; BMI = body mass index; CI = confidence interval; E2 = estradiol; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; n/a = not applicable; RR = relative risk.
[a] Fisher's Exact Test
[b] Student's *t*-test
[c] Welch's *t*-test
[d] Mann-Whitney *U* test
[e] χ^2test

Soliman. Elagolix for ovulation suppression. F S Rep 2024.

TABLE 2

Embryology data.

Characteristics	Elagolix	Ganirelix	*P* value	RR (95% CI)
Mean oocytes retrieved	12.7	12.4	.879[a]	n/a
Mean mature oocytes	10.2	10.1	.679[a]	n/a
Mean oocytes fertilized	8.6	8.2	.9[a]	n/a
Mean blasts generated	5.2	5.2	.569[a]	n/a
Mean no. embryos frozen	4.90	4.50	.467[b]	n/a
Fertilization rate	566/671 (84.4%)	955/1178 (81.1%)	.069[c]	1.041 (0.997–1.086)
Blastulation rate	340/566 (60.1%)	610/955 (63.9%)	.144[c]	0.941 (0.866–1.021)
No. cycles ICSI (%)	50/66 (75.8%)	89/117 (76.1%)	.962[c]	0.996 (0.840–1.181)
No. cycles conventional IVF (%)	16/66 (24.2%)	28/117 (23.9%)	n/a	n/a

Note: CI = confidence interval; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; n/a = not applicable; RR = relative risk.
[a] Mann-Whitney *U* test
[b] Student's *t*-test
[c] χ^2 test.

Soliman. Elagolix for ovulation suppression. F S Rep 2024.

blastocysts were generated, giving a blastulation rate of 63.9%. This difference was not significant (*P*=.144; RR 0.941 [0.866, 1.021]). (Table 2)

Clinical Outcomes

Cycle cancellation. The number of canceled cycles in the E group was 5, 4 of which were canceled because of poor response to stimulation and one because of premature ovulation. The number of canceled cycles in the control group was six, including four because of poor response and two because of premature ovulation. The two groups' overall cycle cancellation rates were similar (E: 7.0% vs. G: 4.9%; *P*=.499; RR 1.486 [0.471, 4.690]) (Table 1).

Frozen ETs. Overall, 51 patients underwent frozen embryo transfers (FETs) in the E group and 93 in the control group. In total, 13 (25.5%) patients in the E group and 30 (32.3%) in the G group underwent a transfer with preimplantation genetic testing for aneuploidy (PGT-A)-tested embryos (*P*=.405). Among those in the E group, 11 (84.6%) were euploid, 1 (7.7%) was mosaic, and 1 (7.7%) was inconclusive. In the G group, 26 (86.7%) were euploid, 4 (13.3%) were mosaic, and 1 (4.7%) was inconclusive, and these proportions were statistically similar (Supplemental Table 3).

The biochemical pregnancy rate was significantly higher in the E group (E: 74.5% vs. G: 55.9%; *P*=.020; RR 1.333 [1.047, 1.697]) (Table 3). Notably, the difference between the biochemical pregnancy rate of the FETs that did and those that did not have PGT-A-tested embryos transferred was

TABLE 3

Clinical outcomes: frozen cycles.

Outcomes	Elagolix (%)	Ganirelix (%)	*P* value	RR (95% CI)
Biochemical pregnancy rate/ET	38/51 (74.5)	52/93 (55.9)	.020[a]	1.333 (1.047–1.697)
Sustained implantation rate/ET	26/51 (51.0)	37/93 (39.8)	.186[a]	1.281 (0.888–1.850)
Miscarriage rate/biochemical pregnancy	12/38 (31.6)	15/52 (28.8)	.779[a]	1.095 (0.581–2.063)

Note: CI = confidence interval; ET = embryo transfer; RR = relative risk.
[a] χ^2 test.

Soliman. Elagolix for ovulation suppression. F S Rep 2024.

not statistically significant (PGT-A: 58.1% vs. No PGT-A 64.4%; *P*=.496; RR 0.903 [0.675, 1.210]) and the differences still failed to reach significance after stratifying based on age (<35 and ≥ 35) years (Supplemental Table 4). The sustained implantation rate was higher for the E group, but the difference was insignificant (51.0% vs. 39.8%; *P*=.186; RR 1.281 [0.888, 1.850]). The miscarriage rate was similar between groups (31.6% vs. 28.8%; *P*=.779; RR 1.095 [0.581, 2.063]).

Fresh ETs. In the E and G groups, 15 and 24 patients underwent a fresh ET, respectively. The biochemical pregnancy rates were similar (33.3% vs. 37.5%; *P*=.794; RR 0.889 [0.368, 2.149]) as were the sustained implantation rates (33.3% vs. 25.0%; *P*=.571; RR 1.333 [0.492, 3.611]). The miscarriage rate was lower in the E group, but this difference was non-significant (0 vs. 33.3%; *P*=.313; RR 0.238 [0.015, 3.857]) (Table 4). For the fresh ET cycles, the proportion of patients with no prior delivery (Para 0) was significantly higher in the E group (E: 93.3% vs. G: 62.5%; *P*=.020; RR 1.492 [1.065, 2.094]). Besides this, the gravidity and parity of each group were similar (Supplemental Table 5).

DISCUSSION

Elagolix is an oral GnRH antagonist that is US Food and Drug Administration-approved for the treatment of endometriosis-induced pain (4, 5). Recently, studies have shown that it effectively suppresses ovulation during the COS cycle as efficiently as the injected antagonist, G (14–16). This retrospective cohort study examined the efficacy of E for ovulation suppression during COS relative to G. The study and control groups did not differ in their baseline characteristics and had similar numbers of oocytes retrieved and blastocysts frozen (Tables 1 and 2). It should be noted that the E group had a significantly lower peak E2 level than the G group, and this was most likely because the dose of E for this group (200 mg twice daily) is higher than the dosage used in previous studies (200 mg once daily) (10). Importantly, the cycle cancellation rates were similar between the E and G groups (Table 1), indicating that ovulation suppression is not compromised with the use of E. Regarding embryology outcomes, there were no differences in fertilization or blastocyst development rates between the study and control groups (Table 2). Furthermore, the groups did not differ in the number of embryos transferred (Supplemental Table 2).

When examining FETs, the E group's biochemical pregnancy rate was significantly higher (E: 74.5% vs. G: 55.9%; *P*=.02, RR 1.333 [1.047, 1.697]). However, this difference was not observed for patients undergoing fresh ETs (Tables 3 and 4). Additionally, the E group displayed a decreased miscarriage rate within the fresh ET subgroup. Still, this difference did not reach statistical significance, and regarding FETs, the groups were similar in this respect. The sustained implantation rates per transfer were similar between the E and the control groups for fresh and frozen ETs (Tables 3 and 4). Importantly, the utilization rate of PGT-A was similar in both groups, with a similar percentage of these patients having euploid embryos transferred (Supplemental Table 4). Moreover, the biochemical pregnancy rate across all FETs seemed unaffected by the use of PGT-A, which was found for patients above and below 35 (Supplemental Table 5). These data suggest that the apparent improvement in biochemical pregnancy in the E group undergoing FETs (E: 74.5% vs. G: 55.9%, *P*=.02, Table 3) is not because of greater utilization of euploid embryos. When analyzing FETs, the higher E2 levels in the G group were likely not the cause of the observed difference in biochemical pregnancy. This is because the endometrial disturbance caused by supraphysiologic E2 levels is removed in FET cycles by allowing time after the ovarian stimulation cycle for hormone level normalization. Additionally, no differences between the groups were observed in any clinical outcomes when analyzing fresh ET cycles, wherein a perturbed uterine environment caused by elevated E2 levels would normally pose an issue (17). One plausible explanation for the higher biochemical pregnancy rate in the E group is the higher incidence of patients with tubal factor infertility and polycystic ovary syndrome in this group. Patients with these etiologies can be considered to have a good prognosis and would be expected to have better outcomes. Thus, the higher proportion of these good prognosis patients in the E group could account for the observed improvement in biochemical pregnancy.

These preliminary findings demonstrate the clinical utility of the oral GnRH antagonist E for ovulation suppression

TABLE 4

Clinical outcomes: fresh cycles.

Outcomes	Elagolix (%)	Ganirelix (%)	*P* value	RR (95% CI)
Biochemical pregnancy rate/ET	5/15 (33.3)	9/24 (37.5)	.794[b]	0.889 (0.368–2.149)
Sustained implantation rate/ET	5/15 (33.3)	6/24 (25.0)	.571[a]	1.333 (0.492–3.611)
Miscarriage rate/Biochemical pregnancy	0/5 (0.0)	3/9 (33.3)	.313[a]	0.238 (0.015–3.857)

Note: CI = confidence interval; ET = embryo transfer; RR = relative risk.
[a] Fisher's exact test.
[b] χ^2 test.

Soliman. Elagolix for ovulation suppression. F S Rep 2024.

during the COS cycle. Our results agree with previous studies showing that E has similar efficacy to injectable antagonists for preventing premature ovulation. (10, 11). To our knowledge, this is the first study to demonstrate that clinical outcomes do not differ significantly between patients using E and G for pituitary suppression. Herein, we observed a potential improvement in the biochemical pregnancy rate in the E group undergoing FETs, regardless of PGT-A utilization. This difference may suggest a potential benefit of E over G. However, the reason for this difference is currently unknown, and randomized clinical trials are needed to address this question.

As the demand for IVF treatment grows, the potential arises to enhance patient care. Oral GnRH antagonists are less invasive, more efficient, and cost effective than the current antagonist and agonist protocols, which require multiple injections and more time for pituitary down-regulation and suppression (1). To expand on the financial benefit of the oral antagonist, patients in the elagolix group took two tablets daily for an average of 5 days, near the end of the stimulation cycle, until they were instructed to trigger. At an average cost of $8.40 Canadian Dollars (CAD) for each tablet of elagolix, patients paid approximately $84.00 for pituitary suppression during their cycles (18). Conversely, patients in the ganirelix group were administered one injection of ganirelix daily for an average of 7 days, near the end of the stimulation cycle. At an average cost of $103.30 CAD for one injection of ganirelix, patients would have paid approximately $723.10 CAD for pituitary suppression (19). Thus, the average savings accrued using elagolix instead of ganirelix amount to approximately $639.10 CAD per ovarian stimulation cycle. Therefore, elagolix could represent a promising alternative to injected antagonists for pituitary suppression in COS (1).

Nonetheless, the current analysis is limited in its retrospective nature and because it was not powered to detect differences in the primary outcomes of biochemical pregnancy, sustained implantation, and cycle cancellation rates because of the small sample size (N = 194). The lack of follow-up to live births poses another limitation, as does the fact that some embryos were cryopreserved and not used for transfer within the study timeframe, meaning their input to the study cannot be considered. Additionally, these data were collected from a single center, thus limiting the generalizability of the findings. Therefore, these preliminary findings must be interpreted cautiously and validated with large, robust, randomized clinical trials.

CONCLUSIONS

The oral GnRH antagonist, elagolix, may be as effective as the injected antagonist, ganirelix, regarding embryological and clinical outcomes and could offer a less invasive, more cost effective, and "patient-friendly" approach to pituitary suppression for IVF treatment.

CRediT Authorship Contribution Statement

David Soliman: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Rita Naoom:** Writing – original draft. **Mohamed Zaied:** Writing – original draft. **Samuel Soliman:** Supervision, Conceptualization.

Declaration of Interests

D.S. has nothing to disclose. R.N. has nothing to disclose. M.Z. has nothing to disclose. S.S. has nothing to disclose.

REFERENCES

1. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2016;4:CD001750.
2. Gordon K, Hodgen GD. GnRH analogues in ovarian stimulation. Ann N Y Acad Sci 1991;626:238–49.
3. Archer DF, Ng J, Chwalisz K, Chiu YL, Feinberg EC, Miller CE, et al. Elagolix suppresses ovulation in a dose-dependent manner: results from a 3-month, randomized study in ovulatory women. J Clin Endocrinol Metab 2020;105:821–32.
4. Lyseng-Williamson KA. Elagolix in endometriosis-related pain: a profile of its use as approved in the USA. Drugs Ther Perspect 2019;35:110–8.
5. Lamb YN. Elagolix: first global approval. Drugs 2018;78:1501–8.
6. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. J Clin Endocrinol Metab 2017;102:1683–91.
7. Giudice LC. Clinical practice. Endometriosis. N Engl J Med 2010;362:2389–98.
8. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.
9. Struthers RS, Nicholls AJ, Grundy J, Chen T, Jimenez R, Yen SS, et al. Suppression of gonadotropins and estradiol in premenopausal women by oral administration of the nonpeptide gonadotropin-releasing hormone antagonist elagolix. J Clin Endocrinol Metab 2009;94:545–51.
10. Boniface C, Schnorr JN, Gray J, McLaughlin J, Cook H, Slowey M, et al. The role of elagolix in the suppression of ovulation in donor oocyte cycles. F S Rep 2023;4:179–82.

11. Mouanness M, Merhi Z. Oral GnRH antagonist (elagolix) could represent a less invasive and more cost-effective alternative to the injectable GnRH antagonist for ovulation suppression in in vitro fertilization. Fertil Steril 2023;120:e3.
12. Saravelos SH, Li TC. Embryo transfer techniques. Best Pract Res Clin Obstet Gynaecol 2019;59:77–88.
13. Rubino P, Tapia L, Ruiz de Assin Alonso R, Mazmanian K, Guan L, Dearden L, et al. Trophectoderm biopsy protocols can affect clinical outcomes: time to focus on the blastocyst biopsy technique. Fertil Steril 2020;113:981–9.
14. Chwalisz K. Clinical development of the oral gonadotropin-releasing hormone antagonist elagolix. F S Rep 2023;4(2 Suppl):65–72.
15. Mannaerts B. Ganirelix and the prevention of premature luteinizing hormone surges. F S Rep 2023;4(2 Suppl):56–61.
16. Paulson RJ. At last, an orally active gonadotropin-releasing hormone antagonist. Fertil Steril 2019;111:30–1.
17. Özdemir AZ, Karli P, Gülümser Ç. Does high estrogen level negatively affect pregnancy success in frozen embryo transfer? Arch Med Sci 2020;18:647–51.
18. Online CP. Orilissa (Elagolix sodium). Canada Pharmacy Online. Available at: https://www.canadapharmacyonline.com/DrugInfo.aspx?name=Orilissa7529. Accessed May 9, 2024.
19. Pharmacy GS. Fertility Medications at Affordable Prices. Glen Shields Pharmacy. Available at: https://glenshieldspharmacy.com/fertility-products. Accessed May 9, 2024.