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ORIGINAL ARTICLE

# Comparison of buserelin and nafarelin in IVF cycles and in subsequent frozen-thawed embryo transfer cycles

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*Objective.* To compare two gonadotropin-releasing hormone agonists for down-regulation prior to superovulation in *in vitro* fertilization/embryo transfer treatment.
*Methods.* Infertility patients ($n$=181) were randomized to receive buserelin (1200 μg/day, $n$=90) or nafarelin (800 μg/day, $n$=91) intranasally starting in the luteal phase. Serum levels of LH, estradiol and progesterone were measured during the treatment. The cycles were compared with regard to number of oocytes, fertilization and implantation rates and achieved pregnancies.
*Results.* Serum LH was lower after two weeks on buserelin: 1.8 (1.3–2.4) IU/L (median, with lower and upper quartile in parenthesis), than after nafarelin: 2.6 (1.8–4.0) IU/L, ($p$=0.0001). No other differences in serum hormone levels could be detected. More oocytes were recovered in the buserelin group: 13.0 (8.0–19.0) *vs* 11.0 (6.8–15.0), ($p$=0.046), but the fertilization rate was higher in the nafarelin group (49.9% *vs* 45.1%, $p$=0.023). Implantation rate was higher in the nafarelin group (26.2% *vs* 15.5%, $p$=0.030), but there were an equal number of deliveries in both groups (20.9% *vs* 15.6% per started stimulation, $p$=0.420). In the subsequent frozen-thawed embryo transfer cycles the implantation rate was 21.1% (nafarelin group) and 10.6% (buserelin group, $p$=0.067), the pregnancy rate/ET was 31.7% and 17.0% ($p$=0.107) and the delivery rate was 22.0% and 10.6% ($p$=0.148), respectively.
*Conclusions.* Differences exist in IVF-cycles down-regulated with buserelin or nafarelin which might affect embryo quality and treatment outcome.

*Key words:* buserelin; frozen-thawed embryo transfer; *in vitro* fertilization-embryo transfer-treatment (IVF-ET-treatment); nafarelin

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The use of GnRH agonists (GnRHa) for pituitary down-regulation prior to ovarian superovulation in *in vitro* fertilization/embryo transfer (IVF/ET) treatments is a standard procedure in most IVF centers nowadays. The main advantage in using the GnRHa, as shown by Hughes and coworkers in their meta-analysis (1), is a higher pregnancy rate. This results mainly from the lower cancellation rate when the spontaneous luteinizing hormone (LH) surge is prevented before oocyte retrieval (2, 3), and the potential to improve qualitatively the folliculogenesis (4). Thereby an increased number of oocytes are retrieved per cycle, leading to more embryos that are available for transfer and cryopreservation. The disadvantage of the use of GnRHa is the higher cost of the medication and

*Abbreviations:*
ET: embryo transfer; hMG: human menopausal gonadotropin; GnRHa: gonadotropin releasing hormone agonists; IVF: *in vitro* fertilization; OHSS: ovarian hyperstimulation syndrome; OPU: oocyte pick-up; pd: period day; TVS: transvaginal sonography; EZ: estradiol; P: progesterone.

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the higher risk of ovarian hyperstimulation syndrome (OHSS) (5). Furthermore, suggestions imply that the use of GnRHa would produce embryos of poorer quality for the subsequent frozen-thawed embryo transfer cycles (6) although more recent reports have been unable to confirm this (7, 8).

Several GnRHa are available, with their route of administration varying from an intranasal (i.n.) spray, to a once-a-day subcutaneous injection, to a once-a-month depot implant (9). Both buserelin and nafarelin are administered as an i.n. spray, the former usually four times daily, the latter twice daily. In two recent studies the efficacy of buserelin and nafarelin was compared in achieving pituitary down-regulation prior to IVF (10, 11). Pregnancy rates did not differ between buserelin and nafarelin in these studies, but the women receiving nafarelin required significantly fewer ampoules of human menopausal gonadotropin (hMG) (10), and the number of days of stimulation with hMG was fewer in the nafarelin group (11).

In the present study, buserelin and nafarelin were compared in fresh IVF/ET with the long protocol, starting with an initial higher dose and decreasing the dose of GnRHa when the gonadotropins were started. Furthermore, the subsequent frozen-thawed embryo transfer cycles were studied.

## Materials and methods

### *Study population and treatment protocol*

During the period September, 1993 to June, 1994, 181 patients entering our IVF/ET program were randomized to receive either buserelin acetate (Suprecur, Hoechst AG, Frankfurt, Germany) or nafarelin acetate (Synarela, Syntex Nordica AB, Södertälje, Sweden) for pituitary down-regulation. The randomization was based on the patient's phone call to inform the clinic the starting date of her period, from which she started the treatment cycle. Every second patient was randomized to the buserelin and nafarelin group, respectively. The study protocol was approved by the local ethics committee. The two study groups (90 in the buserelin, 91 in the nafarelin group) were comparable in regard to age, diagnosis and type of infertility (primary or secondary) (Table I).

Table I. Patient characteristics of 181 women entering IVF/ET treatment, with down-regulation achieved by buserelin or nafarelin. Age given as mean±s.d., other parameters as absolute numbers with percentages in parenthesis

| | Buserelin | Nafarelin | *p* |
|---|---|---|---|
| No. of started cycles | 90 | 91 | |
| Age (years) | 33.3±4.2 | 34.4±3.7 | NS |
| Type of infertility | | | |
| primary | 39 (43.3%) | 40 (44.0%) | NS |
| secondary | 51 (56.7%) | 51 (56.0%) | |
| Diagnosis | | | |
| tubal | 45 (50.0%) | 45 (49.4%) | NS |
| unexplained | 25 (27.8%) | 16 (17.6%) | NS |
| endometriosis | 11 (12.2%) | 12 (13.2%) | NS |
| male factor | 6 (6.7%) | 7 (7.7%) | NS |
| combined | 3 (3.3%) | 8 (8.8%) | NS |
| anovulation | 0 | 3 (3.3%) | NS |

Both GnRHas were administered i.n. (buserelin four times daily at a dose of 1200 μg/day, nafarelin twice daily at 800 μg/day), beginning in the mid-luteal phase. After two weeks on the GnRHa, suppression was confirmed by transvaginal sonography (TVS, no follicles larger than 10 mm in diameter, endometrium less than 5 mm) and by low serum estradiol (E2 less than 0.10 nmol/L) levels. If the patient was not in suppression after two weeks, the GnRHa was continued for an additional 1–2 weeks until suppression was achieved, or if not, the patient was dropped from the study after 4 weeks on the GnRHa. When the patient was in suppression and superovulation was commenced, the dose of GnRHa was halved (buserelin 600 μg/day, nafarelin 400 μg/day). The superovulation with human menopausal gonadotropins (hMG, Pergonal, Laboratories Serono S.A., Aubonne, Switzerland) was started with a dose of 150–225 IU/day; the dosage was adjusted by TVS and serum E2 measurements and continued for 9–13 days. When at least two follicles reached a diameter of 18 mm, 10 000 IU of human chorionic gonadotropin (hCG, Pregnyl, Organon, Oss, The Netherlands) was given for ovulation induction, and administration of GnRHa was discontinued.

Oocyte pick-up (OPU) was performed with TVS guidance 36–38 hours after hCG. Semen was collected on the morning of OPU and prepared by the swim-up technique. Insemination was performed 4–6 hours after OPU. Fertilization was assessed 16 to 20 hours after insemination and cleavage rates and embryo grading 42 to 48 hours after insemination. For comparison the embryos were grouped into three categories: excellent (fragmentation <20%), good (fragmentation 20–50%) or poor (fragmentation >50%). Embryo transfer was routinely performed two days after OPU. As a rule, two embryos were transferred at one time; in only a few cases (age over 36 years and an earlier failed IVF/ET attempt) three embryos were transferred. The remaining embryos were cryopreserved by the slow freezing-thawing protocol with dimethylsulphoxide (DMSO) as a cryoprotectant (modified from 12). If the patient was considered to have an increased risk of developing OHSS (>20 retrieved oocytes and/or serum E2 >10

nmol/L), all good-quality embryos were cryopreserved and then thawed and transferred during subsequent natural or substitution cycles (13). Micronized vaginal progesterone (Lugesterone, Besins Iscovesco, Paris, France) 100 mg three times daily was used for luteal support starting after embryo transfer and continued for two weeks (three weeks if pregnant).

The luteal phase was monitored by serum E2 and progesterone (P) measurement six days after ET, and the treatment outcome by serum hCG measurement 12 days after ET. In cases where serum hCG was positive, TVS was performed five weeks after ET to assess viability of the pregnancy.

The frozen-thawed embryo transfers were done in natural cycles, in which follicle size and endometrial thickness were assessed by TVS on cycle days 10 to 12. The LH surge was determined with home urinary LH-kits (Clearplan, Organon, Oss, The Netherlands), and the embryos were thawed and transferred on the third or fourth day after LH surge. Micronized vaginal progesterone was used for luteal support (200 mg/day). The substitution cycles were done by GnRHa down-regulation (goserelin, Zoladex depot, Zeneca Pharmaceuticals, Macclesfield, UK) with one 3.6 mg implant s.c. which was inserted on period day (pd) 21–24. After the next menstruation, peroral estradiol valerate (Schering Pharma AG, Germany) was started with a dose of 4 mg/day on pd 3. Endometrial thickness was assessed on pd 10–12, and when it reached at least 8 mm, micronized vaginal progesterone was started at a dose of 600 mg/day. The embryos were thawed and transferred on the third or fourth day after the start of progesterone. Treatment with both estradiol and progesterone was continued for two weeks, and, if the pregnancy test was positive, until 12 weeks of gestation.

### *Assays*

Serum LH was measured by solid phase, two-site time-resolved immunofluorometric assay (DELFIA, Pharmacia Wallac, Turku, Finland), and E2 by a modification of the Clinical Assays Estradiol-2 RIA (Sorin Biomedica, Saluggia, Italy). P was assessed by RIA (Orion Diagnostica, Espoo, Finland) and hCG by DELFIA (Pharmacia Wallac, Turku, Finland).

### *Statistics*

The results are expressed as mean±s.d. or as median with the lower and upper quartile in parenthesis. Parametric data (i.e. continuous data) were analyzed with analysis of variance (ANOVA, Tables II and III). As all the comparisons involve comparison of two groups, ANOVA is in this case equivalent to the standard two-sample *t*-test and gives identical *p*-values. The nonparametric data (i.e. categorical or non-continuous data) were analyzed with the Mann-Whitney U test and Chi-Square tests (most of the data in Tables I, IV and V).

## Results

Both GnRH agonists were effective in pituitary down-regulation, but after two weeks on the GnRHa the levels of serum LH were significantly lower in the buserelin group (Table II). No differences between the two groups in serum E2 levels were observed during the down-regulation and subsequent superovulation. Furthermore, the luteal phase was similar in respect to serum E2 and serum P levels in the two study groups (Table II).

In both groups a similar number of cycles were cancelled before superovulation was started or did not reach OPU (11.1 *vs* 6.6%, Table III). Of these 16 patients, eight were not in suppression after 4 weeks, four were pregnant (leading to two spontaneous abortions, one tubal pregnancy and one normal delivery), two had a poor response to hMG, one had a functional cyst and one withdrew for personal reasons. No difference in number of days of hMG stimulation or number of ampoules of hMG could be observed between the two groups (Table III). There were significantly more follicles and also more oocytes recovered in the buserelin group (Table III). However, the number of fertilized oocytes was similar in both groups due to a significantly higher fertilization percentage in the

Table II. Hormonal characteristics of IVF/ET cycles in patients down-regulated by buserelin or nafarelin. Results given as median with the lower and upper quartile in parenthesis. LH was measured on the day the GnRH agonist was started and after 2 weeks' down-regulation (first hMG day). E2 and P were measured 9–10 days (maximal E2), 12–15 days (day OPU) and 19–22 days (luteal phase) after hMG start

| | Buserelin | Nafarelin | *p* |
|---|---|---|---|
| LH (IU/L) | | | |
| first GnRHa day | 4.8 (3.2–6.7) | 4.9 (3.3–6.8) | NS |
| first hMG day | 1.8 (1.3–2.4) | 2.6 (1.8–4.0) | 0.0001 |
| Estradiol (nmol/L) | | | |
| first GnRHa day | 0.40 (0.31–0.52) | 0.44 (0.26–0.55) | NS |
| first hMG day | 0.05 (0.05–0.05) | 0.05 (0.05–0.05) | NS |
| maximal E2 | 3.30 (1.99–6.11) | 3.52 (1.73–5.68) | NS |
| day OPU | 3.06 (1.74–4.59) | 3.00 (1.97–4.44) | NS |
| luteal phase | 1.35 (0.79–2.75) | 1.71 (0.80–2.44) | NS |
| Progesterone (nmol/L) | | | |
| day OPU | 18.8 (10.6–27.3) | 17.6 (11.6–25.9) | NS |
| luteal phase | 58.2 (41.6–91.3) | 66.9 (48.6–94.3) | NS |

Table III. Outcome of IVF treatment in patients down-regulated by buserelin or nafarelin. Results given as absolute numbers, with percentages in parenthesis or as median with the lower and upper quartile in parenthesis

| | Buserelin | Nafarelin | *p* |
|---|---|---|---|
| No. of started cycles | 90 | 91 | |
| Withdrawn | 10 (11.1%) | 6 (6.6%) | NS |
| not in suppression | 5 | 3 | |
| other reasons | 5 | 3 | |
| Cycles with COH+OPU | 80 | 85 | NS |
| Days of hMG | 11 (10–12) | 11 (10–12) | NS |
| No. of 75 IU hMG amps. | 22 (20–30) | 22 (20–30) | NS |
| No. of follicles at OPU | 17.0 (12.0–24.5) | 14.0 (10.0–21.0) | 0.034 |
| No. of oocytes recovered | 13.0 (8.0–19.0) | 11.0 (6.8–15.0) | 0.046 |
| No. of fertilized oocytes | 5.0 (2.0–8.0) | 5.0 (2.0–8.0) | NS |
| Fertilization % | 45.1% | 49.9% | 0.027 |
| Embryo quality | | | |
| excellent | 271 (54.0%) | 264 (52.5%) | NS |
| good | 54 (11.1%) | 74 (15.3%) | NS |
| poor | 172 (34.9%) | 159 (32.2%) | NS |
| Embryos transferred | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | NS |
| Embryos cryopreserved | 3.0 (0.0–6.0) | 3.0 (0.0–6.0) | NS |
| Cycles with no ET | 14 (15.6%) | 15 (16.5%) | NS |
| no fertilization | 9 | 12 | |
| risk of OHSS | 5 | 3 | |
| Cycles with ET | 66 (73.3%) | 70 (76.9%) | NS |
| Cycles with cryopreserv. | 44 (62.0%) | 47 (64.4%) | NS |

Table IV. Pregnancies and live births following embryo transfer in patients down-regulated by buserelin or nafarelin. Absolute numbers or percentages given

| | Buserelin | Nafarelin | *p* |
|---|---|---|---|
| Cycles with ET | 66 | 70 | NS |
| Pregnancy test negative | 44 | 30 | 0.005 |
| Biochemical pregnancy | 5 | 10 | NS |
| Implantation % | 15.5% (20/109) | 26.2% (39/110) | 0.030 |
| Clinical pregnancies | 17 | 30 | 0.036 |
| pregn/Started stim | 18.9% | 33.0% | |
| pregn/OPU | 21.3% | 35.3% | |
| pregn/ET | 25.8% | 42.9% | |
| Spontaneous abortions | 3 | 10 | NS |
| Tubal pregnancies | 0 | 1 | NS |
| Delivered | 14 | 19 | NS |
| singletons | 11 | 13 | |
| twins | 3 | 6 | |
| deliv./Started stim | 15.6% | 20.9% | |
| deliv./OPU | 17.5% | 22.4% | |
| deliv./ET | 21.2% | 27.1% | |

nafarelin group. Embryo quality was similar in both groups, as was the number of embryos transferred and the number of embryos cryopreserved (Table III). The number of cycles with embryo transfers (73.3% *vs* 76.9%) and the number of cycles with embryos cryopreserved (62.0% *vs* 64.4%) were also similar (Table III).

Overall pregnancy rate was 26.0% per started cycle, 28.5% per OPU and 34.6% per ET. Although a significantly higher implantation rate and significantly more clinical pregnancies were observed in the nafarelin group (Table IV), no significant difference appeared in the number of deliveries between the two groups (15.6% versus 20.9% per started stimulation in the buserelin and nafarelin groups, respectively).

In 63.2% of the treatment cycles embryos were also frozen with no difference between buserelin or nafarelin cycles. Thus far, 95 frozen-thawed embryo-transfer cycles have been performed, 62 of these in natural cycles and 33 in substitution cycles. An average of 1.8 embryos have been transferred per cycle, the implantation rate being 15.5% (10.6% in the buserelin group, 21.1% in the nafarelin group, $p=0.067$) and the clinical pregnancy rate 23.9% per embryo transfer (17.0% in the buserelin group, 31.7% in the nafarelin group, $p=0.107$). There have been more deliveries in the nafarelin group, although the difference is not significant

Table V. Treatment outcome in frozen-thawed (F/T) embryo transfer (ET) cycles following IVF treatment in patients down-regulated by buserelin or nafarelin. Absolute numbers or percentages given

| | Buserelin | Nafarelin | *p* |
|---|---|---|---|
| Patients with F/T ET cycles | 31 | 28 | NS |
| Number of F/T ET cycles | 52 | 43 | NS |
| natural cycles | 34 (65.4%) | 28 (65.1%) | NS |
| substitution cycles | 18 (34.6%) | 15 (34.9%) | NS |
| Patients with no F/T ET cycles | 13 | 19 | NS |
| no reason | 4 | 5 | |
| pregnant | 7 | 14 | |
| embryos disposed | 2 | 0 | |
| Embryos thawed | 150 | 135 | NS |
| Embryos transferred | 85 (56.7%) | 76 (56.3%) | NS |
| Number of cycles with: | | | |
| no embryos alive | 5 | 2 | |
| one embryo transfer | 12 | 11 | |
| two embryo transfer | 32 | 25 | |
| three embryo transfer | 3 | 5 | |
| Embryos transferred/cycle | 1.8 | 1.9 | |
| Outcome: | | | |
| pregn. test negative | 34 | 25 | NS |
| biochem. pregn. | 5 | 3 | NS |
| Implantation % | 10.6% (9/85) | 21.1% (16/76) | NS |
| Clinical pregnancies | 8 | 13 | NS |
| pregn/ET | 17.0% | 31.7% | |
| Spontaneous abortions | 2 | 3 | |
| Tubal pregnancies | 1 | 1 | |
| Ongoing/Delivered | 5 (10.6%) | 9 (22.0%) | NS |
| singletons | 4 | 6 | |
| twins | 1 | 3 | |

(10.6% in the buserelin group, 22.0% in the nafarelin group, $p=0.148$, Table V).

## Discussion

The choice of GnRH agonist in superovulation regimens for IVF-ET might affect both embryo quality and endometrial receptivity and subsequently the implantation and pregnancy rates. Two previous studies have compared buserelin and nafarelin in IVF-ET cycles using the long protocol (10, 11). Our study is the only one where a difference in clinical pregnancy rates, when calculated per embryo transfer, could be detected (25.8% with buserelin, 42.9% with nafarelin). On the other hand, because we had more miscarriages in the nafarelin group, there was no significant difference between the two groups in delivery rate (21.2% with buserelin, 27.1% with nafarelin). This is in line with the two previous reports showing no differences in pregnancy or delivery rates (10, 11).

The present study showed lower serum LH levels in the buserelin group after two weeks treatment with the GnRHa, but ovarian suppression was equal when assessed by TVS and serum E2 measurements. Stimulation with hMG lasted on average 11 days and did not differ between the groups in the present study. Lockwood and coworkers (11) reported a significant difference in stimulation days (9.4 days with nafarelin, 10.4 days with buserelin), and Goldman and coworkers (10) had a similar result (9.1 days with nafarelin, 13.2 with buserelin), although this difference did not reach significance. Furthermore, we found no difference in the amount of 75 IU hMG ampoules used between the groups (median 22/cycle). This is well in line with results in the study from the UK (25 amp. with nafarelin, 28 amp. with buserelin, NS) (11), whereas in the Israeli study significantly more hMG was required (32 amp. with nafarelin, 42 amp. with buserelin, $p<0.01$) (10). Interestingly enough, we did collect more oocytes at ovum pick up (12 oocytes, ref. 10: 8 oocytes, ref. 11: 7 oocytes), but in contrast to this we had the lowest fertilization percentage (48%, ref. 10: 61%, ref. 11: 74%). Both these differences could be a reflection of our policy to puncture all visible follicles at ovum pick up, and therefore it is possible that a greater number of immature oocytes are included in our study. Furthermore, it is interesting to speculate if the higher number of oocytes but a lower fertilization rate in the buserelin group could indicate different dynamics of follicular development, that is more medium sized follicles with more immature oocytes in the buserelin group and therefore a lower fertilization potential.

No previous study has determined the relative potency of buserelin and nafarelin, and therefore the dose equivalency of these compounds is not known (9). The effect of GnRHa in general is dose dependent. Buserelin at a dose of 1200 μg/day required a significantly longer duration of hMG treatment and a greater total dose of hMG than did buserelin at 600 μg/day (14). With nafarelin, a dose of 800 μg/day required a significantly shorter time to down-regulation than did nafarelin at 400 μg/day (11). Similarly, triptorelin at a dose range from 25 to 200 μg, shows a clear dose-dependent suppression (15) and even the lowest dose used produced a considerable degree of pituitary suppression. What all this suggests is that more dose-finding studies are required. In the present study the dose of GnRHa was halved upon initiation of superovulation. The initial high dose increases the probability of the patients' being in suppression after two weeks on the GnRHa, as also suggested in the study of Lockwood and coworkers (11) comparing nafarelin at two different doses (800 ug *vs* 400 ug). Consequently, a lower cancellation rate is achieved, which is an advantage for both the patient and the clinic. There are potential advantages in reducing the dose of the GnRHa when superovulation begins: First, assuming that GnRHa might have adverse effects on the developing oocyte or on granulosa cells, these effects could be minimized by reducing the dose (16). Secondly, this lowers the cost of the treatment as less GnRHa and possibly less hMG is needed.

The implantation and pregnancy rates in an IVF program are affected by two major determinants: oocyte quality and endometrial receptivity. Testart and coworkers (6) suggested that, when compared to treatment without a GnRHa, GnRHa treatment in a long protocol has a positive influence on uterine receptivity but a negative influence on oocyte and embryo quality. In the present study we could detect a small difference between the two GnRHa in fertilization rates, no difference in embryo quality and a significantly higher implantation rate in the nafarelin group. In a study comparing buserelin to triptorelin, no difference in fertilization rates could be detected, but the buserelin group had a significantly higher implantation rate (17), suggesting that different GnRHas could influence the luteal phase differently. In our study no differences in luteal phase serum estradiol or progesterone (reflecting also the micronized progesterone supplementation) levels could be detected, but it might be the case that these variables are too crude to detect true differences in the luteal phase.

To gain further insight into the effect of GnRHa on embryo quality and endometrial receptivity, the subsequent frozen thawed ET cycles were studied. Previous reports have compared the results in

frozen-thawed ET cycles in patients where the superovulation for IVF was done with or without GnRHa. The original suggestion that use of GnRHa led to a much lower implantation rate in the subsequent frozen-thawed ET cycle (6) has, in more recent studies, remained unconfirmed (7, 8). Our present study is the first to compare two GnRHas in the subsequent frozen-thawed ET cycles. As in the fresh ET following IVF stimulation, similarly the implantation and clinical pregnancy rates in the frozen-thawed cycles were higher for nafarelin than for buserelin (31.7% *vs* 17.0%), although this difference is not significant possibly due to the small numbers. The difference is, however, at least suggestive that the two GnRHa would rather affect embryo quality than endometrial receptivity.

The preferred route of administration for GnRHa in IVF has (at least in Europe) been intranasal, although its bioavailability is only around 3% (18). The disadvantage with buserelin has been the frequent doses (4–6 times daily). In this respect nafarelin has been preferred by patients, as it is dosed only twice a day. In addition, a significantly higher incidence of headaches and hot flushes occurs in patients using buserelin, than in those using nafarelin (11). This could be due to the somewhat deeper down-regulation caused by buserelin, as shown in our study.

In conclusion, differences exist in IVF-cycles down-regulated with nafarelin or buserelin, leading to higher fertilization and implantation rates in the nafarelin group, however, no differences in the number of deliveries were seen between the two groups.

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