Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles

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Objective: To evaluate the efficacy of GnRH agonists (GnRH-a) as sole luteal phase support in patients undergoing IVF in antagonist-based cycles compared with standard vaginal P preparations.
Design: Retrospective cohort.
Setting: Private fertility clinic.
Patient(s): Patients who underwent antagonist-based cycles performed at our clinic between 2009 and 2015.
Intervention(s): Intranasal GnRH-a or vaginal P as luteal support.
Main Outcome Measure(s): Live birth rates.
Result(s): A total of 2,529 antagonist-based cycles from 1,479 women were available for analysis, in which GnRH-a were used in 1,436 cycles (56.7%) and P supplementation in 1,093 cycles (43.2%). Significantly higher live birth rates were demonstrated for the entire GnRH-a group compared with the P group. This result was even more prominent when women older than 35 years were considered separately. Furthermore, after adjustment for age, body mass index (BMI), past obstetric history, number of IVF cycles, oocyte retrieved and embryos transferred, GnRH-a was still associated with a higher rate of live birth (odds ratio 1.46, 95% confidence interval 1.10–1.94). Once a positive β-hCG was achieved, chemical pregnancy rates (PRs) and miscarriage rates were not statistically different between the GnRH-a and the P supplementation group, and GnRH-a was associated with a higher rate of live births (odds ratio 1.59, 95% confidence interval 1.07–2.36).
Conclusion(s): This large retrospective study suggests that repeated intranasal GnRH-a for luteal phase support is associated with a higher live birth rate compared with standard P supplementations. (Fertil Steril® 2017;107:130–5. ©2016 by American Society for Reproductive Medicine.)
Key Words: GnRH analogue, luteal phase support, in vitro fertilization (IVF), pregnancy, live birth rate

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Luteal phase deficiency is an unfavorable sequel of assisted reproduction technology (ART). To compensate for this lack, luteal phase support is routinely incorporated in ART cycles with supplementation in various forms and doses. Progesterone is the hallmark of luteal supplementation and is commonly used as the sole preparation for support, or in combination with hCG preparations, E_2 preparations, or both.

In addition to the standard luteal phase support, the administration of a single or multiple boluses of luteal GnRH agonists (GnRH-a) has gained popularity in ART protocols in recent years. It has been found to improve pregnancy and live birth results (1).

In 2005 Pirard et al. (2) investigated the use of GnRH-a as a substitute to P for luteal phase support. They conducted a feasibility study followed by a pilot study in 2006 (3) and a prospective randomized comparative study in 2015 (4). All three studies demonstrated that continued luteal intranasal administration of GnRH-a as a sole preparation for luteal phase support is effective in nondown-regulated cycles.

To our knowledge, this is the first large study (2,529 ART cycles)

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investigating the administration of daily, repeated intranasal GnRH-a as a sole preparation for luteal phase support. We retrospectively evaluated GnRH-a for luteal support in patients undergoing IVF and/or intracytoplasmic sperm injection (ICSI) in antagonist-based cycles, and compared its efficacy to that of standard vaginal P preparations.

MATERIALS AND METHODS

This study is a retrospective evaluation of 2,529 antagonist-based cycles performed in 1,479 women aged 25–45 years in our clinic between December 2009 and May 2015 (The Fertility Clinic from A to Z, Ramat Aviv, Tel-Aviv, Israel). Oocyte pickup and ET procedures were performed in Assuta Medical Centre Rishon LeZion.

Stimulation in these patients was initiated on day 3 of the menstrual cycle with either recombinant FSH (Gonal-F, Puregon, Pergoveris, Elonva) or hMG (Menogone, Menogpur HP). A flexible approach for antagonist co-treatment (Orgalutran or Cetrotide) was initiated whenever the leading follicle reached 15 mm or the E_2 level was >1,000 pmol/L, and was continued until, and including, the day of ovulation induction. Final oocyte maturation was triggered with a single double bolus of Ovitrelle (0.250 mg each). Oocyte pick-up was performed 36 hours later.

Patients were presented upon initiation of every cycle with a choice of luteal support—GnRH-a inhaler or traditional vaginal P tablets—in light of new research published before their treatment during the study period (3). It was stated that according to this new research they seem to have comparable efficacy and the ease of use seems to be in favor of the inhaler. No attempt was done to convince the patients to use either one of these luteal support methods. Subsequently, luteal support patients were treated with either nasal inhaler (GnRH-a group) or common vaginal preparations (P supplementation group). Cycles during which luteal support was switched from the inhaler to vaginal route were excluded from analysis. There were two reasons for switching: patient inconvenience or low midluteal P levels (<30 mmol/L). Switching from vaginal preparation to the inhaler was not performed due to what we assumed as the presumed mechanism. In cases of low midluteal P levels, we doubled the vaginal dosage.

In the GnRH-a group luteal support was initiated on the evening of oocyte retrieval (one puff of 200 μg of nafareline [Synarel]) followed by 200 μg twice daily (total, 400 μg/d). Gonadotropin-releasing hormone administration was terminated 2 weeks after oocyte pickup. In cases with a positive hCG result no additional luteal support was provided (5). In the P supplementation group our patients received either Endometrin (200 mg twice a day) or Crinone 8% (1 application twice a day) starting the morning after egg retrieval. This support was also terminated 2 weeks after oocyte pickup in cases with a positive hCG results.

In both groups, P and E_2 levels were evaluated in the midluteal phase to confirm satisfactory luteal support levels. Satisfactory levels were considered as 30 mmol/L for P and 300 mmol/L for E_2, the SD cutoff calculated from previous cycles performed at our clinic. Progesterone and E_2 levels were also evaluated with positive pregnancy tests.

All of our patients have electronic charts using Clicks software, where baseline characteristics and current treatment outcomes are registered. The baseline variables used were age, body mass index (BMI), previous IVF cycles, number of children, and number of previous pregnancies. Current treatment outcomes used were number of oocytes retrieved, number of embryos transferred, implantation rate (calculated as number of sacs on ultrasound divided by number of embryos transferred), midluteal P and E_2 levels, positive pregnancy test (defined as a β-hCG level of $\geq$40 mIU/mL), chemical pregnancy (β-hCG <1,000 mIU/mL), miscarriage (after demonstration of a intrauterine gestational sac), and live birth (>24 weeks gestation) outcomes.

A detailed statistical analysis was performed using STATA, version 12.0. Differences between mean values were assessed by *t* tests and Pearson χ^2 tests. Logistic regressions were used to estimate the effect of GnRH-a on several pregnancy outcomes, and odd ratios were obtained. Multivariable models simultaneously adjusted for age, BMI, number of cycle, number of children, number of previous pregnancies, number of oocytes retrieved, and number of embryos transferred. In further analysis we also controlled for midluteal P and E_2 levels. When midluteal P and E_2 levels were considered, the values of their natural logs were used to normalize their distributions. Regression analysis was conducted with robust standard errors to adjust for patients having multiple IVF treatments. All *P* values were two-sided and a probability of <.05 was considered to be statistically significant. An Institutional Review Board approval for the study was provided by the Assuta Medical Center Institutional Review Board committee.

RESULTS

Between December 2009 and May 2015, a total of 2,529 ART cycles from 1,479 women aged 25 to 45 years at treatment time were available for analysis. In 1,436 treatment cycles (56.7%) GnRH-a was used, whereas traditional P supplementation was used in 1,093 treatment cycles (43.2%).

Women in the GnRH-a group were younger (37.7 $\pm$ 4.8 vs. 39.6 $\pm$ 3.9 years old; $P<.001$) and had fewer IVF cycles (1.6 $\pm$ 1.1 vs. 1.9 $\pm$ 1.4; $P<.001$). Number of children, number of previous pregnancies, and BMI were not significantly different between groups (Table 1). After treatment they had a higher number of oocytes retrieved (9.7 $\pm$ 7.6 vs. 4.7 $\pm$ 5.3; $P<.001$) and embryos transferred (2.0 $\pm$ 1.0 vs. 1.9 $\pm$ 1.0; $P<.001$), and a higher implantation rate (12.9% vs. 9.8%; $P<.001$). Positive β-hCG was achieved in 27.9% of the GnRH-a cycles compared with 19.8% of P cycles ($P<.001$). In cases of a positive β-hCG, chemical pregnancy rates (PRs) were not statistically different between the GnRH-a and the P supplementation groups, compared with miscarriage rates, which were significantly lower, and live birth rates, which were significantly higher among women treated with GnRH-a.

Women treated with GnRH-a had significantly higher levels of midluteal P and E_2 levels (194.3 $\pm$ 146.0 vs 134.0

TABLE 1

Baseline characteristics and primary results for the GnRH agonist (GnRH-a) and the P supplementation groups.

Variable	GnRH-a (n = 1,436)	P (n = 1,093)	*P* value
Baseline characteristic			
Age (y), mean ± SD	37.7 ± 4.8	39.6 ± 3.9	< .001
BMI (kg/m^2)	23.4 ± 4.6	23.4 ± 4.5	.81
Previous pregnancies	1.5 ± 1.4	1.5 ± 1.4	.63
Live children	0.6 ± 0.7	0.6 ± 0.8	.87
IVF cycles	1.6 ± 1.1	1.9 ± 1.4	< .001
Primary results			
Oocytes retrieved	9.7 ± 7.6	4.7 ± 5.3	< .001
Embryos transferred	2.0 ± 1.0	1.9 ± 1.0	< .001
Implantation rate, % (n)	12.9 (387/2,997)	9.8 (207/2,100)	< .001
Positive β-hCG, n (%)	401 (27.9)	217 (19.8)	< .001
Chemical pregnancy	51/401 (12.7)	32/217 (14.7)	.48
Miscarriage	74/401 (18.4)	65/217 (29.9)	.001
Live birth	254/401 (63.3)	108/217 (49.7)	.001
Midluteal P (mmol/L)	194.3 ± 146.0	134.0 ± 113.4	< .001
Midluteal E_2 (mmol/L)	3,453.7 ± 2,826.8	1,810.1 ± 2,314.2	< .001
Pregnancy with P (mmol/L)	222.1 ± 155.0	144.9 ± 82.6	< .001
Pregnancy with E_2 (mmol/L)	6,921.3 ± 4,476.7	3,407.5 ± 2,970.0	< .001

Note: Data presented as mean ± SD, unless stated otherwise. BMI = body mass index.

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± 113.4 mmol/L; *P*< .001 and 3,453.7 ± 2,826.8 vs. 1,810.1 ± 2,314.2 mmol/L; *P*< .001, respectively). When pregnancy was achieved, significantly higher E_2 and P levels were demonstrated in the GnRH-a group (6,921.3 ± 4,476.7 vs. 3,407.5 ± 2,970.0 mmol/L for E_2 and 222.1 ± 155.0 vs. 144.9 ± 82.6 mmol/L for P; *P*< .001) (Table 1).

Positive pregnancy test rates (positive β-hCG) were significantly higher for the GnRH-a group when all women were included in the analysis (27.9% vs. 19.8%; *P*< .001). When the analysis was conducted according to women's age, positive β-hCG rates were significantly higher for the GnRH-a group for women aged 35 to 39 years (33.4% vs. 24.9%; *P*= .01), but not among women younger than 35 years and women aged ≥40 years (*P*= .16 and *P*= .16, respectively) (Table 2).

Live birth rates were also significantly higher for the GnRH-a group when all women were included in the analysis (17.6% vs. 9.8%; *P*< .001). When the analysis was conducted according to women's age, live birth rates were significantly higher for the GnRH-a group for women aged ≥35 years (20.2% vs. 14.3%; *P*= .04 and 8.3% vs. 5.0%; *P*= .01 for women aged 35–39 years and women aged ≥40 years, respectively), but not for women younger than 35 years (*P*= .52) (Table 2).

TABLE 2

Positive β-hCG and live birth rates in the GnRH agonist (GnRH-a) and P supplementation groups, stratified by age.

Variable	GnRH-a (n = 1,436)	P (n = 1,093)	*P* value
Positive β-hCG			
All patients	401/1,436 (27.9)	217/1,093 (19.8)	< .001
Patient age (y)			
<35	157/375 (41.8)	48/137 (35.0)	.16
35–39	147/439 (33.4)	71/285 (24.9)	.01
≥40	97/622 (15.5)	98/671 (14.6)	.61
Live births			
All patients	254/1,436 (17.6)	108/1,093 (9.8)	< .001
Patient age (y)			
<35	113/375 (30.1)	33/137 (24.0)	.18
35–39	89/439 (20.2)	41/285 (14.3)	.04
≥40	52/622 (8.3)	34/671 (5.0)	.01

Note: Data presented as cases/patients within age strata (%).

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In a multivariate regression analysis, after controlling for age, BMI, number of IVF cycles, number of children, number of previous pregnancies, number of oocytes retrieved, and number of embryos transferred, whereas GnRH-a luteal support was not associated with significantly higher positive β-hCG (odds ratio [OR] 1.07, *P*= .52 and OR 1.12, *P*= .31, respectively), it was still associated with a higher live birth rate (OR 1.46, *P*= .009) (Table 3).

To further analyze the effect of GnRH-a on specific pregnancy outcomes we focused our attention on women with positive β-hCG (Table 1). In a multivariate regression analysis age, BMI, number of IVF cycles, number of children, number of past pregnancies, number of oocytes retrieved, and number of embryos transferred were used as controls. We found that conditional on positive β-hCG, live birth rates were significantly higher among the GnRH-a group (OR 1.59, *P*= .02), whereas chemical PRs and miscarriage rates were not statistically different between the GnRH-a and the P supplementation groups (OR 0.83, *P*= .52 and OR 0.74, *P*= .16 respectively) (Table 4).

DISCUSSION

The results of this study suggests that administration of daily, repeated intranasal GnRH-a for luteal phase support is associated with a higher live birth rate in comparison with the traditional vaginal P. To our knowledge, this is the first large study investigating the sole administration of daily, repeated intranasal GnRH-a for luteal phase

TABLE 3

Regression results: the effect of GnRH agonist (GnRH-a) on positive β-hCG and live birth.

	Positive β-hCG			Live birth		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
GnRH-a (yes)	1.07	0.86–1.34	.52	1.46	1.10–1.94	.009
Age (y)	0.88	0.86–0.90	<.001	0.85	0.82–0.87	<.001
BMI (kg/m^2)	0.99	0.97–1.02	.94	0.97	0.94–1.001	.06
IVF cycle (n)	0.89	0.81–0.98	.02	0.88	0.78–0.99	.03
Children (n)	1.75	1.52–2.03	<.001	2.40	1.98–2.91	<.001
Previous pregnancies (n)	1.02	0.94–1.11	.49	0.95	0.84–1.07	.45
Oocytes retrieved (n)	1.02	1.007–1.04	.004	1.002	0.98–1.01	.80
Embryos transferred (n)	1.11	1.009–1.22	.03	1.10	0.97–1.25	.11

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

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support, as a substitute for the much less convenient P supplementation. At present, only three small studies (2–4), all by Pirard et al., have investigated this issue. All of them demonstrated that continued luteal intranasal administration of GnRH-a as a sole preparation for luteal phase support is effective in nondown-regulated cycles. We have also recently demonstrated GnRH-a efficacy in high-responder patients triggered with GnRH-a (6). Our results are thus in concordance with these pioneer studies.

We also found that among women with positive β-hCG, live birth rates were significantly higher among the GnRH-a group (Table 4). This suggests that the advantage of GnRH-a is not only unique to the luteal phase and that even after a pregnancy is achieved, for which luteal support is used, may still have a positive effect on live birth.

The study also demonstrates significantly higher levels of midluteal P and E_2 levels among the GnRH-a group (Table 1). This may indicate a possible mechanism for the favorable PR in the GnRH-a group, as luteal P plays an important role in conceiving (7). To further assess the independent effect of treatment and control for possible higher endogenous levels of hormones in the GnRH-a group, we analyzed the effect of GnRH-a on positive β-hCG, implantation rates, and live birth rates in a multivariate logistic regression analysis after adjustment for midluteal P and E_2 levels (Supplemental Table 1, available online). We found that GnRH-a was no longer significantly associated with higher live birth rates (OR 1.31, $P=.09$), implying that this may be the mechanism.

A major limitation of our study is its retrospective nature. In addition, substantial differences in initial conditions were observed between women treated with GnRH-a and those treated with conventional P supplementation (Table 1). Women in the GnRH-a group were younger, had fewer IVF cycles, higher number of oocytes retrieved, and higher number of embryos transferred. However, even when analysis stratified by age groups was conducted, higher positive β-hCG rates were observed for women aged 35–39 years in the GnRH-a group, and higher live birth rates were observed for all women aged ≥35 years in the GnRH-a group (Table 2).

To further evaluate whether baseline characteristics were the reason for the better pregnancy outcomes among women treated with GnRH-a, we also conducted a multivariate logistic regression analysis controlling for various characteristics including age, and found that although GnRH-a was not

TABLE 4

Regression results: the effect of GnRH agonist (GnRH-a) on chemical pregnancy, miscarriage and live birth: patients with a positive β-hCG only.

	Chemical pregnancy		Miscarriage		Live birth	
Variable	**OR [95% CI]**	***P* value**	**OR [95% CI]**	***P* value**	**OR [95% CI]**	***P* value**
GnRH-a (yes)	0.83 (0.46–1.47)	.52	0.74 (0.48–1.13)	.16	1.59 (1.07–2.36)	.02
Age (y)	1.01 (0.96–1.07)	.47	1.13 (1.07–1.19)	>.001	0.90 (0.86–0.93)	<.001
BMI (kg/m^2)	0.99 (0.94–1.05)	.96	1.02 (0.97–1.06)	.36	0.95 (0.91–0.99)	.02
IVF cycles (n)	1.16 (0.97–1.38)	.09	.099 (0.79–1.24)	.96	0.95 (0.81–1.12)	.59
Children (n)	0.66 (0.41–1.07)	.09	0.55 (0.41–0.75)	<.001	2.1 (1.57–2.94)	<.001
Past pregnancies (n)	1.02 (0.84–1.24)	.77	1.18 (1.02–1.38)	.02	0.87 (0.75–1.02)	.09
Oocytes retrieved (n)	1.02 (0.98–1.05)	.20	0.99 (0.96–1.01)	.59	0.97 (0.94–0.99)	.02
Embryos transferred (n)	1.16 (0.89–1.49)	.25	0.87 (0.69–1.09)	.23	1.03 (0.84–1.25)	.73

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

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associated with significantly higher positive β-hCG rates (OR 1.073, $P=.52$), it was still associated with significantly higher live birth rates (OR 1.469, $P=.009$) (Table 3).

Administration of midluteal single or multiple boluses of GnRH-a as an addition to P supplementation has gained popularity in ART cycles in recent years (8). A Cochrane meta-analysis (9) demonstrated significantly higher PRs when P luteal phase support was combined with GnRH-a compared with P alone, without influencing either miscarriage rate or multiple PR.

The exact mechanism for the beneficial effects of GnRH-a is still an enigma. At present, it is hypothesized to work at three different levels, or some combination thereof—the corpus luteum (CL), the endometrium, and the embryo. Gonadotropin-releasing hormone agonist stimulates the secretion of LH by pituitary gonadotropin cells and hence promotes CL maintenance (3). Gonadotropin-releasing hormone agonist also promotes the expression and secretion of relaxin by the CL (10). Furthermore, LH release has been demonstrated to have a beneficial effect on the endometrium, including stimulation of angiogenic growth factors and cytokine discharge involved in implantation (11–15). It should be noted that GnRH receptors are expressed in both the stroma and epithelial cells of the endometrium with greatest intensity during the luteal phase (3, 16, 17). Last, the effect of GnRH-a on implantation, delivery, and birth rates also suggests a direct GnRH-a effect on the embryo (1, 18). The findings of this study suggest that daily luteal GnRH-a administration in nondown-regulated cycles may lead to the consecutive secretion of pituitary LH. By maintaining the required luteal LH, the function of the CL is preserved and adequate luteal phase support is achieved.

Concerning safety, preclinical toxicology animal studies did not indicate any teratogenic effects of GnRH-a (19). Until 1998, >340 unexpected spontaneous pregnancies have been inadvertently exposed to GnRH-a administration in the midluteal phase (20). Among these, a congenital abnormality incidence of 2.5% and a pregnancy loss of 15% were found. The prevalence of both appear to be within the expected figures when compared with the 2.39% and 22% rate of abnormalities and miscarriages within the IVF and general spontaneous population (20–22). It should be noted that GnRH-a depots, such as decapeptyl 3.75 mg, have been routinely incorporated in many long protocol ART treatments for many years (23). In depot preparation, the active GnRH-a peptide can be detected in the circulation between 7 and 9 weeks after administration (24). Considering their very long half-life, it is clear that significant peptide exposure is found during the luteal phase in these many long IVF protocols with no apparent harmful effect.

Luteal support with intranasal GnRH-a administration has several advantages versus the luteal supplementation routinely used at present. A nasal spray provides a much more convenient route of administration, avoiding irritating vaginal preparations or IM painful injections.

In summary, our findings suggest that repeated administration of GnRH-a as a sole luteal support in antagonist-based IVF cycles results in improved live birth rates in comparison with traditional inconvenient vaginal preparations. These findings should be further evaluated in a prospective randomized manner.

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SUPPLEMENTAL TABLE 1

Regression results: the effect of GnRH agonist (GnRH-a) on positive β-hCG and live birth, including midluteal hormone levels.

	Positive β-hCG			Live birth		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
GnRH-a (yes)	0.94	0.73–1.22	.68	1.31	0.95–1.80	.09
Age (y)	0.88	0.86–0.90	<.001	0.84	0.81–0.86	<.001
BMI (kg/m^2)	0.99	0.96–1.02	.72	0.97	0.94–1.004	.09
IVF cycle (n)	0.90	0.81–0.98	.02	0.88	0.78–0.99	.03
Children (n)	1.80	1.53–2.12	<.001	2.44	1.94–3.06	<.001
Previous pregnancies (n)	1.03	0.94–1.13	.45	0.96	0.84–1.10	.64
Oocytes retrieved (n)	1.01	0.98–1.03	.26	0.99	0.96–1.01	.55
Embryos transferred (n)	1.09	0.98–1.22	.09	1.11	0.96–1.29	.14
Midluteal P (mmol/L)	1.23	1.01–1.50	.03	1.25	0.99–1.58	.06
Midluteal E_2 (mmol/L)	0.97	0.82–1.16	.81	0.89	0.72–1.09	.26

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

Bar Hava. GnRH analogues as luteal support in IVF. Fertil Steril 2016.