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GnRH-agonist versus GnRH-antagonist IVF cycles: is the reproductive outcome affected by the incidence of progesterone elevation on the day of HCG triggering? A randomized prospective study[†]

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BACKGROUND: In view of the current debate concerning possible differences in efficacy between the two GnRH analogues used in IVF stimulated cycles, the current study aimed to explore whether progesterone control in the late follicular phase differs when GnRH antagonist is used as compared with GnRH agonist, and if so, to what extent the progesterone rise affects the probability of pregnancy.

METHODS: Overall 190 patients were randomized: 94 in the GnRH-agonist group and 96 in the GnRH-antagonist group. The GnRH-agonist long protocol started on Day 21 of the preceding cycle with intranasal buserelin (600 mg per day). The GnRH-antagonist protocol started on Day 6 of the stimulation with ganirelix or cetrorelix (each 0.25 mg). All blood samples were analysed with the Elecsys analyzer. An intention-to-treat analysis was applied.

RESULTS: A progesterone rise >1.5 ng/ml was noticed in 23.0% of the antagonist group, comparable with 24.1% incidence within the agonist group. Per patient randomized, delivery rates were also comparable: 28.1% in the antagonist group and 24.5% in the agonist group (odds ratio = 1.21, 95% confidence interval: 0.63–2.31, $P = 0.56$). However, there was a reduction in delivery rates when progesterone exceeded the threshold of 1.5 ng/ml, both in the agonist group (9.5 versus 31.8%, $P = 0.03$) and in the antagonist group (14.3 versus 34.3%, $P = 0.07$).

CONCLUSIONS: Although the incidence of a progesterone rise was similar between the two analogues, our findings reconfirm previous observations that insufficient progesterone control (>1.5 ng/ml) on the day of ovulation triggering is related to poor delivery rates in both protocols. The current study has shown that the reproductive outcomes with the two GnRH analogues are comparable. Possible modes of action to circumvent late follicular progesterone rise should be explored.

Trial registration number: NCT01191710

Key words: GnRH agonist / GnRH antagonist / progesterone / pregnancy outcome / premature luteinization

[†]The current paper was presented as a preliminary report at ESHRE 2008 in Barcelona, as an oral communication.

Introduction

The use of GnRH antagonists in assisted reproduction has increased substantially since their introduction in clinical practice. Nonetheless, despite the widespread use of these agents, there is still a considerable debate concerning their efficacy to achieve similar reproductive outcomes when compared with the most commonly used GnRH agonists.

Numerous randomized trials have been conducted over the last decade involving head-to-head comparisons of agonists versus antagonists' protocols in IVF/ICSI cycles. Despite the extensive literature available, it is unclear whether the use of GnRH antagonists may lead to a significant reduction in clinical and ongoing pregnancies. Whereas a meta-analysis Al Inani and Aboulghar published in 2002 reported a significant decrease in clinical pregnancy rates when GnRH antagonists were used in ART, an update of this meta-analysis in 2011 (Al Inany et al., 2011), and another meta-analysis (Kolibianakis et al., 2006) with projected live birth rates, failed to support this finding, suggesting that both GnRH analogues result in comparable pregnancy rates.

Based on these conflicting reports, a key question is whether differences in the endocrinological profile between the two GnRH protocols may account for differences in pregnancy outcome. A progesterone rise during the late follicular phase has been considered a negative predictive factor for clinical outcome in both GnRH agonist (Schoolcraft et al., 1991; Silverberg et al., 1991; Elnashar, 2010) and GnRH antagonist protocols (Bosch et al., 2003; Papanikolaou et al., 2009). The underlying mechanism behind this observation may be the fact that high serum progesterone levels on the day of HCG administration induce both advanced endometrial histological maturation (Saadat et al., 2004) and differential endometrial gene expression (Labarta et al., 2011; Van Vaerenbergh et al., 2011) which may be related to implantation failure.

Despite the fact that a previous meta-analysis failed to demonstrate any relationship between progesterone levels and clinical pregnancy rates (Venetis et al., 2007), diversity in the progesterone cut off levels (even 0.9 ng/ml which is actually normal) and in the type of the analogue utilized among eligible trials considerably questions the validity of the results. Data from large prospective randomized studies like the Merit study (Andersen et al., 2006) and huge retrospective cohorts with, for example, >4000 cycles (Bosch et al., 2010) consistently support that pregnancy rates are inversely related to progesterone levels on the day of HCG administration, especially when a threshold of 1.5 ng/ml is adopted. This threshold cannot be considered arbitrary, as it signifies the transition from the follicular phase to the luteal phase in the natural cycle (Hoff et al., 1983), and a previous statistical analysis with equal percentile analysis has shown that above this threshold, especially with cleavage stage embryos, the pregnancy rates are significantly reduced (Papanikolaou et al., 2009).

However, none of the available trials up to date have prospectively evaluated whether a difference in the incidence of progesterone rise among GnRH-agonist and GnRH-antagonist protocols exists. We therefore set out to perform a randomized controlled trial to investigate whether progesterone levels on the day of HCG differ between the two GnRH treatment protocols and to determine if differences in the incidence of a serum progesterone rise could eventually result in a compromise to pregnancy rates.

Material and Methods

Study design and patients

This was a single centre randomized controlled trial conducted between August 2007 and December 2009. From primarily 208 patients eligible to participate, 190 were randomized: 94 in the GnRH-agonist group and 96 in the GnRH-antagonist group (Fig. 1). Patients were eligible for inclusion in the trial if they: (i) were of an age <39 years, (ii) had FSH <12 mIU/ml, (iii) could start gonadotrophin at a dose fixed for 5 days and with a range of 100–300 IU and (iv) had <3 previous IVF cycles. Key exclusion criteria included: (i) known endocrine disorders, (ii) endometriosis Stages III and IV, (iii) cases where blood was drawn and analysed in another laboratory and (iv) ovarian stimulation cancellation if progesterone was >1.5 ng/ml and estradiol >80 pg/ml, on the day of initiation of gonadotrophins (Day 2 for antagonists or after a minimum of 14 days down-regulation for agonists).

The current study was approved by our Institutional Review Board, and all the patients gave their signed informed consent. The study has been registered in clinicaltrials.gov and the identifier number is NCT 01191710.

Randomization and masking

Randomization was performed on Day 21 of the preceding cycle with a computer-generated list. Patients' allocation to treatment arms was performed by a consulting nurse who had no intervention in the patients' treatment. Both patients and treating physicians were aware of the exact protocol followed, but treating physicians were not involved in the allocation procedure.

Procedures

The GnRH-agonist long protocol started on Day 21 of the preceding cycle with intranasal buserelin (600 mg per day). Gonadotrophins were administered after 2–3 weeks of down-regulation and once hormones were basal.

In the GnRH-antagonist protocol, gonadotrophins were administered from Day 2 of the cycle if the hormonal levels were basal, and co-treatment with the GnRH antagonist 0.25 mg ganirelix (MSD Organon, Oss, The Netherlands) or 0.25 mg cetrorelix (Merck-Serono, Geneva, Switzerland) started on Day 6 of stimulation.

The initial recombinant gonadotrophin dose (Puregon, MSD Organon, Oss, The Netherlands or Gonal-F, Merck-Serono, Geneva, Switzerland) was predefined at 150–300 IU for all patients and remained fixed for 5 days. After this period, the dose could be adjusted and individualized until the final day of HCG administration, based on follicular growth and serum estradiol levels.

For both study groups, final oocyte maturation was induced with the administration of 250-μg rec-HCG (Ovitrelle; Merck-Serono, Geneva, Switzerland) when at least three follicles of 17–18 mm were present. Oocyte retrieval was performed 36 h after the administration of the rec-HCG preparation.

Sperm preparation, IVF and ICSI procedures, and embryo culture were carried out as described elsewhere (Papanikolaou et al., 2006). Day 3 embryo transfer was performed in the majority of patients, however, 10 patients had Day 2 embryo transfers and 9 patients had Day 5 embryo transfers. Embryo quality was assessed daily until the day of transfer. The embryo transfer policy in our centre is single embryo transfer for women up to 30 years of age, double embryo transfer for women aged between 30 and 35 years old and up to three embryos for women between 35 and 39 years.

The implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. Clinical pregnancy was defined as the presence of a heart beat in Week 7. Early pregnancy loss

Figure 1 Flow diagram of patient's allocation
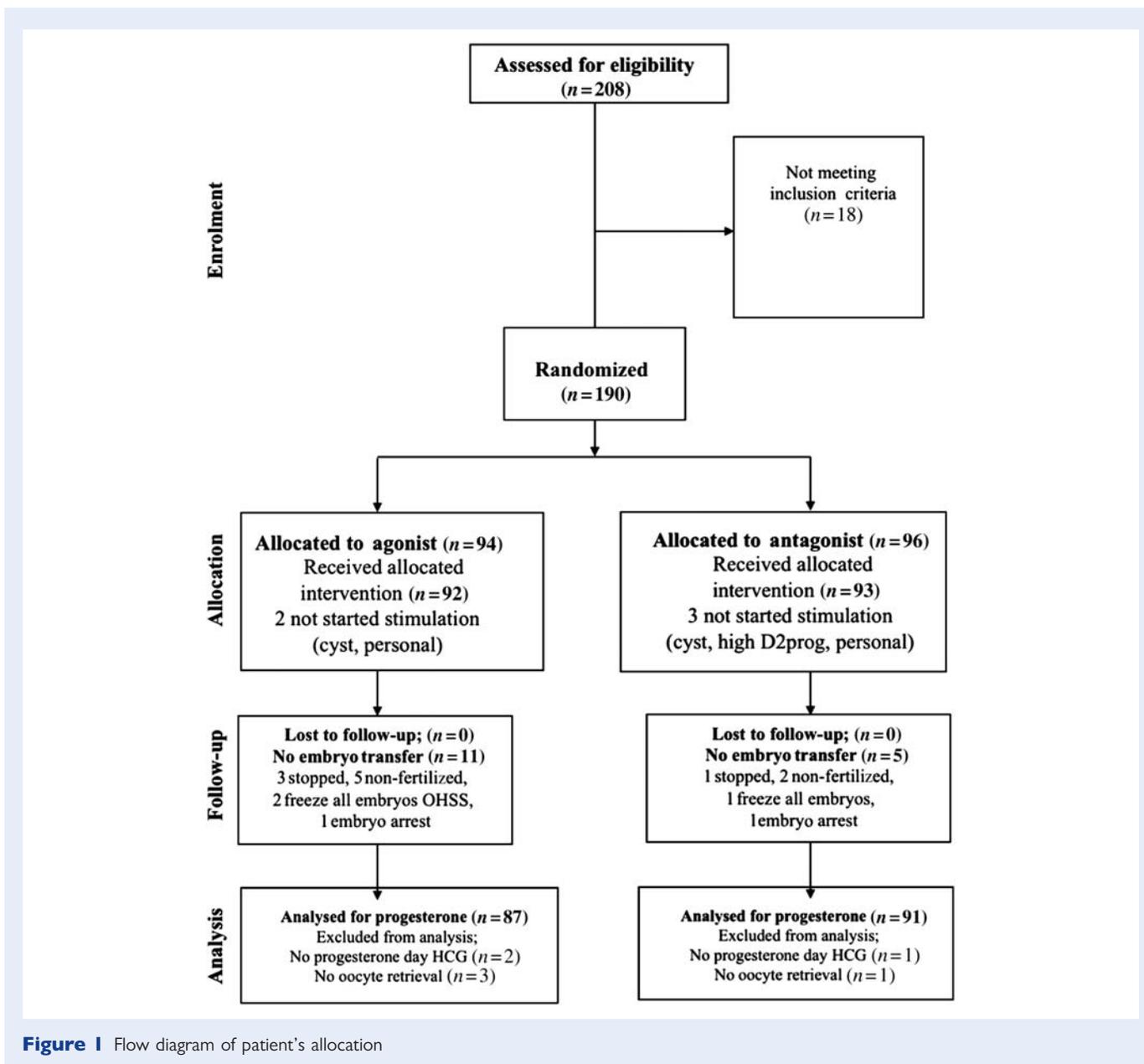
was defined as abortions before 7 weeks of gestation. The ongoing pregnancy was defined as a gestational sac showing a positive heart beat at ultrasound after 12 weeks. Data were further collected during pregnancy until delivery.

All blood samples for hormone measurements were analysed in our laboratory with the Elecsys (Hitachi Roche) analyzer. Each blood sample was analysed on the day of collection. The upper limit of the assay was 60 ng/ml and the lower limit was 0.03 ng/ml and the within run imprecision was 2.44%.

Sample size calculation

Group sample sizes of 81 in group one and 81 in group two would achieve 80% power to detect a difference between the group proportions of 20% (0.20). The proportion (incidence of progesterone rise) in group one (the treatment group, antagonist) was assumed to be 20% under the null hypothesis and 40% under the alternative hypothesis. The progesterone

rise proportion in group two (the control group, agonist) was assumed to be 20%. The test statistic used is the two-sided Mantel–Haenszel test. The significance level of the test was targeted at 0.05. The significance level actually achieved by this design is 0.05.

Statistical analysis

An intention-to-treat analysis was applied in the comparison between the two GnRH protocols. Primary outcomes were the incidence of progesterone elevation >1.5 ng/ml and the delivery rate. Secondary outcomes were the ovarian hyperstimulation syndrome (OHSS) rate, the clinical pregnancy rate and the pregnancy loss rate. The within-group analysis was not intention-to-treat based, as subjects with no progesterone measurements or not starting stimulation, or who stopped stimulation should be excluded.

Continuous variables were compared using an independent Student's t-test or Mann–Whitney test, according to the distribution of their

Table I Demographics and stimulation parameters.

	Antagonist group (n = 96)	Agonist group (n = 94)	P-value
Age (years[a])	32.2 (0.3)	32.8 (0.3)	0.19
Days of stimulation[a]	9.8 (0.9)	11.1 (1.0)	0.03
Mean starting r-FSH dose (IU[a])	194.9 (4)	205.1 (5)	0.08
Progesterone levels Day 1 of stimulation	0.76 (0.03)	0.72 (0.10)	0.71
Progesterone levels Day-HCG of stimulation	1.15 (0.03)	1.24 (0.03)	0.26
Number of patients with >10 follicles >11 mm on the day of HCG triggering[a]	59.4%	58.8%	0.85
OHSS	2 (3.4%)	1 (1.6%)	
Incidence of premature progesterone elevation >1.5 ng/ml	23.0% (21/91)	24.1% (21/87)	0.84

[a]Metrical values are expressed as mean (standard error of the mean).

values. Categorical variables were compared using pairs of two-tailed Fisher's exact tests. The significance level was set at 5% ($P < 0.05$).

Results

Patients' characteristics

The flowchart of the patients' selection process is presented in Fig. 1. Among 96 patients randomized in the GnRH-antagonist group, 3 patients did not start stimulation and 5 patients did not undergo embryo transfer. Similarly, from 94 patients initially randomized in the GnRH-agonist group, 2 did not initiate ovarian stimulation and 11 did not undergo embryo transfer.

Age [32.2 (0.3) versus 32.8 (0.3), $P = 0.19$], starting dose of gonadotrophin [194.9 (4) versus 205.1 (5), $P = 0.08$], cumulus−oocyte complex retrieved [13.4 (1.3) versus 12.1 (1.8), $P = 0.17$] and embryos transferred [2.3 (0.06) versus 2.4 (0.07), $P = 0.31$] were all comparable between GnRH-antagonist and GnRH-agonist groups, respectively (the standard error of the mean is shown in parenthesis). Only the number of stimulation days was significantly higher in agonist treated women [9.8 (0.9) versus 11.1 (0.1), $P = 0.03$; Tables I and II].

Premature progesterone elevation

The incidence of premature progesterone elevation (>1.5 ng/ml) did not significantly differ between GnRH antagonist- and agonist-treated patients. Twenty-one patients in both arms exhibited a progesterone rise above the threshold of 1.5 ng/ml on the day of HCG administration, suggesting that no significant difference exists (23% for antagonist versus 24.1% for agonist-treated patients, $P = 0.84$; Table I).

Pregnancy outcome

Per patient randomized, the initial positive HCG test was 43.8% ($n = 42/96$) in the antagonist group and 40.4% ($n = 39/94$) in the agonist group (odds ratio (OR): 1.16, 95% confidence interval (CI): 0.64−2.04, $P = 0.64$). The clinical pregnancy rate was 33.3% ($n = 32/96$) versus 26.6% ($n = 25/94$), respectively (OR = 1.38, 95% CI: 0.79−2.57, $P = 0.31$). The delivery rate was also comparable at 28.1% in the antagonist group and 24.5% in the agonist group (OR = 1.21, 95% CI: 0.63−2.31, $P = 0.56$; Table III).

Table II Embryological data.

	Antagonist group (n = 96)	Agonist group (n = 94)	P-value
COCs retrieved[a]	13.4 (1.3)	12.1 (1.8)	0.17
2PN embryos[a]	7.0 (0.5)	7.7 (0.5)	0.32
No of embryos transferred[a]	2.3 (0.06)	2.4 (0.07)	0.31
Embryos cryopreserved[a]	1.2 (0.03)	1.3 (0.03)	0.90
Not undergoing embryo transfer though started stimulation	5/96	11/94	0.10
SET	04 (4.3%)	03 (3.6%)	0.88
DET	62 (68.1%)	60 (72.3%)	
TET	25 (27.5%)	20 (24.1%)	

COCs, cumulus−oocyte complex; 2PN, two pronuclear embryos; SET, single embryo transfer; DET, double embryo transfer; TET, triple embryo transfer.
[a]Metrical values are expressed as mean (standard error of the mean).

Pregnancy outcome in relation to the incidence of premature progesterone elevation (within-group comparisons)

Clinical pregnancy rates in relation to the incidence of premature progesterone rise were significantly impaired in both agonist and antagonist protocols. In the GnRH-agonist group, the difference in pregnancy rates between women with elevated and women with normal progesterone was 9.5 (2/21) versus 33.3% (22/66), respectively, $P = 0.03$, whereas in GnRH-antagonist treated women, the difference was 14.3 (3/21) versus 41.4% (29/70), respectively, $P = 0.02$.

On the contrary delivery rates, whereas lower in women with elevated progesterone in both treatment protocols, were only significantly lower in agonist-treated patients (9.5% in women with progesterone >1.5/ng/ml versus 31.8% in women with progesterone <1.5 ng/ml, $P = 0.03$). Among women treated with GnRH antagonists, delivery

Table III Pregnancy outcome [% (n)] in antagonist versus agonist group per randomized patient.

	Antagonist group (n = 96)	Agonist group (n = 94)	P	Odds ratio (95% CI)
Positive-HCG rate	43.8 (42)	40.4 (39)	0.64	1.16 (0.64–2.04)
Early first trimester abortion[a]	23.8 (10)[b]	35.9 (14)	0.20	0.55 (0.21–1.46)
Clinical pregnancy rate	33.3 (32)	26.6 (25)	0.31	1.38 (0.79–2.57)
Late first trimester abortion[c]	9.5 (4)	2.5 (1)	0.36[b]	4 (0.42–37.46)
Ongoing pregnancy rate	29.1 (28)	25.5 (24)	0.32	1.20 (0.63–2.27)
Second trimester abortion[a]	2.3 (1)	2.5 (1)	1.0[b]	0.92 (0.05–15.34)
Delivery rate	28.1 (27)	24.5 (23)	0.56	1.21 (0.63–2.31)

[a]Early first trimester, pregnancy loss <7 weeks; late first trimester, pregnancy loss after heart activity from 7 to 12 weeks; second trimester, pregnancy loss beyond 12 weeks and up to 24 weeks of gestation.
[b]Fisher's exact test.
[c]One ectopic pregnancy included.

Table IV Pregnancy outcome [% (n)] when progesterone was elevated >1.5 ng/ml.

	Progesterone >1.5 ng/ml	Normal progesterone	P	Odds ratio (95% CI)
Agonists only (n = 87)[a]	(n = 21)	(n = 66)		
Positive-HCG rate	28.6 (6)	48.5 (32)	0.11	0.42 [0.14–1.23]
Clinical pregnancy rate	09.5 (2)	33.3 (22)	0.03	0.21 [0.45–0.98]
Delivery rate	09.5 (2)	31.8 (21)	0.04	0.29 [0.48–1.00]
Antagonists only (n = 91)[b]	(n = 21)	(n = 70)		
Positive-HCG rate	23.8 (5)	52.9 (37)	0.01	0.27 [0.09–0.84]
Clinical pregnancy rate	14.3 (3)	41.4 (29)	0.02	0.23 [0.06–0.87]
Delivery rate	14.3 (3)	34.3 (24)	0.07	0.31 [0.08–1.19]
Total study population (n = 178)				
Delivery rate	11.9 (5/42)	33.1 (45/136)	0.01	0.27 [0.10–0.74]

[a]Seven patients with agonist protocol were not analysed because of the following reasons: (two not started stimulation, three stopped and two did not give blood for progesterone levels on the day of HCG one of them had a pregnancy loss).
[b]Five patients with antagonist protocol were not analysed because of the following reasons: (three not started stimulation, one stopped and one did not give blood for progesterone levels on the day of HCG).

rates were 14.3% in women with progesterone >1.5/ng/ml versus 34.3% in women with progesterone <1.5 ng/ml, P = 0.07; Table IV).

Nevertheless, it has to be noted that the study was not designed to determine, and then focus on within-group comparisons of those exhibiting a progesterone rise versus those without, and therefore conclusions should be drawn carefully.

Discussion

This study is the first prospective comparison addressing the incidence of late follicular phase progesterone rise among the two GnRH IVF protocols and its plausible impact on the reproductive outcome. According to our results, no difference in terms of the incidence of progesterone rise can be substantiated, whereas in both protocols elevated progesterone appears to result in a significant demise in

pregnancy rates. Furthermore, in overall patients, with or without premature progesterone rise, the delivery rates were similar between the two GnRH analogues (28.1% with GnRH antagonist versus 24.5% with GnRH agonist).

Interestingly, a quarter of the patients included in our trial, experienced a serum progesterone elevation above the threshold of 1.5 ng/ml on the day of HCG administration in both treatment protocols. Importantly, however, and irrespective of the protocol used, a serum progesterone rise above this specific threshold inversely affected the clinical outcome, with statistically significantly lower clinical pregnancy rates in both GnRH analogue groups. This reconfirms the crucial role of progesterone levels in the final IVF outcome previously described by Papanikolaou et al. (2009) and Bosch et al. (2010). According to our analysis, ~9 out of 10 patients failed to achieve a clinical pregnancy whenever progesterone levels exceeded the threshold of 1.5 ng/ml, regardless of the protocol used. However, the study was not

powered for within-group pregnancy outcome analysis and therefore interpretation of the findings need to be careful.

The source of progesterone in the early follicular phase is merely of adrenal origin. However, later in the late follicular phase, progesterone mainly accumulates from the growing follicles and on rare occasions due to premature luteinization of the leading follicle. The role of exogenous-administered FSH in progesterone accumulation has been advocated and it plays an important role in the late progesterone rise (Papanikolaou et al., 2009; Elnashar, 2010).

Although we did not find a difference in the incidence of progesterone rise among agonist- and antagonist-treated patients, we cannot exclude that such a difference may indeed be present in every day clinical practice. Interestingly, none of the previous randomized trials that included a head-to-head comparison of GnRH agonists and GnRH antagonists has focused on the measurement of progesterone levels during the late follicular phase. Previous reports have shown that an LH rise during ovarian stimulation is eight times higher in GnRH-antagonist cycles (Kolibianakis et al., 2006) signifying the high risk for premature luteinization in antagonist cycles. Other reports have found that late HCG administration (which is a common practice with agonist protocols) increases the mean progesterone values on that day and is furthermore related to a lower probability of pregnancy in antagonist protocols (Kolibianakis et al., 2004). Taking into account the fact that high progesterone is related to the number of follicles recruited, it is possible that, especially in high responder patients, by delaying HCG triggering in order to achieve a larger cohort of follicles around 18 mm, one takes the risk of a progesterone rise either by simply accumulating progesterone from each follicle or by premature luteinization of the leading follicle. Consequently, one could speculate that RCTs favouring GnRH agonists in terms of pregnancy rates might have included more patients with a progesterone rise during the late follicular phase in the GnRH-antagonist arm, by managing the follicular phase of the antagonist patient in the way they were accustomed to treating patients in the agonist protocol, resulting in an imbalance with regards to the incidence of progesterone rise. Such differences in the incidence of progesterone rise between agonist- and antagonist-treated patients may substantiate differences in pregnancy rates found in previous meta-analyses in favour of the GnRH-agonist arm.

The detrimental effect of high progesterone levels, during the late follicular phase on the final IVF outcome, has been supported by many investigators though others have not found this (Venetis et al., 2007). However, one of the major strengths of our trial is that for the first time we demonstrated, in a prospective randomized trial, that progesterone rise on the day of HCG equally affects agonist and antagonist protocols with a deleterious effect on pregnancy outcome. Even modest rise in progesterone may negatively affect implantation rates of a good quality cleavage stage embryo (Papanikolaou, 2009; Bosch, 2003) as we observed here. An endometrial pathophysiology appears to correlate well with the diminished implantation potential of even top-quality embryos (Bourgain and Devroey, 2007). A premature progesterone rise has been demonstrated (by histology and endometrial ultrastructure in IVF-stimulated cycles as compared with natural and artificial cycles of donor oocytes' recipients) to lead to advanced endometrial maturation during the luteal phase of cycles utilizing ovarian stimulation (Kolb and Paulson, 1997). On the one hand, elevation of serum progesterone during the late follicular phase of these cycles appears to be the inciting cause of this precocious endometrial development. On the other hand, the role of high follicular phase estradiol cannot be neglected as the higher the estradiol values the higher the up-regulation of progesterone endometrial receptors and hence the higher the impact of even modest increases of late follicular progesterone leading to premature endometrial advancement (Papanikolaou et al., 2005).

The crucial question however is how should clinicians manage patients with elevated progesterone levels during the late follicular phase? One way is to simply cancel the cycle and proceed to embryo freezing (Herrero et al., 2011). However, is this the optimal solution? According to our trial almost 10% of GnRH agonist-treated and almost 15% of antagonist-treated patients with elevated progesterone succeeded in achieving a clinical pregnancy. Therefore, we must seriously consider the fact that a single progesterone measurement cannot be a reliable marker for the IVF outcome. Serial measurements of progesterone during the late follicular phase may indeed be a more reliable solution and possibly a prospective trial assessing the effect of elevated progesterone levels will provide specific cut-off levels at which the likelihood of pregnancy will drop close to zero and will identify specific candidates who should immediately proceed to cycle cancelation and embryo freezing. Until however, such a trial becomes available, we recommend that the management of patients with elevated progesterone levels on the day of HCG administration should be individualized. Clinicians should always consider that a progesterone rise lowers the likelihood of treatment success irrespectively of the type of GnRH analogue used; on the other hand, strictly speaking we cannot predict which of these patients will eventually achieve a clinical pregnancy. Other clinical parameters should be evaluated in order to decide whether or not to cancel the fresh embryo transfer (such as number of embryos available, performance of the freezing programme, availability of blastocyst culture and number of IVF cycles performed).

Regarding the ongoing debate concerning the superiority or not of the GnRH-agonist protocol over the GnRH-antagonist protocol and vice versa, as physicians we should appreciate the fact that we have the choice of two protocols and place emphasis on evidence rising mainly from randomized studies combined with clinical experience gained over the years. For example, the antagonist protocol has the advantage of triggering with agonist especially high responders and therefore eliminating the OHSS risk (Humaidan et al., 2011). For that reason in oocyte donation programs the antagonist has became the protocol of choice (Bodri et al., 2011).

Concluding, late follicular-phase progesterone rises above a certain threshold indicates worse prognosis regarding pregnancy achievement regardless of which GnRH protocol is used, agonist or antagonist. Serial late follicular measurements of progesterone might assist the treating physician to individualize cycle management, either by allowing medium follicles to grow in case of early growth of the leading follicle when progesterone is normal, otherwise by administering earlier HCG when progesterone gradually escalates, or by opting for single blastocyst transfer when the progesterone is relatively high (Papanikolaou et al., 2009), or even cancelling the embryo transfer in cases where the progesterone rise occurred even some days before the final triggering.

Authors' roles

E.G.P. wrote the manuscript, recruited patients and analysed data. G.P. recruited patients and revised the manuscript. G.G. recruited

patients and revised the manuscript. E.B. recruited patients and revised the manuscript. K.L. analysed the blood hormones and revised the manuscript. N.P. analysed data and wrote the manuscript. P.H. wrote the manuscript and analysed data. H.T. designed the study and revised the manuscript. B.T. designed the study, recruited patients and revised the manuscript.

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Conflict of interest

None declared.

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