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Effect of oral contraceptive pill pretreatment on ongoing pregnancy rates in patients stimulated with GnRH antagonists and recombinant FSH for IVF. A randomized controlled trial

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BACKGROUND: The objective of this randomized controlled trial was to assess the effect of oral contraceptive pill (OCP) pretreatment on the probability of ongoing pregnancy in patients treated with a GnRH antagonist for IVF. METHODS: A fixed dose of 200 IU recombinant FSH (rFSH) was started in 425 patients either on day 2 of the menstrual cycle (non-OCP group: *n* = 211) or 5 days after discontinuing the OCP (OCP group: *n* = 214). GnRH-antagonist was initiated on day 6 of stimulation, and triggering of final oocyte maturation was performed with 10,000 IU of HCG. RESULTS: Ongoing pregnancy rates per started cycle in the non-OCP and OCP group were 27.5% and 22.9%, respectively [95% confidence interval (CI) of the difference: −3.7 to +12.8]. Pregnancy loss was significantly increased in the OCP (36.4%) compared with the non-OCP group (21.6%) (95% CI of the difference: −28.4 to −2.3). CONCLUSION: Pretreatment with OCP, as compared with initiation of stimulation on day 2 of the cycle in patients treated with GnRH antagonist and recombinant FSH, appears to be associated with a not significant difference in ongoing pregnancy rates per started cycle and results in a significantly higher early pregnancy loss.

Key words: GnRH antagonists/oral contraceptive pill/randomized controlled trial/recombinant FSH

Introduction

Oral contraceptive pill (OCP) pretreatment has been used in *in vitro* fertilization since the pre-analogue era to assist in cycle programmation and to avoid a premature LH surge (Templeton *et al.*, 1984; Gonen *et al.*, 1990). Since the establishment of down-regulation with GnRH agonists as a standard method for performing ovarian stimulation for IVF, OCP pretreatment has been used to improve the outcome in poor responders (al-Mizyen *et al.*, 2000) or in high responders (Damario *et al.*, 1997), as well as to avoid cyst formation after agonist administration (Biljan *et al.*, 1998).

After the recent introduction of GnRH antagonists in ovarian stimulation, OCP has been used for cycle scheduling purposes. Cycle programmation has become more difficult with the use of GnRH antagonists, as stimulation initiation is dependent on the occurrence of menstruation. Several studies using GnRH antagonists for inhibition of premature LH surge have been performed using OCP pretreatment to assist in cycle scheduling (Cedrin-Durnerin *et al.*, 2004; Barmat *et al.*, 2005; Shapiro *et al.*, 2005).

The effect of this intervention on the probability of pregnancy has so far been examined only in a small randomized controlled trial (RCT) (Fischl *et al.*, 2001). However, prior to adopting a modification in an already established protocol of treatment such as the daily GnRH antagonist protocol (Borm and Mannaerts, 2000), its effect on the probability of pregnancy needs to be evaluated. The objective of the present study was to assess the effect of OCP pretreatment on ongoing pregnancy rates in patients stimulated with recombinant FSH (rFSH) and GnRH antagonist for IVF.

Materials and methods

Patient population

Five hundred and four women undergoing IVF treatment at the Centre for Reproductive Medicine of the Dutch-speaking Free University of Brussels from May 2002 to December 2004 were randomized at the outpatient clinic by the treating physician on the basis of a computer-generated list to OCP pretreatment (OCP group) or no OCP pretreatment (non-OCP group); see patient flowchart (Fig. 1). The sequence of allocation to the two groups was not concealed and thus it was possible for the treating physicians (n = 7) to be aware of the next treatment to be allocated. The randomization was performed as

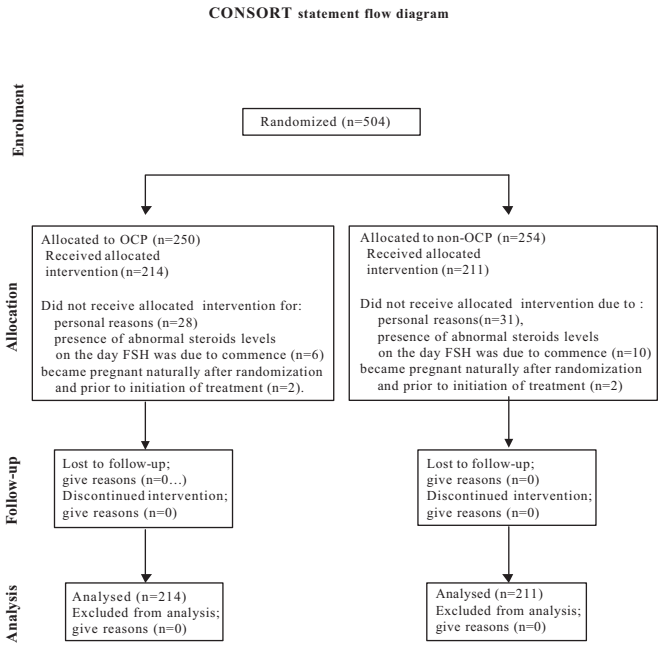

Figure 1. Patient flow chart.

planned according to the randomization list. Patients could participate in the study only once.

Inclusion criteria were: age <39 years; ≤3 previous assisted reproduction (ART) attempts; body mass index (BMI) of 18–29 kg/m^2; regular menstrual cycles; no polycystic ovaries according to Rotterdam definition (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004); no endometriosis > stage II; basal hormonal levels of FSH (<10 IU/l) and LH (<10 IU/l) at initiation of stimulation for the non-OCP group and at initiation of OCP in the OCP group; and no previous poor response to ovarian stimulation. Poor ovarian response was characterized either by cancellation of the cycle due to poor follicular development after at least 10 days of gonadotropin stimulation, or by retrieval of no more than five cumulus–oocyte–complexes (COCs) at oocyte retrieval (Kolibianakis *et al.*, 2004*a*).

Patients could start stimulation and complete the study if estradiol (E_2) was <80 pg/ml and progesterone was <1.6 ng/ml on the day stimulation was due to start (day 2 of the cycle in the non-OCP group or 5 days after OCP discontinuation in the OCP group). These are the normal upper limits for E_2 and progesterone in our unit. In addition, there is an indication that elevated progesterone levels at initiation of stimulation are associated with a decreased probability of pregnancy in patients treated with GnRH antagonist and rFSH (Kolibianakis *et al.*, 2004*b*). The same appears to be true for patients with elevated E_2 (E.M.Kolibianakis, personal communication).

The research project was approved by the Institutional Review Board of the Centre for Reproductive Medicine of the Dutch-Speaking Brussels Free University and informed consent was obtained from all patients.

Ovarian stimulation

Recombinant FSH (Puregon; NV Organon, Oss, the Netherlands) and GnRH antagonist Ganirelix (Orgalutran; NV Organon, Oss, the Netherlands) were used for ovarian stimulation. Recombinant FSH was started on day 2 of the menstrual cycle in the non-OCP group or 5 days after discontinuation of the OCP in the OCP group at 200 IU per day. OCP treatment was administered for 2 weeks starting on day 1 of the cycle. A low-dose monophasic combined oral contraceptive containing 150 μg desogestrel and 30 μg ethinylestradiol (Marvelon®; Organon) was used for OCP pretreatment. The dose of rFSH remained the same in all patients during stimulation.

Ovulation triggering was performed using 10,000 IU of HCG (Pregnyl; Organon) when at least ≥3 follicles ≥17 mm were present on ultrasound scan. Conventional IVF was performed in 149 couples and ICSI in 251 couples, while combined IVF and ICSI were performed in 25 couples. One to two embryos were transferred on day 3 or day 5 after fertilization. Embryos were classified as top quality (score 1), medium quality (score 2) and low quality (score 3) as described previously (Staessen *et al.*, 1992; Gardner and Schoolcraft, 1999). The mean score of the embryos transferred to each patient was used to calculate the mean quality score of all embryos transferred.

Hormonal measurements and ultrasound assessment of follicular development

Hormonal assessment was performed at initiation of stimulation (day 2 of the cycle for the non-OCP group and 5 days after discontinuation of the OCP in the OCP group) on days 6, 8, 10 of rFSH stimulation and on the day of HCG administration. Serum LH, FSH, E_2 and progesterone levels were measured by means of the automated Elecsys immunoanalyser (Roche Diagnostics, Mannheim, Germany). Intra-assay and inter-assay coefficients of variation (CVs) were <3% and <4% for LH, <3% and <6% for FSH, <5% and <10% for E_2 and <3% and <5% for progesterone, respectively. Ultrasound was performed concomitantly with hormonal assessment at each visit, or more frequently as necessary.

Outcome measures

The main outcome measure was ongoing pregnancy per started cycle. Secondary outcome measures were stimulation length, gonadotrophin consumption and early pregnancy loss.

Ongoing pregnancy was defined as pregnancy developing beyond 12 weeks, while early pregnancy loss was defined as the proportion of patients with initially positive HCG in whom pregnancy failed to develop before 12 weeks of gestation.

Statistical analysis

Sample sizes of 1286 patients in each group achieve 80% power at a 5% significance level using a two-sided equivalence test of proportions when the pregnancy rate in the non-OCP group and in the OCP group is 25%, and the maximum allowable difference between pregnancy rates that still results in equivalence is 5%. This is not a realistic task for a single-centre study. The modest aim of the current study was to provide an estimate of the effect of OCP pretreatment on ongoing pregnancy rates on a relatively large patient population and to be included in a future meta-analysis focusing on OCP use in GnRH antagonist cycles. To the best of our knowledge, this is the largest RCT evaluating OCP pretreatment in GnRH antagonist cycles.

Normally distributed metric variables were analysed using the independent sample *t*-test, while not normally distributed variables were analysed using the Mann–Whitney *U*-test. The Wilcoxon test was used to compare paired continuous variables. Nominal variables were analysed in the form of frequency tables by the use of the Fisher exact test. All tests were two-tailed with a confidence level of 95% ($P < 0.05$). Unless stated otherwise, values are expressed as mean ± SD.

Results

Five hundred and four women undergoing IVF were randomized, prior to initiation of stimulation, to receive OCP pretreatment or not. Fifty-nine patients (non-OCP group: n = 31, OCP group: n = 28) did not start an IVF cycle after the initial consultation for personal reasons. Sixteen patients

Table I. Baseline characteristics in the oral contraceptive pill (OCP) and non-OCP group

	OCP group	Non-OCP group	*P*
Female age (years)	31.2 ± 0.3	31.5 ± 0.3	ns
Body mass index (BMI)	22.8 ± 0.3	23.1 ± 0.4	ns
Primary infertility (%)	52.1	55.0	ns
Secondary infertility (%)	47.9	45.0	
Duration of infertility (years)	5.3 ± 0.3	4.9 ± 0.2	ns
Number of previous IVF trials	0.34 ± 0.1	0.46 ± 0.1	ns
Indication for treatment (%)			
Male factor	62.0	61.1	ns
Tubal factor	17.6	14.9	
Endometriosis	3.2	2.7	
Idiopathic	17.2	21.3	

ns = not significant.

(non-OCP group: $n = 10$, OCP group: $n = 6$) did not start stimulation because of the presence of abnormal steroids levels on the day FSH was due to commence, while four patients (non-OCP group: $n = 2$, OCP group: $n = 2$) became pregnant spontaneously after randomization and prior to initiation of treatment. Finally, 425 patients started recombinant FSH stimulation (non-OCP group: $n = 211$, OCP group: $n = 214$).

No significant differences were observed between the two groups for the mean age at initiation of stimulation, number of previous IVF trials and indication for treatment in patients who started stimulation (Table I).

Similarly, no significant differences were observed for baseline hormonal values between the two groups compared. However, in the OCP group, significantly lower values were observed for LH, E_2 and progesterone, 5 days after discontinuing the OCP compared with the corresponding values in the same patients at OCP initiation. Moreover, LH, E_2 and progesterone were significantly lower in the OCP group 5 days after discontinuing the OCP compared with the corresponding values present on day 2 of the cycle in the non-OCP group (Table II). During stimulation, LH remained significantly lower in the OCP group on day 6 of stimulation and on the day of HCG administration compared with the non-OCP group.

Stimulation characteristics of the patients in the two groups compared are given in Table III. A significantly longer duration of stimulation and thus a significantly increased requirement for gonadotrophins was present in the patients who received OCP pretreatment. Although no differences were observed between the two groups in follicular development on the day of HCG administration, significantly more follicles were present in the non-OCP group on day 6 of stimulation. Similarly, although endometrial thickness was similar between the two groups on the day of HCG administration, a significantly lower endometrial thickness was present on day 6 of stimulation in the OCP group.

No differences were observed between the two groups in the number of 2-pronucleate (2pn) oocytes available, in fertilization rates, and in the number and quality of the embryos transferred. Four patients in the OCP group and one in the non-OCP group were admitted due to ovarian hyperstimulation syndrome (OHSS).

Pregnancy outcome is shown in Table IV. A not significant difference in favour of the non-OCP group in ongoing pregnancy rate per started cycle (4.6%) and per patient randomized (3.2%) was observed. On the other hand, a significantly higher early pregnancy loss was present in the OCP group compared with the non-OCP group (36.4% versus 21.6%, respectively; $P \leq 0.05$). A 17.8% ongoing twin pregnancy rate was observed in the present study, which did not differ between the non-OCP group (19%) and the OCP group (16.3%).

Figure 2 shows receiver operating characteristic (ROC) curve analysis of LH levels on day 6 of stimulation, on day 8 of stimulation, and on the day of HCG administration in the OCP and non-OCP group with dependent variable ongoing pregnancy per started cycle. In the OCP group, no significant associations were present; however, a negative association between

Table II. Hormonal values in the non- oral contraceptive pill (non-OCP) group and OCP group

	Non-OCP group	OCP group		
	At initiation of stimulation	At initiation of stimulation 5 days after OCP discontinuation	*P*	At OCP initiation
FSH	7.5 ± 2.4	7.7 ± 3.20	ns	7.5 ± 2.4[b]
LH	5.2 ± 2.2	4.8 ± 2.7[a]	<0.01	5.2 ± 2.2[b]
E_2	39.1 ± 13.7	31.2 ± 17.4[a]	<0.01	41.1 ± 20.5[b]
Progesterone	0.7 ± 0.3	0.5 ± 0.3[a]	<0.01	0.7 ± 0.3[b]
	Day 6 of stimulation			
FSH	15.2 ± 4.4	16.0 ± 4.3	ns	
LH	2.7 ± 3.6	1.9 ± 1.9	<0.01	
E_2	723 ± 472	676 ± 465	ns	
Progesterone	0.7 ± 0.4	0.6 ± 0.3	ns	
	Day of HCG			
FSH	14.8 ± 4.4	14.6 ± 4.4	ns	
LH	2.1 ± 1.9	1.3 ± 1.9	<0.001	
E_2	2071 ± 1038	1901 ± 1038	ns	
Progesterone	1.3 ± 0.9	1.4 ± 0.9	ns	

[a]Significant difference compared to the values present at OCP initiation, and compared to the values present at initiation of stimulation in the non-OCP group.
[b]Difference not significant compared with non-OCP group prior to treatment. ns = non significant.

Table III. Characteristics of stimulation and embryological data in the non-oral contraceptive pill (OCP) and OCP group

	Non-OCP group	OCP group	*P*
Duration of recombinant FSH (rFSH) stimulation (days)	9.1 ± 2.0	9.7 ± 2.0	<0.001
Dose of rFSH (IU)	1818 ± 398	1943 ± 402	<0.001
Follicles 11–14 mm on day 6 of stimulation	4.6 ± 3.9	3.2 ± 3.5	<0.001
Follicles 15–16 mm on day 6 of stimulation	0.4 ± 0.8	0.3 ± 0.8	<0.02
Follicles ≥17 mm on day 6 of stimulation	0.2 ± 0.4	0.1 ± 0.3	<0.02
Endometrial thickness on day 6 of stimulation (mm)	7.9 ± 2.1	6.8 ± 2.2	<0.001
Follicles 11–14 mm on the day of HCG	6.1 ± 0.4	6.1 ± 0.4	ns
Follicles 15–16 mm on the day of HCG	1.8 ± 2.3	2.4 ± 3.0	ns
Follicles ≥17 mm on the day of HCG	4.5 ± 0.1	4.5 ± 0.3	ns
Endometrial thickness on the day of HCG (mm)	9.5 ± 2.3	9.3 ± 2.0	ns
Cumulus-oocyte complexes	13.2 ± 8.8	12.8 ± 7.7	ns
Fertilization method (%)			
ICSI	57.5	60.7	ns
IVF	36.4	33.6	
IVF versus ICSI	6.1	5.7	
2 pn oocytes	7.4 ± 5.2	7.5 ± 5.1	ns
Fertilization rate (%)	58.7 ± 22.7	59.3 ± 22.0	ns
Embryos transferred	1.7 ± 0.9	1.6 ± 0.7	ns
Day of embryo transfer			
Day 3	64.1%	66.5%	ns
Day 5	35.9%	33.5%	
Embryos cryopreserved	3.0 ± 3.7	3.1 ± 3.3	ns
Mean quality score of transferred embryos	1.6 ± 1.8	1.6 ± 1.7	ns

ns = non significant.

Table IV. Pregnancy outcome in the non-oral contraceptive pill (OCP) and OCP group

	Non-OCP group	OCP group	
Patients who started stimulation	211	214	
Patients who reached oocyte retrieval	203	209	
Patients who reached embryo transfer	187	191	
			Difference (95% confidence interval)
Positive HCG per started cycle	35.1% (74/211)	36.0% (77/214)	0.9% (–9.9 to +8.1)
Ongoing pregnancy rate per started cycle	27.5%(58/211)	22.9%(49/214)	4.6% (–3.7 to +12.8)
Ongoing pregnancy rate per patient randomized*	20.4%(60/254)	23.6%(51/250)	3.2% (–4.0 to +10.4)
Ongoing pregnancy rate per oocyte retrieval	28.6% (58/203)	23.4% (49/209)	5.1% (–3.3 to +13.5)
Ongoing pregnancy rate per embryo transfer	31.0% (58/187)	25.7% (49/191)	5.4% (–3.7 to +14.3)
Ongoing implantation rate (%)	24.4 ± 39.0	18.2 ± 33.6	6.2% (–1.2 to +13.5)
Early pregnancy loss	21.6% (16/74)	36.4% (28/77)	–14.7% (–28.4 to –2.3)

All differences between the two groups are not significant with the exception of the comparison of early pregnancy loss in which $P < 0.05$. *Including the spontaneously occurred pregnancies in patients randomized in the two groups.

LH levels and the probability of pregnancy was observed in the patients who did not receive OCP on day 6 and on day 8 of stimulation.

Discussion

The present study has shown that, in GnRH antagonist cycles, OCP pretreatment followed by a 5-day pill-free interval is associated with a not significant difference in ongoing pregnancy rates per started cycle compared with initiation of stimulation on day 2 of the cycle after a normal luteal phase. Although the current study is the largest RCT to test the effect of OCP pretreatment on ongoing pregnancy rates, it is under-powered to detect a difference in ongoing pregnancy rate of 5%, which was considered to be clinically significant. Further studies to test the same intervention are therefore needed to estimate more accurately the association of OCP pretreatment and the probability of pregnancy in GnRH antagonist cycles. This is important since a significantly higher early pregnancy loss was present after OCP pretreatment.

The results of the current study are in agreement with the results reported by Fischl *et al.* (2001), which tested the use of monophasic OCP pretreatment in 150 patients. A small and not significant difference in clinical pregnancy rate per embryo transfer was present in favour of the group which did not receive the OCP pretreatment (42.1% versus 39.7%). Stimulation in that study was also performed with rFSH and GnRH antagonist was administered daily starting from day 6 of stimulation, which was initiated either on day 3 of the cycle or 4 days after pill discontinuation.

The two groups compared in the current study received the same fixed FSH dose, while the endogenous FSH levels were not significantly different at initiation of stimulation and during follicular development (Table II). Therefore, it appears that

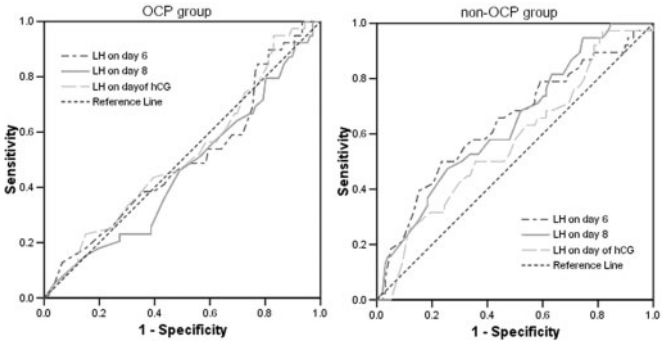

Figure 2. Area under the receiver operating characteristic (ROC) curve for LH on day 6, on day 8 and on the day of HCG administration with dependent variable achievement of ongoing pregnancy per started cycle in the OCP and non-OCP groups. A significant association was present only for LH on day 6 and on day 8 in the non-OCP group (area under the curve = 0.64; 95% confidence interval = 0.53–0.74; for both days).

OCP pretreatment for 2 weeks results in a slower follicular recruitment associated with an increased consumption of gonadotrophins, which is not attributed to a difference in exogenous or endogenous FSH levels. This might be explained by the significantly lower LH levels observed in the OCP group, since LH has been shown to assist in follicular development (Filicori *et al.*, 2002). In addition, OCP pretreatment might exert a suppressive effect on the cohort of existing follicles. Although Fanchin *et al.* (2003) showed that luteal E_2 administration synchronizes the follicular cohort and is associated with more follicles and oocytes retrieved, it appears that the combination of ethinylestradiol with desogestrel is not associated with a similar effect on follicular development. However, this might also be attributed to the different time FSH was initiated [1 versus 5 days after E_2 and OCP discontinuation in the study by Fanchin *et al.*, (2003) and in the current study, respectively]. As demonstrated by Van Heusden *et al.* (1999), OCP is able to suppress the luteofollicular transition and the endogenous FSH rise occurs 3 days after OCP withdrawal. The same effect is described by De Ziegler *et al.* (1998) after E_2 withdrawal. On day 5 after the last OCP, this phenomenon could already have occurred.

A significantly higher early pregnancy loss was observed in the patients who received OCP pretreatment. It is not clear what the source of this difference is, although it might be associated with the lower levels of LH present in the OCP group (Westergaard *et al.*, 2000). However, no association between LH and ongoing pregnancy per started cycle was present in the OCP group while, in the non-OCP group, a small but significant negative association between LH levels and the probability of pregnancy was observed (Fig. 2). This is in agreement with observations previously published in GnRH antagonist cycles suggesting that the lower the LH levels the higher the probability of pregnancy (Kolibianakis *et al.*, 2004*c*).

A significantly lower endometrial thickness was present on day 6 of stimulation in the OCP compared with the non-OCP group. No clear explanation regarding the source of this difference is present. However, it might be attributed to differences in the menstruation pattern following pill discontinuation. All patients in the non-OCP group start stimulation on the 2nd day of their period. In the OCP group, however, menstruation is likely to be delayed in a proportion of patients, resulting in a lower endometrial thickness by day 6 of stimulation. Unfortunately, no details were recorded for menstruation patterns in this study, although retrospectively this might have introduced interesting information. The lower E_2 levels at initiation of stimulation in the OCP group might also be involved in the difference observed in endometrial thickness between the two groups on day 6 of stimulation, although by that time similar E_2 levels were observed in the two groups.

In the current study, 5 days was selected for the OCP free interval since shorter intervals have been associated with poor ovarian response—probably as a result of deeper suppression of endogenous gonadotrophins (personal communication, E.M.Kolibianakis). However, even after 5 days of pill discontinuation, significantly lower values for LH, E_2 and progesterone were observed compared with the non-OCP group. It might be interesting in future studies to evaluate the effect of the OCP on the probability of pregnancy after a longer pill-free interval, which would result in similar hormonal levels at initiation of stimulation and perhaps similar stimulation characteristics and pregnancy outcome.

In conclusion, pretreatment with OCP compared with initiation of stimulation on day 2 of the cycle in patients treated with GnRH antagonist and rFSH appears to be associated with a not significant difference in ongoing pregnancy rates per started cycle and results in a significantly higher early pregnancy loss after a longer stimulation period and an increased dose of FSH.

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References

al-Mizyen E, Sabatini L, Lower AM, Wilson CM, al-Shawaf T and Grudzinskas JG (2000) Does pretreatment with progestogen or oral contraceptive pills in low responders followed by the GnRHa flare protocol improve the outcome of IVF-ET? J Assist Reprod Genet 17,140–146.

Barmat LI, Chantilis SJ, Hurst BS and Dickey RP (2005) A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. Fertil Steril 83,321–330.

Biljan MM, Mahutte NG, Dean N, Hemmings R, Bissonnette F and Tan SL (1998) Effects of pretreatment with an oral contraceptive on the time required to achieve pituitary suppression with gonadotropin-releasing hormone analogues and on subsequent implantation and pregnancy rates. Fertil Steril 70,1063–1069.

Borm G and Mannaerts B (2000) Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. The European Orgalutran Study Group. Hum Reprod 15,1490–1498.

Cedrin-Durnerin I, Grange-Dujardin D, Laffy A, Parneix I, Massin N, Galey J, Theron L, Wolf JP, Conord C, Clement P et al. (2004) Recombinant human LH supplementation during GnRH antagonist administration in IVF/ICSI cycles: a prospective randomized study. Hum Reprod 19,1979–1984.

Damario MA, Barmat L, Liu HC, Davis OK and Rosenwaks Z (1997) Dual suppression with oral contraceptives and gonadotrophin releasing-hormone agonists improves in vitro fertilization outcome in high responder patients. Hum Reprod 12,2359–2365.

de Ziegler D, Jaaskelainen AS, Brioschi PA, Fanchin R and Bulletti C (1998) Synchronization of endogenous and exogenous FSH stimuli in controlled ovarian hyperstimulation (COH). Hum Reprod 13,561–564.

Fanchin R, Salomon L, Castelo-Branco A, Olivennes F, Frydman N and Frydman R (2003) Luteal estradiol pretreatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists. Hum Reprod 18,2698–2703.

Filicori M, Cognigni GE, Samara A, Melappioni S, Perri T, Cantelli B, Parmegiani L, Pelusi G and DeAloysio D (2002) The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction. Hum Reprod Update 8,543–557.

Fischl F, Huber JC and Obruca A (2001) Zeitliche Optimierung der kontrollierten Hyperstimulation (KOH) in Kombination mit GnrH-Antagonisten und Ovulationshemmer in einem IVF-Programm. Journal für Fertilität und Reproduktion 11,50–51.

Gardner DK and Schoolcraft WB (1999) In vitro culture of human blastocysts. In Jansen, R and Mortimer, D (eds) Towards Reproductive Certainty: Infertility and Genetics beyond 1999. Parthenon Press, Carnforth, UK, pp. 377–388.

Gonen Y, Jacobson W, Casper RF (1990) Gonadotrophin Suppression with oral contraceptives before in vitro fertilization. Fertil Steril 53,282–287.

Kolibianakis E, Albano C, Zikopoulos K, Kahn JA, Van Steirteghem A and Devroey P (2004a) GnRH antagonists in poor responders. Acta Obstet Gynecol Scand 83,1216–1217.

Kolibianakis EM, Zikopoulos K, Smitz J, Camus M, Tournaye H, Van Steirteghem AC and Devroey P (2004b) Elevated progesterone at initiation of stimulation is associated with a lower ongoing pregnancy rate after IVF using GnRH antagonists. Hum Reprod 19,1525–1529.

Kolibianakis EM, Zikopoulos K, Schiettecatte J, Smitz J, Tournaye H, Camus M, Van Steirteghem AC and Devroey P (2004c) Profound LH suppression after GnRH antagonist administration is associated with a significantly higher ongoing pregnancy rate in IVF. Hum Reprod 19,2490–2496.

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19,41–7.

Shapiro DB, Mitchell-Leef D, Carter M and Nagy ZP (2005) Ganirelix acetate use in normal- and poor-prognosis patients and the impact of estradiol patterns. Fertil Steril 83,666–670.

Staessen C, Camus M, Bollen N, Devroey P and Van Steirteghem AC (1992) The relationship between embryo quality and the occurrence of multiple pregnancies. Fertil Steril 57,626–630.

Templeton A, van Look P, Lumsden MA, Angell R, Aitken J, Duncan AW and Baird DT (1984) The recovery of pre-ovulatory oocytes using a fixed schedule of ovulation induction and follicle aspiration. Br J Obstet Gynaecol 91,148–154.

van Heusden AM and Fauser BC (1999) Activity of the pituitary-ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. Contraception 59,237–243.

Westergaard LG, Laursen SB and Andersen CY (2000) Increased risk of early pregnancy loss by profound suppression of luteinizing hormone during ovarian stimulation in normogonadotrophic women undergoing assisted reproduction. Hum Reprod 15,1003–1008.

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