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Importance of a 5- versus 7-day pill-free interval in a GnRH antagonist protocol using corifollitropin alfa: a prospective cohort study in oocyte donors

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KEY MESSAGE

Extending the pill-free interval to 7 days significantly reduces the total dose of gonadotrophins, duration of stimulation, total cost of medication and total number of injections in oocyte donors treated with oral contraceptives for over 22 days.

A B S T R A C T

In this prospective cohort study, oocyte donors were recruited prospectively and assigned to receive corifollitropin alfa: 5 days after pill discontinuation (group D5; 42 donors), or 7 days after pill discontinuation (group D7; 50 donors) in a gonadotrophin-releasing hormone antagonist protocol. Fixed additional daily doses of 200 IU recombinent FSH (rFSH) were started after 7 days of corifollitropinalfa, until triggering. No significant differences in basal characteristics were observed between both groups. In group D5, mean (SD) total additional rFSH dose was 659 (452) IU; in group D7, total rFSH dose was 459 (356) IU (P = 0.022). Duration of stimulation was significantly longer in group D5 compared with group D7 (P = 0.002). No differences were found in total number of oocytes obtained. Total number of injections was significantly lower in group D7 compared with group D5 (9.8 [3.2] versus 11.9 [3.9], respectively; P = 0.004). Total cost of medication used for donor treatment was significantly higher in group D5 than in group D7 (P = 0.015). After more than 22 days of pill-taking, extending the pill-free interval to 7 days significantly reduces the total dose of gonadotrophins, duration of stimulation, total cost of medication and total number of injections.

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Introduction

Since the first successful pregnancy was achieved after oocyte donation (Lutjen et al., 1984), its use and effectiveness has expanded notably. The indications for undergoing an oocyte donation cycle have increased, as has the efficiency of this technique (Practice Committee Report, 2008).

The design of optimal ovarian stimulation protocols is important for all patients undergoing an assisted reproduction technique, although it is particularly desirable for oocyte donors, for whom the utmost safety, efficiency and convenience should be guaranteed and risks minimized.

Current treatment regimens usually consist of administration of daily injections of exogenous gonadotrophins and gonadotrophin-releasing hormone (GnRH) analogues, generally self-administered, which can last up to 2 weeks. To simplify ovarian stimulation protocols, corifollitropin alfa was introduced, enabling the first seven daily injections of any FSH preparation to be replaced (Devroey et al., 2009; Fensore et al., 2015). This relatively new compound is usually administered on day 2 or 3 of the menstrual cycle, with the advantage of being more patient friendly, as less injections cause less distress to the patient, help to improve treatment compliance and prevent errors during the administration of gonadotrophins (Fauser et al., 2009; Requena et al., 2013; Verberg et al., 2008). In our oocyte donation programme, the use of corifollitropin alfa is a convenient alternative to the use of daily FSH injections (Pérez-Calvo et al., 2015).

As in patients undergoing IVF and intracytoplasmic sperm injection (ICSI), the use of the GnRH antagonist protocol in oocyte donors reduces treatment duration and total consumption of gonadotrophins; GnRH antagonists are better tolerated and easier to manage compared with GnRH agonists (Martinez et al., 2008), providing similar pregnancy and implantation rates in the recipients (Martinez et al., 2008; Prapas et al., 2005). Moreover, final oocyte maturation can be induced with a GnRH agonist bolus, thus preventing the risk of the ovarian hyperstimulation syndrome (OHSS) (Bodri et al., 2010; Galindo et al., 2009). Because of its effectiveness and safety potential, the GnRH antagonist protocol combined with GnRH agonist triggering has been advocated as the treatment of first choice for oocyte donors (Bodri et al., 2010).

Donors are often prescribed a pre-treatment with oral contraceptive pills (OCP) before ovarian stimulation with gonadotrophins to facilitate appointment-making and treatment scheduling. Scheduling donor stimulation is important to reduce weekend oocyte retrievals and to distribute the workload throughout the week, therefore reducing the amount of unplanned work. Adequate scheduling facilitates synchronization with the recipients in the event of fresh donation, according to patients' or physicians' preferences.

Nevertheless, there is an ongoing debate about the pros and cons of OCP pre-treatment, especially the outcomes of GnRH antagonist cycles in patients undergoing ovarian stimulation for IVF (Garcia-Velasco and Fatemi, 2015; Griesinger et al., 2010, 2015), and the effect of OCP use on the total dose of gonadotrophins consumed, the duration of the stimulation and the clinical pregnancy rate. Even when given for a short period of time and even if ovarian stimulation is started after a wash-out period, OCP pre-treatment might negatively affect endometrial receptivity and IVF outcome (Garcia-Velasco and Fatemi, 2015; Griesinger et al., 2015). The possible effect in oocyte donation cycles is probably negligable, as the oocyte quality is not hindered in case of pretreatment with OCP in IVF cycles (Pinkas et al., 2008; Hauzman et al., 2013).

No studies addressing this issue in a donor population have been published, to our knowledge. Combined hormonal contraception inhibits the hypothalamic–pituitary axis causing a decrease in FSH and LH, leading to the suppression of follicular activity and ovulation. Current OCPs result in a decrease in pituitary gonadotrophin secretion, particularly during the pill-free interval (PFI) (Baerwald et al., 2004). The degree of suppression of ovarian activity varies after PFI modifications (van Heusden and Fauser, 2002). After FSH suppression induced by OCP, the recovery of endogenous FSH to the normal values of a natural cycle takes 5 days in most patients (Cédrin-Durnerin et al., 2007).

An endocrine wash-out period of 5 days had been suggested to start ovarian stimulation. A shorter interval between the last OCP and gonadotrophin stimulation would result in a poorer and slower response owing to a strong early suppression, with higher gonadotrophin consumption (Barmat et al., 2005; Griesinger et al., 2008; Huirne et al., 2006). It has been calculated that OCP pre-treatment would imply that 542 IU of gonadotrophins and 1.4 more days of stimulation would be needed (Griesinger et al., 2010). Increasing the wash-out period to more than 5 days has also resulted in higher gonadotrophin consumption compared with women who had not been pre-treated with OCP (Barmat et al., 2005; Griesinger et al., 2008; Huirne et al., 2006). These studies were carried out using daily injections of gonadotrophins for ovarian stimulation in patients undergoing IVF–ICSI.

A later beginning of ovarian stimulation with recombinant FSH (rFSH) in the follicular phase in patients undergoing IVF results in a reduction in total gonadotrophin consumption (Blockeel et al., 2011; Hohmann et al., 2003). Moreover, a randomized clinical trial in which ovarian stimulation with corifollitropin alfa was initiated on day 4 instead of day 2 of the cycle, resulted in a significant reduction of the additional consumption of rFSH (Blockeel et al., 2014),

The aim of the present study was to evaluate whether the administration of corifollitropin alfa 7 days after discontinuation of the OCP instead of 5 days resulted in a decrease in the total consumption of gonadotrophins in a GnRH antagonist protocol for oocyte donors.

Material and methods

Study design

This prospective cohort study included oocyte donor patients from the Oocyte Donation Programme at the Hospital UniversitarioDexeus of Barcelona, and was conducted between February 2015 and May 2016. The study was approved by the Ethical Committee of the Dexeus University Hospital on 27 November 2014 (reference number CPMP/ICH/135/95) and the Department of Health of the Government of Catalonia on 25 February 2015 (reference number 03365/2789/2015), and was registered in clinicaltrials.gov (NCT02490150).

Eligibility criteria

The women included in the study were healthy oocyte donor patients aged between 18 and 35 years, with regular menstrual cycles (i.e. between 26 and 35 days), and body mass index between 18 and 28 kg /m^2 without any relevant personal or family history. The patients had a normal karyotype and a negative screening for sexually

transmitted diseases. The patients agreed to participate in the study and signed an informed consent.

The exclusion criteria included oocyte donors with an antral follicle count over 20, hypersensitivity to the active substance or to any of its excipients, abnormal vaginal bleeding of unknown cause, presence of ovarian cysts or enlarged ovaries, history of ovarian hyperstimulation syndrome (OHSS), a previous ovarian stimulation cycle with more than 30 follicles of 11 mm or wider (as recommended by the Elonva® Summary of Product Characteristics).

Ovarian stimulation protocol

The donor patients were recruited prospectively and assigned to one of the two treatment groups: 'group D5' included oocyte donors, who started ovarian stimulation with corifollitropin alfa 5 days after OCP discontinuation, whereas in 'group D7', the oocyte donors started 7 days after OCP discontinuation. The GnRH antagonist protocol was prescribed in both groups (**Figure 1**).

Taking into account the Summary of Product Characteristics, corifollitropin alfa can be administered in the early follicular phase (second to fourth day of bleeding). Treatment assignment was carried out by the coordinating nurse to equally distribute the workload throughout a 7-day working schedule. Donors were consecutively assigned to take the last OCP on a Wednesday and to have the corifollitropin alfa administered at the clinic on the following Monday (Group D5) or Wednesday (Group D7). All donors were pre-treated with combined oral contraceptives for 17–23 days (ethinylestradiol 30 µg and levonorgestrel 150 µg; Ovoplex®, Wyeth Farma, Spain). A total of 42 oocyte donors were assigned to group D5 and 50 oocyte donors were assigned to group D7.

Corifollitropin alfa (Elonva®, MSD, Spain) was used for ovarian stimulation. Administration of the GnRH antagonist ganirelix (Orgalutran®, MSD, Spain) was initiated on stimulation day 6 in both treatment arms at a daily dose of 0.25 mg to prevent a premature LH surge. Suppression with the GnRH antagonist was continued until the day of final oocyte maturation. Endocrine monitoring (with serum oestradiol evaluation) and ultrasound scan were carried out on day 6 of stimulation and repeated every second day thereafter until trigger, depending on the patients' response. The administration of fixed daily doses of 200 IU rFSH (Puregon®, MSD, Spain) was initiated after the seventh day of corifollitropin alfa (if needed), until the criteria of triggering final oocyte maturation (i.e. ≥3 follicles of ≥18 mm) were met. Cycles were cancelled if less than six follicles measuring more than 12 mm in diameter were observed on the day 8 of of stimulation.

A GnRH agonist (triptorelin [Decapeptyl®, Ipsen Pharma, Spain], 0.2 mg) bolus was used to induce final oocyte maturation. Oocyte retrieval was carried out 36 h later. The recruited mature oocytes were either vitrified or donated to the corresponding recipient for a fresh cycle (Solé et al., 2013).

End-points

The primary end-point of the study was total gonadotrophin consumption. Secondary end-points included the cycle characteristics: duration of stimulation, serum oestradiol levels, number of oocytes retrieved and cancellation rate.

Power calculation

Power calculation assumed mean rFSH consumption of the reference group to be 463 units (Pérez-Calvo et al., 2015), the mean of the experimental group to be 246 units and the standard deviation of both groups to be 300 units, to reach 80% power in a Student's t-test for two independent samples, with a significance level set at 5%; it was necessary to include 31 donors in the control group (group D5) and 31 donors in the experimental group (group D7), totalling 62 donors in the study. Estimating a anexpected percentage of dropouts is 10%, it would be necessary to recruit at least 70 donors in the study.

Statistical analysis

Continuous variables were described by mean and standard deviation. To compare means between groups, the t-test or Wilcoxon Mann–Whitney test were used according to normality assumptions. IBM® SPSS® Statistics v22.0 software was used for statistical analyses. $P < 0.05$ was considered statistically significant.

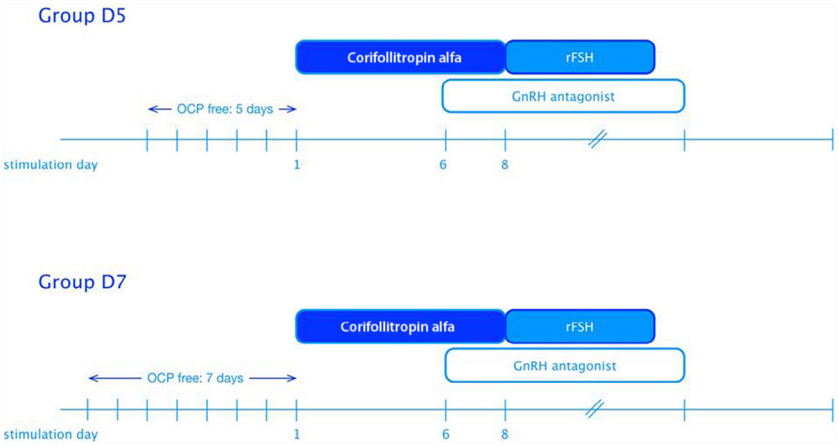

Figure 1 – Ovarian stimulation protocol. In group D5, corifollitropin alfa was administered 5 days after discontinuing the oral contraceptive pill. In group D7, corifollitropin alfa was administered 7 days after discontinuing the oral contraceptive pill. The GnRH antagonist protocol was prescribed in both groups. OCP, oral contraceptive pill; rFSH, recombinant FSH.

Table 1 – Baseline characteristics.[a,b]

	Group D5[c] (n = 42)	Group D7[d] (n = 50)
Age (years)	26.1 (4.9)	25.8 (4.4)
AMH (ng/ml)	2.8 (1.4)	3.2 (1.6)
AFC	16.4 (2.9)	16.6 (2.9)
Weight (kg)	59.9 (9.4)	58.7 (7.7)

[a] Values presented as mean (SD).
[b] No statistically significant differences were observed between the two groups.
[c] Group D5: oocyte donors who started ovarian stimulation with corifollitropin alfa 5 days after oral contraceptive pill discontinuation.
[d] Group D7: oocyte donors who started ovarian stimulation with corifollitropin alfa 7 days after oral contraceptive pill discontinuation.
AFC, antral follicle count; AMH, anti-Müllerian hormone; OCP, oral contraceptive pill.

Results

A total of 92 oocyte donors were included, 42 in group D5 and 50 in group D7, with a mean age of 26.0 (SD 4.6) years and plasma anti-Müllerian hormone (AMH) levels of 3.0 (SD 1.6) ng/ml; antral follicle count 17 (SD 3) and body weight 59.2 (SD 8.5) kg. Baseline characteristics by treatment group are shown in **Table 1**. No significant differences in these characteristics were observed between both groups. The mean duration of OCP intake before pill-free interval was 22.3 days (SD 8.0) in group D5 and 22.1 days (SD 6.9) in group D7.

The mean duration of stimulation was 9.8 days (SD 1.7), with a total additional dose of daily gonadotrophins of 550 IU (SD 413). A mean of 14.1 oocytes (SD 7.5) were obtained. The cycle characteristics by treatment group are presented in **Table 2**. None of the cycles were cancelled. The patients in group D7 needed a significantly lower total dose of gonadotropins ($P = 0.022$) and fewer days of stimulation ($P = 0.002$). No differences were found in the total number of oocytes obtained. The total number of injections (corifollitropin alfa injection, GnRH antagonist, daily rFSH, GnRH agonist trigger) was significantly lower in group D7 compared with group D5, namely 9.8 [SD 3.2] and 11.9 [SD 3.9] injections, respectively; ($P = 0.004$). No additional administration of rFSH was needed in 9 nine donors (three from group D5 and 6 from group D7), as the triggering criteria on day 8 of stimulation was reached. Plasma oestradiol levels on day 6 of corifollitropin alfa injection were significantly higher in group D7 compared with group D5 ($P = 0.001$).

The same differences persisted when the analysis took into account the duration of OCP intake before pill-free interval (data not shown). The total number of days of OCP intake before the interval did not affect the outcomes. The total cost of medication used for donor treatment (including total consumption of contraceptive pills, gonadotrophins, GnRH antagonist injections and GnRH agonist bolus) was calculated for both treatment groups. Total cost of medication used for donor treatment was significantly higher in group D5 (€1124.6 [SD 237.7]) than in group D7 (€1009.8 [SD 204.6]); $P = 0.015$.

Discussion

This is the first study to assess the use of corifollitropin alfa given after pre-treatment with oral contraceptives with two different pill-free intervals prior to the administration of corifollitropin alfa in oocyte donors using a GnRH antagonist protocol. It clearly demonstrates that increasing the pill-free interval from 5 to 7 days significantly reduces the duration of ovarian stimulation, total gonadotropin consumption and the number of injections without affecting the total number of oocytes obtained.

In our trial, after a single injection of corifollitropin alfa, the criteria for final oocyte maturation were met in 7.14% of the patients in Group D5 compared with 12% of the patients in Group D7, obviating the need for any additional rFSH injections. IVF patients prefer fewer injections in the stimulation treatment as long as the results are the same (Van den Wijngaard et al., 2015). Requena et al. (2013) evaluated the degree of donor satisfaction after stimulation with corifollitropin alfa. The results of the study did not show significant differences in the clinical parameters or in clinical pregnancy rates (Requena et al., 2013). Donors treated with corifollitropin alfa who had been treated with daily rFSH in an earlier oocyte donation cycle expressed a preference for corifollitropin alfa. In our study, a wider interval, together with the administration of corifollitropin alfa, reduced the total number of injections, presumably an attractive aspect for the donor.

The reduction in the number of injections (2.14), total dose of gonadotrophins used (200 IU), and the duration of stimulation (1 day) also translated into a significant reduction in the total cost of medication, namely €115, according to the Spanish market. In the study by Blockeel et al. (2014), the reduction in cost of medication was only

Table 2 – Characteristics of the response to stimulation.[a]

	Group D5[b] (n = 42)	Group D7[c] (n = 50)	Mean difference (95% CI)	*P*-value
Oestradiol (D6) (pg/ml)	773.8 (551.4)	1245.3 (741.7)	−471.49 (−755.84 to −187.13)	0.001
Days of stimulation	10.3 (1.6)	9.3 (1.6)	1.00 (0.33 to 1.66)	0.002
Total dose of daily rFSH (IU)	659 (452)	459 (356)	200 (33 to 367)	0.022
Total number of injections	11.9 (3.9)	9.8 (3.2)	2.1 (0.7 to 3.6)	0.004
Total treatment cost (€)	1124.6	1009.8	114.8 (23.2 to 206.4)	0.015
Number of oocytes	13.1 (5.2)	15.0 (8.9)	−1.97 (−4.96 to 1.01)	NS
Number of MII oocytes	10.6 (4.9)	12.4 (7.4)	−1.78 (−4.35 to 0.77)	NS

[a] Values presented as mean (SD).
[b] Group D5: oocyte donors who started ovarian stimulation with corifollitropin alfa 5 days after oral contraceptive pill discontinuation.
[c] Group D7: oocyte donors who started ovarian stimulation with corifollitropin alfa 7 days after oral contraceptive pill discontinuation.
MII, metaphase II; NS, not statistically significant; rFSH, recombinent FSH.

apparent in gonadotrophin consumption, but not in GnRH antagonists used, when the initiation of stimulation was initiated on day 4 of the cycle (Blockeel et al., 2014).

In patients undergoing an IVF or ICSI treatment, an interval of at least 5 days between the last pill and the beginning of stimulation has been recommended so that the capacity to respond to the exogenous stimulus of gonadotropins is not affected (Cédrin-Durnerin et al., 2007). The use of OCP to schedule a GnRH antagonist cycle increases the duration of stimulation and a greater total dose of gonadotropins is used (Garcia-Velasco and Fatemi, 2015; Griesinger et al., 2010). Coinciding with these authors, our study demonstrates the importance of PFI and the administration of corifollitropin alfa for donor stimulation and hypothalamic-pituitary axis recovery, because fewer days of stimulation (9.3 [1.6] versus 10.3 [1.6] days) and a lower total additional dose of daily gonadotrophins (459 [356] versus 659 [452] IU) were needed in group D7 compared with group D5. Our results do not concur with the authors who found that increasing the washout period by more than 5 days also resulted in higher gonadotrophin consumption compared with women who had not been pre-treated with OCP, as mentioned in the Introduction (Barmat et al., 2005; Griesinger et al., 2008; Huirne et al., 2006).

Interestingly, the duration of OCP intake before the PFI did not affect the cycle outcomes. The degree of pituitary–ovarian recovery that emerges during the PFI has been related to the ethinylestradiol dose of the OCP (Van Heusden and Fauser, 1999). In this study, an OCP with ethinylestradiol 30 µg and levonorgestrel 150 µg was used.

The lower requirements of gonadotrophins in group D7 could also be related to the duration of pill taking (22.1 days [SD 6.9] in Group D7 and 22.3 days [SD 8.0] in group D5), longer than the standard 14–20 days interval. This may have led to a more profound pituitary suppression and, thus, the longer pill free interval may have been beneficial. It should be stressed, however, that long OCP intake (i.e. for several months) should be avoided, as suboptimal response after GnRH agonist can occur in these patients, because of pituitary suppression (Meyer et al., 2015).

A significantly higher serum oestradiol level was observed in group D7 on day 6 of ovarian stimulation. One could speculate that this is probably the reflection of the lower degree of hypothalamic–pituitary endogenous suppression owing to the longer pill-free interval (Cédrin-Durnerin et al., 2007). After OCP pre-treatment and a PFI of 4 days, an increase in the length of stimulation and higher LH requirement was observed in suppressed (serum FSH and LH ≤1.2 mIU/ml) IVF patients over the age of 35 years (Schmitz et al., 2012). The donor population in our study was younger than 35 years. No supplementary LH was used and FSH plasma levels were not measured. No differences were found in the number of oocytes retrieved between both treatment groups, although this study was not designed to show or refute such difference.

There has been a concern about higher OHSS risk after delayed administration of corifollitropin (Blockeel et al., 2014). In a recent meta-analysis, seven randomized clinical trials were examined, including 2138 patients who were given corifollitropin alfa and 1788 women who were given daily rFSH in ovarian stimulation protocols in IVF (Fensore et al., 2015). The investigators concluded that corifollitropin alfa was as effective as rFSH in live birth and clinical pregnancy rates. The greater number of oocytes retrieved shows the higher effectiveness of this new long-acting FSH, but they also warned about the possible increased risk of OHSS in high-responders. To avoid this complication, a GnRH agonist bolus should be used, which was applied in all patients included in our trial. Additionally, donors with an antral follicle count over 20, or a prior history of OHSS, were excluded from the study. No cases of OHSS were reported in our study.

The non-randomized design is certainly a limitation, because any bias cannot be ruled out. According to Spanish legislation, randomized trials require significant financial support, that we could not raise. The population of oocyte donors is homogenous owing to the strict eligibility criteria. We did not analyse pregnancy rates in the corresponding recipients because it was not the initial aim of the study, and also because many of the oocytes are still vitrified. Another limitation is the absence of the endocrine profile at the end of the stimulation, because no information can be provided on the progesterone level, which is of major importance when applying this new approach in patients undergoing fresh embryo transfer for some (Bosch et al., 2010; Santos-Ribeiro et al., 2014) but not for all authors (Martinez et al., 2016).

In conclusion, adequate scheduling of ovarian stimulation cycles remains crucially important, especially in oocyte donor patients. When using oral contraceptives for more than 22 days before ovarian stimulation with corifollitropin alfa, extending the pill-free interval to 7 days reduces the consumption of gonadotrophins, the duration of stimulation, and therefore the total cost of the treatment and the total number of injections. Before this strategy could be generally recommended, however, it should be evaluated in patients undergoing an IVF–ICSI treatment.

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REFERENCES

Baerwald, A.R., Olatunbosun, O.A., Pierson, R.A., 2004. Ovarian follicular development is initiated during the hormone-free interval of oral contraceptive use. Contraception 70, 371–377.

Barmat, L.I., Chantilis, S.J., Hurst, B.S., Dickey, R.P., 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.

Blockeel, C., Sterrenburg, M.D., Broekmans, F.J., Eijkemans, M.J., Smitz, J., Devroey, P., Fauser, B.C., 2011. Follicular phase endocrine characteristics during ovarian stimulation and GnRH antagonist cotreatment for IVF: RCT comparing recFSH initiated on cycle day 2 or 5. J. Clin. Endocrinol. Metab. 96, 1122–1128.

Blockeel, C., Polyzos, N.P., Derksen, L., De Brucker, M., Vloeberghs, V., van de Vijver, A., De Vos, M., Tournaye, H., 2014. Administration of corifollitropin alfa on Day 2 versus Day 4 of the cycle in a GnRH antagonist protocol: a randomized controlled pilot study. Hum. Reprod. 29, 1500–1507.

Bodri, D., Guillén, J.J., Trullenque, M., Schwenn, K., Esteve, C., Coll, O., 2010. Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study. Fertil. Steril. 93, 2418–2420.

Bosch, E., Labarta, E., Crespo, J., Simón, C., Remohí, J., Jenkins, J., Pellicer, A., 2010. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Hum. Reprod. 25, 2092–2100.

Cédrin-Durnerin, I., Bständig, B., Parneix, I., Bied-Damon, V., Avril, C., Decanter, C., Hugues, J.N., 2007. Effects of oral contraceptive, synthetic progestogen or natural estrogen pre-treatments on the hormonal profile and the antral follicle cohort before GnRH antagonist protocol. Hum. Reprod. 22, 109–116.

Devroey, P., Boostanfar, R., Koper, N.P., Mannaerts, B.M., Ijzerman-Boon, P.C., Fauser, B.C., Investigators, E.N.G.A.G.E., 2009. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. Hum. Reprod. 24, 3063–3072.

Fauser, B.C., Mannaerts, B.M., Devroey, P., Leader, A., Boime, I., Baird, D.T., 2009. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum. Reprod. Update 15, 309–321.

Fensore, S., Di Marzio, M., Tiboni, G.M., 2015. Corifollitropin alfa compared with daily FSH in controlled ovarian stimulation for in vitro fertilization: a meta-analysis. J. Ovarian. Res. 8, 33.

Galindo, A., Bodri, D., Guillén, J.J., Colodrón, M., Vernaeve, V., Coll, O., 2009. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. Gynecol. Endocrinol. 25, 60–66.

Garcia-Velasco, J.A., Fatemi, H.M., 2015. To pill or not to pill in GnRH antagonist cycles: that is thequestion! Reprod. Biomed. Online 30, 39–42.

Griesinger, G., Venetis, C.A., Marx, T., Diedrich, K., Tarlatzis, B.C., Kolibianakis, E.M., 2008. Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists for IVF: a systematic review and meta-analysis. Fertil. Steril. 90, 1055–1063.

Griesinger, G., Kolibianakis, E.M., Venetis, C., Diedrich, K., Tarlatzis, B., 2010. Oral contraceptive pretreatment significantly reduces ongoing pregnancy likelihood in gonadotropin-releasing hormone antagonist cycles: an updated meta-analysis. Fertil. Steril. 94, 2382–2384.

Griesinger, G., Venetis, C.A., Tarlatzis, B., Kolinianakis, E.M., 2015. To pill or not to pill in GnRH-antagonist cycles: the answer is in the data already! Reprod. Biomed. Online 31, 6–8.

Hauzman, E.E., Zapata, A., Bermejo, A., Iglesias, C., Pellicer, A., Garcia-Velasco, J.A., 2013. Cycle scheduling for in vitro fertilization with oral contraceptive pills versus oral estradiol valerate: a randomized, controlled trial. Reprod. Biol. Endocrinol. 28, 11–96.

Hohmann, F.P., Macklon, N.S., Fauser, B.C., 2003. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. J. Clin. Endocrinol. Metab. 88, 166–173.

Huirne, J.A., Hugues, J.N., Pirard, C., Fischl, F., Sage, J.C., Pouly, J.L., Obruca, A., Braat, D.M., van Loenen, A.C., Lambalk, C.B., 2006. Cetrorelix in an oral contraceptive-pretreated stimulation cycle compared with buserelin in IVF/ICSI patients treated with r-hFSH: a randomized, multicentre, phase IIIb study. Hum. Reprod. 21, 1408–1415.

Lutjen, P., Trounson, A., Leeton, J., Findlay, J., Wood, C., Renou, P., 1984. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 307, 174–175.

Martinez, F., Clua, E., Parera, N., Rodríguez, I., Boada, M., Coroleu, B., 2008. Prospective, randomized, comparativestudyofleuprorelin + humanmenopausalgonadotropins versus ganirelix + recombinantfollicle-stimulatinghormone in oocytedonorsandpregnancy rates amongthecorrespondingrecipients. Gynecol. Endocrinol. 24, 188–193.

Martinez, F., Rodriguez, I., Devesa, M., Buxaderas, R., Gómez, M.J., Coroleu, B., 2016. Should progesterone on the human chorionic gonadotropin day still be measured? Fertil. Steril. 105, 86–92.

Meyer, L., Murphy, L.A., Gumer, A., Reichman, D.E., Rosenwaks, Z., Cholst, I.N., 2015. Risk factors for a suboptimal response to gonadotropin-releasing hormone agonist trigger during in vitro fertilization cycles. Fertil. Steril. 104, 637–642.

Pérez-Calvo, A., Martínez, F., Clua, E., Rodríguez, I., Coroleu, B., 2015. Use of corifollitropin alfa for ovarian stimulation in oocyte donors. Poster presented at 6th International IVI Congress, Alicante, Spain, April 23–25.

Pinkas, H., Sapir, O., Avrech, O.M., Ben-Haroush, A., Ashkenzi, J., Fisch, B., Farhi, J., 2008. The effect of oral contraceptive pill for cycle scheduling prior to GnRH-antagonist protocol on IVF cycle parameters and pregnancy outcome. J. Assist. Reprod. Genet. 25, 29–33.

Practice Committee of Society for Assisted Reproductive Technology, Practice Committee of American Society for Reproductive Medicine, 2008. 2008 Guidelines for gamete and embryo donation: a Practice Committee report. Fertil. Steril. 90, S30–S44.

Prapas, N., Prapas, Y., Panagiotidis, Y., Prapa, S., Vanderzwalmen, P., Schoysman, R., Makedos, G., 2005. GnRH agonist versus GnRH antagonist in oocyte donation cycles: a prospective randomized study. Hum. Reprod. 20, 1516–1520.

Requena, A., Cruz, M., Collado, D., Izquierdo, A., Ballesteros, A., Muñoz, M., García-Velasco, J.A., 2013. Evaluation of the degree of satisfaction in oocyte donors using sustained-release FSH corifollitropin alfa. Reprod. Biomed. Online 26, 253–259.

Santos-Ribeiro, S., Polyzos, N.P., Haentjens, P., Smitz, J., Camus, M., Tournaye, H., Blockeel, C., 2014. Live birth rates after IVF are reduced by both low and high progesterone levels on the day of human chorionic gonadotrophin administration. Hum. Reprod. 29, 1698–1705.

Schmitz, C., Bocca, S., Beydoun, H., Stadtmauer, L., Oehninger, S., 2012. Does the degree of hypothalamic-pituitary-ovarian recovery after oral contraceptive pills affect outcomes of IVF/ICSI cycles receiving GnRH-antagonist adjuvant therapy in women over 35 years of age? J. Assist. Reprod. Genet. 29, 877–882.

Solé, M., Santaló, J., Boada, M., Clua, E., Rodriguez, I., Martinez, F., Coroleu, B., Barri, P.N., Veiga, A., 2013. How does vitrification affect oocyte viability in oocyte donation cycles? A prospective study to compare outcomes achieved with fresh versus vitrified sibling oocytes. Hum. Reprod. 28, 2087–2092.

Van den Wijngaard, L., Rodijk, I.C., van der Veen, F., Gooskens-van Erven, M.H., Koks, C.A., Verhoeve, H.R., Mol, B.W., van Wely, M.,

Mochtar, M.H., 2015. Patient preference for a long-acting recombinant FSH product in ovarian hyperstimulation in IVF: a discrete choice experiment. Hum. Reprod. 30, 331–337.
Van Heusden, A.M., Fauser, B.C., 1999. Activity of the pituitary-ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. Contraception 59, 237–243.
van Heusden, A.M., Fauser, B.C., 2002. Residual ovarian activity during oral steroid contraception. Hum. Reprod. Update 8, 345–358.
Verberg, M.F., Eijkemans, M.J., Heijnen, E.M., Broekmans, F.J., de Klerk, C., Fauser, B.C., Macklon, N.S., 2008. Why do couples drop-out from IVF treatment? A prospective cohort study. Hum. Reprod. 23, 2050–2055.