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COMMENTARY

Can oestradiol pretreatment be used to reliably avoid weekend oocyte retrievals?

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Abstract Scheduling the initiation of ovarian stimulation in a gonadotrophin-releasing hormone (GnRH)-antagonist protocol by sex steroid pretreatment has been suggested as a means to reduce the incidence of oocyte retrievals during weekends. The rationale is that by manipulating the initiation of gonadotrophin stimulation, Thursday or Friday will be avoided as days on which triggering of final oocyte maturation will be performed and thus weekend oocyte retrievals will not occur. Apparently, the assumption behind such an approach is that duration of stimulation is homogenous enough to serve this purpose reliably. However, existing data suggest that large inter-individual variation exists in the duration of gonadotrophin stimulation required to reach predefined criteria for triggering final oocyte maturation, regardless of whether stimulation was initiated with spontaneous menstruation or after pretreatment with sex-steroids. Therefore, it is highly unlikely that any type of pretreatment aiming to allow initiation of stimulation on a certain day will result in avoidance of weekend oocyte retrievals, when predefined criteria for triggering final oocyte maturation are used.

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Soon after the introduction of gonadotrophin-releasing hormone (GnRH)-antagonists, it was claimed that sex-steroid pretreatment could be used to avoid weekend oocyte retrievals that have important organizational and economical implications (Fischl et al., 2001). Oral contraceptive pill (OCP) (ethinyl oestradiol plus desogestrel/levonorgestrel) administration for 14–28 days before initiation of stimulation in a GnRH-antagonist protocol was studied in a number of randomized controlled trials. While the objectives of the individual trials on OCP pretreatment were quite heterogenous, it was shown that OCP pretreatment resulted in a statistically and clinically significant decrease in ongoing pregnancy rate (summarized in Griesinger et al., 2008, 2010). As an alternative, for decreasing the incidence of oocyte retrievals on weekends, natural oestradiol pretreatment has been evaluated (Guivarc'h-Levêque et al., 2010). However, until recently, no randomized studies have been performed on this issue.

We thus read with great interest the article by Blockeel et al. (2011), reporting a randomized trial that examined the number of oocyte retrievals occurring during weekends in patients treated by GnRH-antagonists and gonadotrophins. Patients in the study group received 4 mg oral oestradiol valerate from cycle day 25 onwards until initiation of ovarian stimulation, which occurred 1 day after cessation of oestradiol intake. The duration of oestradiol administration ranged between 6 and 10 days depending on the day of the week on which cycle day 25 occurred. With this regimen, 5/7 of patients would initiate ovarian stimulation on a Friday, while 1/7 and 1/7 of patients would initiate ovarian stimulation on a Saturday and Sunday, respectively. In brief, the authors observed that 1/37 oocyte retrievals

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(2.7%) occurred during a weekend in the study group, while in the control group (conventional GnRH-antagonist protocol without oestradiol pretreatment) this was the case for 8/39 oocyte retrievals (20.5%).

Although appealing as a concept, the underlying rationale of this approach is difficult to adopt. In a recently reported, large GnRH-antagonist trial (Fauser et al., 2010), the duration of stimulation in a well-defined population of patients with regular cycles and no endocrine abnormalities ranged from 6 to 15 days. Similar information has been available from the initial comparative randomized controlled trials (RCT) between agonists and antagonists in the early 2000s, where the range of the duration of gonadotrophin stimulation was reported to be between 6 and 18 days in the antagonist group and between 6 and 19 in the agonist group (Borm and Mannaerts, 2000). The corresponding figures in the European and Middle East Orgalutran Study Group (2001) were between 6 and 14 days for the antagonist-treated and between 7 and 16 days for the agonist-treated groups. With this variation in mind, observed in well-selected populations, it is not easy to explain how the goal of avoiding weekend oocyte retrievals can ever be reliably achieved when strict criteria for triggering final oocyte maturation are used without possessing clairvoyant abilities. Unfortunately, it is unclear by reading the corresponding sentence in the manuscript by Blockeel et al. (2011) 'Final oocyte maturation was triggered ... when three follicles of 17 mm diameter were observed on ultrasound scan' whether strict or loose criteria were used for triggering final oocyte maturation. It should also be noted that although the difference observed by Blokeel et al. was statistically significant ($P = 0.029$), if only one additional weekend case occurred in either of the groups compared, the statistically significant difference in the occurrence of weekend oocyte retrieval would no longer be present.

The duration of stimulation necessary to reach predefined criteria for triggering final oocyte maturation cannot be predicted on an individual basis. It was recently reported that even distinguishing early responders (requiring $\leq$8 days of stimulation) from late responders (requiring $>$8 days of stimulation) cannot be done on the basis of conventionally used clinical criteria (age, body mass index, antral follicle count, basal FSH) (Mardešiè et al., 2011).

If the assumption by Blockeel et al. (2011) that by scheduling the day that gonadotrophin stimulation starts it is possible to avoid weekend oocyte retrievals was true, one should expect that weekend oocyte retrievals would be a rare phenomenon in agonist cycles (long protocol). In agonist cycles, initiation of stimulation is not dependent on occurrence of menstruation as is the case with GnRH antagonists and can be controlled by the clinician. Apparently, however, weekend oocyte retrieval is not a phenomenon that occurred for the first time in IVF following the introduction of GnRH antagonists. Weekend oocyte retrievals do also occur in agonist cycles (Rombauts et al., 2006) despite the ability to control the day that ovarian stimulation starts.

Interestingly, oestradiol pretreatment apparently does not result in less variation in stimulation duration, since Blockeel and colleagues (2011) report similar standard deviations between the two groups compared in their RCT (oestradiol pretreatment versus no pretreatment) for this outcome. This was also the case in the RCTs comparing OCP pretreatment versus no pretreatment, where no reduction in the variation in stimulation duration was observed in patients pretreated with OCP (summarized in Griesinger et al., 2010). Moreover, duration of oestradiol administration itself is significantly associated with duration of ovarian stimulation as well as with gonadotrophin consumption (Guivarc'h-Levêque et al., 2011).

A more rational approach for avoiding weekend oocyte retrievals has recently been proposed from a large retrospective case series on GnRH-antagonist stimulation (Tremellen and Lane, 2010). Advancing or delaying human chorionic gonadotrophin (HCG) administration by 24 h had no impact on delivery rates, thus allowing the skipping of weekends on a routine basis for all patients. Although this is a retrospective analysis, the data are relatively robust because a 'real-life' population has been evaluated, the onset of menstruation occurs evenly distributed over the week days (Gordon et al., 2011) and the day of HCG administration is only determined by the individual patient response. Thus, the effect of the intervention (advancing or delaying HCG administration) could be studied without high risk for bias. Moreover, a small RCT comparing HCG administration as soon as three or more follicles of $\geq$16 mm were present or 1 day later did not suggest the presence of significant differences in pregnancy rates (Kyrou et al., 2011). Finally, a retrospective analysis of a large clinical trial (Hillensjo et al., 2011) similarly suggested that delaying HCG by 1 day does not affect the chance of pregnancy.

If the aim of treatment scheduling were to distribute work load to different weeks of the year, or to determine the oocyte retrieval for a patient on a tight business schedule well in advance, oestradiol pretreatment for up to 10 days will not suffice. Although it may be desirable to decrease the number of oocyte retrievals during weekends with the help of oestradiol pretreatment, if personnel still need to be at short-notice disposal for weekend work, this is far from being an ideal solution.

In conclusion, it is highly unlikely that any type of pretreatment aiming to allow initiation of stimulation on a certain day will avoid weekend oocyte retrievals when predefined criteria for triggering final oocyte maturation are used.

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