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Commentary

Timing of Luteal Phase Support along with Optimum Drugs to be Used: A Short Commentary

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Controlled ovarian stimulation (COS) during ART leads to disruption of the pulsatile secretion of LH from the anterior pituitary, that causes normal physiological support of corpus luteum (CL) hence there is need of giving a luteal phase support (LPS). With this suggested mechanism need for starting LPS is once the action of HCG on CL has finished till luteal support is replaced by the HCG from embryonic origin. HCG derived from urinary source or that is recombinant in origin has got pharmacokinetic features which give long duration of action on the CL present. Thus one can hold LPS until several days in luteal phase like following embryo transfer (ET), as was the routine action in initial time of artificial reproductive technology (ART).

This got more complicated during nineties, once there was availability of high frequency high resolution vaginal ultrasound probes by which uterine contractility started getting studied. With these scans one could see the uterine contractions along with getting the frequency on fast played ultrasound scans. Fanchin., *et al.* found an inverse relation between the number of uterine contractions during the time of cleavage stage ET's along with implantation or pregnancy rates [1]. It is known that E2 causes the rise in uterine contractions at the end of follicular phase, the thought came to mind regarding the effects of high E2 observed during COS on uterine contractility. Hence to study this Ayoubi., *et al.* carried out a prospective study to see the difference in uterine contractions in a normal menstrual cycle vis a vis COS in the same women [2]. It was seen that frequency of contractions at the end of the follicular phase either on day of LH surge or HCG administration was similar be it in the menstrual cycle or COS [2]. Thus this showed that increased E2 seen during COS was not responsible for increasing uterine contraction frequency over the number of 5 contractions/min that was seen during the normal menstrual cycle in the late follicular phase [2]. But what was different between the 2 conditions was the decrease in uterine contraction frequency during the luteal phase secondary to the uterus quietening properties of P between the menstrual cycle and COS [2]. This quietening of uterus happened as early as 4 days following LH surge, in contrast to the same happening after 48 hrs, i.e. at the time of blastocyst transfers in COS done in same patients [2].

Although these high E2 levels during COS don't raise the uterine frequency, they change the normal decrease in uterine frequency that is achieved by P Fanchin., *et al.* showed that if E2 was increased by giving vaginal E2 tablets it blunted the uterine quietening properties of P [3]. In another study by Fanchin., *et al.* it was seen that P administration early, on day of oocyte retrieval decreased the frequency of uterine contraction on the day of cleavage stage ET'S [4]. Thus it was concluded that the high levels of E2 seen during COS caused some degree of blocking of the uterine quietening properties of P.

This work on uterine contractility caused a tussle between timing of LPS. Although giving LPS as early as on day of oocyte retrieval might be beneficial but there are doubts that giving too early LPS might close the window of implantation prematurely and thus cause an harm for ET be it at cleavage stage or at blastocyst stage [5].

Recently Gao., *et al.* conducted a randomized controlled trial which studied differences in timing of starting LPS on day of oocyte retrieval/1 day later in outcome of ART [6]. COS was done with the use of an agonist protocol and ET done either at cleavage or blastocyst stage. They gave daily IM 60 mg P for LPS and found no difference in outcome of ART whether early LPS was done or 1 day later [6]. Thus he showed that early onset of LPS is not harmful, i.e. it does not cause premature closure of window of implantation. However the effects of the 2 LPS timing on uterine contractility and thus the outcome is not that clear. It might be assumed that early onset of LPS has no beneficial action on uterine contractions and thus ART outcome. But it is too early to draw conclusions as ET was done at either cleavage or blastocyst stage. Early LPS does not affect uterine contractions at the time of blastocyst transfer [4]. There might be a way of explaining no difference in ART outcome between early and late LPS in Gao's work by late onset of LPS might be enough to stop uterine contractions at the time of day 3 transfers [6]. Also Gao did not take up the issue of when to stop LPS rather than the conventional 10 weeks.

Another question that one needs to address is which P has to be used. With the disadvantages of IM P causing severe pain and abscess formation some time. Griesinger found oral dydrogesterone is at least as effective as micronized vaginal support in fresh IVF cycles [7]. We have successfully used oral dydrogesterone reolacing the cumbersome IM P getting equal results as has been proved in the LOTUS Trial.

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