7th World Congress on Ovulation Induction
BOLOGNA, ITALY 3-5 SEPTEMBER 2015

Ways to deliver progesterone subcutaneously: Development and features

D. de Ziegler, V Gayet, P Pirtea, C. Chapron, P. Santulli Clinical Director
Université Paris Descartes - Hôpital Cochin, Paris, France
Email: ddeziegler@me.com

Introduction Controlled ovarian stimulation (COS) designed for enabling multiple oocyte harvests in ART has been classically associated with anomalies of progesterone production during the luteal phase. These result from alterations of the normal support of the corpus luteum by LH produced in a pulsatory manner by the anterior pituitary. The pituitary dysfunction encountered in COS results from the excessive levels of E2, use of agonist or antagonist analogues of GnRH and lastly, the administration of exogenous hCG for triggering the final phases of oocyte maturation.

Luteal phase support (LPS) There is now overwhelming evidence that progesterone administration during the luteal phase (LPS) of COS is mandatory for optimizing outcome. The duration of LPS is still mater for discussion. There are mounting evidence that LPS can be harmlessly discontinued once there is a positive pregnancy test or after the first ultrasound, 2-3 weeks later. Yet, most ART centers – it includes ours – extend LPS until the luteo-placental transition is assured 10 weeks after embryo transfer (ET).

Frozen embryo transfers (FET) Exogenous E2 and progesterone administration is also used for priming endometrial receptivity in preparation for frozen embryo transfers (FET), following models developed in donor egg – ART (dART). Here exogenous progesterone must be mandatorily continued until the autonomous take over of progesterone production by the placenta is assured 10 weeks after ET.

New progesterone option Classically, progesterone for LPS was delivered by injections or vaginally, as the oral and transdermal routes are not available. Up to now, injectable progesterone preparations were oil-base preparations that mandated IM administration. Today a new progesterone preparation is offered in aqueous form for sub cutaneous administration, Prolutex®. The efficacy of this new progesterone preparation was tested in E2 and progesterone treatment – of frozen embryo transfer type – and in real life ART conditions. The former phase II trial led to select the dose of 25mg/day as being the minimal effective dose that produces the endometrial transformations encountered in the luteal phase of the menstrual cycle.
Subsequently, phase III trials – in Europe and US – offered evidence that Prolutex is equally effective for LPS as the vaginal products existing in real life COS as commonly used in ART.

Conclusion Recently, accumulating evidences have pointed at differences in obstetrical outcome following the transfer of fresh or cryopreserved ART embryos. Fresh embryo ART is associated with a slight increase incidence in preeclampsia, premature birth and small for gestational age (SGA) and generally leads to slightly earlier deliveries of slightly smaller babies. Conversely, frozen embryo ART does see these alterations but is associated with a slight increase in macrosomia. None of these alterations are readily explainable. Yet all point at early placentation issues and therefore call for reassessing whether all LPS are equal and whether the hormonal levels to which the endometrium is exposed at embryo implantation time should not be controlled better.