# PROGRAM AT A GLANCE

## 7th World Congress on Ovulation Induction

**Bologna, Italy • 3-5 September 2015**

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Thursday • 3 September 2015

OPENING CEREMONY
14:00 Welcome and opening of the Congress
Filicori M (IT), Pilu G (IT)

SESSION I
BASIC ASPECTS AND DIAGNOSTICS
Chairpersons:
Plant TM (US)
Parmegiani L (IT)

14:30 Folliculogenesis control in primates (AB-01)
Stouffer R (US)

15:00 Relevance of oocyte aneuploidy in ovulation induction and assisted reproduction (AB-02)
Wells D (UK)

15:30 Use of antimüllerian hormone to design ovarian stimulation (AB-03)
Nelson S (UK)

16:00 LH vs. hCG to provide LH activity (AB-04)
Simoni M (IT)

16:30 COFFEE BREAK

17:00 PROGESTERONE: THE KEYSTONE OF REPRODUCTION
IBSA Farmaceutici Italia Symposium
Chairpersons:
Bosch E (ES)
Palomba S (IT)

17:00 The corpus luteum: Control and functions (SS-01)
Stouffer R (US)

17:25 Progesterone and implantation (SS-02)
Lessey B (US)

17:50 Ways to deliver progesterone subcutaneously: Development and features (SS-03)
De Ziegler D (FR)

18:15 Discussion

18:30 WELCOME RECEPTION
at Foyer EUROPA
SESSION II
STIMULATION REGIMENS

Chairpersons:
Lessey B (US)
Borini A (IT)

08:30 GnRH agonists and antagonists in controlled ovarian stimulation: A 2015 perspective (AB-05)
Filicori M (IT)

09:00 Ovarian stimulation in polycystic ovary syndrome (AB-06)
Palomba S (IT)

09:30 Rationale and outcome of LH activity supplementation (AB-07)
Alviggi C (IT)

10:00 Mixed vs. single gonadotropin administration: A transatlantic perspective (AB-08)
Schattman GL (US)

10:30 Gonadotropin-stimulated late follicular gonadal steroid levels: Mechanisms and effects (AB-09)
Bosch E (ES)

11:00 COFFEE BREAK

11:30 PROGRESS IN HIGHLY PURIFIED GONADOTROPIN DEVELOPMENT

IBSA Institut Biochimique SA Symposium

Chairpersons:
Lockwood G (UK)
Humaidan P (DK)

11:30 Physiology and clinical impact of gonadotropin isoforms: From FSH to hCG (SS-04)
Andersen CY (DK)

12:00 Endocrine and clinical features of a new highly purified hMG preparation (SS-05)
De Geyter C (CH)

12:30 Discussion

13:00 LUNCH

13:00 Free Communications Session I
(Refreshments will be made available to attendees)
PROGESTERONE:
THE KEYSTONE OF REPRODUCTION

Chairpersons: Bosch E (ES), Palomba S (IT)
The corpus luteum: Control and functions
Stouffer R1,2, Bishop C1, Xu F1, Hennebold J1
1Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Beaverton, OR, USA
2Department of Obstetrics & Gynecology, Division of Reproductive Endocrinology and Infertility, University of South Carolina, School of Medicine, Greenville, SC, USA
e-mail: stouffr@ohsu.edu

Introduction: The primate corpus luteum is a transient endocrine gland that differentiates from the ovulatory follicle midway through the ovarian/menstrual cycle (Stouffer, RL et al. Reprod Biol 13:259-271, 2013). Its formation and limited lifespan is critical for fertility, as luteal-derived progesterone is the essential steroid hormone for embryo implantation and maintenance of intra-uterine pregnancy until the placenta usurps this steroidogenic function. The pituitary gonadotropin, luteinizing hormone (LH), and the LH-like hormone, chorionic gonadotropin (CG), are vital luteotropic hormones during the menstrual cycle and early pregnancy, respectively. However, it is increasingly recognized that local factors, including angiogenic factors (e.g., vascular endothelial growth factor, VEGF), prostaglandins (e.g., PGE2 and PGF2α), and steroids (e.g., progesterone) act in an autocrine or paracrine manner to mediate or counteract the luteotropic effects of LH/CG.

Methods and Results: Recent advances from this research group identify the critical local role of progesterone and its receptor-signaling pathways in the formation and regression of the monkey (macaque) corpus luteum during the menstrual cycle. First, to examine the role of the genomic progesterone receptor (PGR) in ovulation and luteinization of the dominant follicle, adenoviral vectors (AdV) expressing short-hairpin (sh) RNA that recognizes the rhesus macaque PGR or a non-targeted scrambled shRNA (control) were injected into the preovulatory follicle 20 hours before administering an hCG bolus to induce periovulatory events. Follicles injected with the control AdV-scrambled shRNA ovulated in a timely manner, and serum P levels increased to typical (ng/ml) levels in a functional luteal phase. In contrast, intrafollicular injection of AdV-PGR shRNA typically blocked follicle rupture (except one animal) and prevented the rise in circulating P levels. Ovarian samples confirmed the presence of a trapped oocyte in the AdV-PGR shRNA treated follicles and the absence of intense nuclear staining for PGR. In contrast, intense immunohistochemical staining for PGR was evident in the luteinizing follicle wall of control follicles. Second, to determine if the numbers of immune cells or their activity in the primate corpus luteum are regulated by the loss of LH support or indirectly via loss of LH-dependent P production/action, female monkeys received no treatment (controls), a GnRH antagonist (Antide) or Antide plus a progestin (R5020). Antide treatment markedly increased the numbers of CD11b (primarily granulocytes, as well as monocytes and activated lymphocytes) and CD14 (monocytes/macrophages)-positive immune cells in luteal tissue, but not CD16 (natural killer cells)-positive cells. Adding R5020 with Antide reduced the numbers of CD11b- and CD14-positive cells to those of controls. Further studies established that progesterone levels must decline to baseline (0.3 < ng/ml) for 3-4 days at the end of the menstrual cycle for the increase in immune cells to occur. Moreover, these cells produced 16 cytokines during acute incubation in vitro, including chemokines such as MCP-1 and MDC, as well as several interleukins.

Conclusions: The data support the concepts that: (1) induction of P and its receptor in response to the mid-cycle gonadotropin surge is critical for ovulation and luteal development, whereas (2) the decline in P and P-receptor signaling during functional luteal regression is required for subsequent structural luteolysis involving immune cell attraction and activation.

Federal grant awards supporting the research R01HD020869 and P50DO11092

Progesterone and Implantation
Lessey B
Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of South Carolina, School of Medicine, Greenville, SC, USA
e-mail: blessey@ghs.org

Progesterone is a critical mediator of endometrial receptivity. The pathway between ovulation and progesterone production from the corpus luteum involves complex paracrine mechanisms involving the Indian Hedgehog signaling pathway allowing communication between epithelial and stromal compartments. In normal, fertile women progesterone initiates a large number of mediators that ultimately down-regulate estrogen receptors, a key step in implantation success. In certain inflammatory conditions, such as endometriosis and hydrosalpinx, these pathways are disrupted, leading to progesterone resistance. The link between these reversible inflammatory conditions and implantation failure have remained poorly understood. Increasingly, women with unexplained infertility or pregnancy loss are recognized to have defects in their endometrial response to progesterone, maintaining an excessive endogenous estrogen response that favors proliferation and is anti-apoptotic. Progesterone resistance and estrogen dominance are central to the association between inflammation and infertility. This presentation will focus on the normal progesterone signaling pathways for successful pregnancy but also examine the mechanisms of how disruption in progesterone signaling occurs, leading to endometrial receptivity defects, infertility and IVF failure.
**Ways to deliver progesterone subcutaneously: Development and features**

De Ziegler D, Gayet V, Pirtea P, Chapron C, Santulli P
Université Paris Descartes - Hôpital Cochin, Paris, France

**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.
IBSA Institut Biochimique SA
Symposium

Friday • 4 September 2015
11:30 – 13:00

PROGRESS IN HIGHLY PURIFIED GONADOTROPIN DEVELOPMENT

Chairpersons: Lockwood G (UK), Humaidan P (DK)
A fine-tuned interplay between hormones of the hypothalamus-pituitary-ovarian axis leads to the development of just one pre-ovulatory follicle during the natural menstrual cycle. During the first half of the follicular phase of the menstrual cycle stimulation of follicular growth takes place resulting in selection of the follicle destined to ovulate, whereas in the second half the selected follicle acquires dominance and is subsequently ovulated. Due to the low levels of both oestradiol and Inhibin-B in the beginning of the follicular phase FSH rise and exceed the threshold level that stimulates follicular growth. FSH is released from the pituitary in a variety of isoforms that all share a similar peptide backbone but have different oligosaccharides attached, which especially differ in the number of terminal sialic acid residue affecting the overall circulatory half-life. FSH isoforms with relatively many terminal sialic acid residues (i.e., acid isoforms) are shielded from hepatic clearance and show longer half-life as compared to FSH isoforms with fewer terminal sialic acid residues (i.e., less acid isoforms). The FSH isoform composition released from the pituitary is under hormonal control. Circulatory levels of oestradiol determine the FSH isoform profile and while levels of oestradiol during the first part of the follicular phase are low the FSH isoform composition released is primarily acid. Only when levels of oestradiol rise as ovulation is approaching will the FSH isoform composition change and become less acid, while the pituitary release of FSH at the same time is becoming reduced as the oestradiol and Inhibin-B exert a negative feed-back inhibition on the pituitary.

To compensate for the reduced FSH levels the selected follicle starts to develop LH receptors, which – when activated – during the second half of the menstrual cycle stimulate follicular growth and oestradiol production. Thus, a combination of FSH and LH drives follicular development during the second half of the menstrual cycle. In connection with controlled ovarian stimulation (COS) levels of FSH in the second half of the menstrual cycle remain high due to exogenous administration and it is well established that these high levels of FSH may drive follicular development without or with only low levels of LH or hCG activity. Alternatively, high levels of LH-like activity (i.e. LH or hCG) may drive follicular development with only low levels of FSH and in that sense the two gonadotropins may substitute for one another. As for FSH, hCG exists in different forms, which exert different functions – in particular sulphated hCG, hyperglycosylated hCG and normal hCG show different characteristics, which may be of importance in connection for controlled ovarian stimulation. The lecture will provide an overview of the hormonal regulation of follicular development in the follicular phase.

**Endocrine and clinical features of a new highly purified hMG preparation**

De Geyter C

University Hospital of Basel, University of Basel, Basel, Switzerland
e-mail: christian.degeyter@usb.ch

A prospective, investigator-blind, randomized, multicentre, non-inferiority study was carried out in 270 infertile women to compare a new highly purified hMG preparation (IBSA) with another highly purified hMG preparation (Menopur, Ferring) for controlled ovarian hyperstimulation (COH) in ART. The study was funded by Institut Biochimique SA (IBSA). The new IBSA highly purified menotrophin (hMG) preparation contains 75 IU (or 150 IU) follicle stimulating hormone (FSH) and 75 IU (or 150 IU) luteinizing hormone (LH) activity per vial and is extracted from the urine of menopausal women while the IBSA highly purified menotrophin (hMG) preparation contains 75 IU (or 150 IU) of FSH of chorionic origin extracted from the urine of pregnant women. The study aimed to i) confirm the non-inferiority of the new IBSA hMG vs. a commercially available hMG comparator with regard to clinical outcome and to ii) compare the incidence of clinically significant OHSS. 270 women aged 18–39 years, with a BMI ≤30 kg/m², with <3 prior completed assisted reproductive technology (ART) cycles, undergoing in vitro fertilization (IVF) were randomized from March 2011 through April 2013. Standard long down-regulation with GnRH-agonist was performed before starting COH. Ovulation was induced with hCG. Primary efficacy assessment was the total number of oocytes retrieved. Most of the clinically significant endpoints including fertilization rate, cleavage rate, mean implantation rate, positive s-hCG test rate, clinical pregnancy rate, delivery and live births rate, miscarriage rate were similar among both groups. In addition, neonatal efficacy parameters including gestational age at delivery, baby weight, singleton and multiples rate similar among both groups. The quality of the embryos obtained was also equivalent in the two treatment groups, but the number of retrieved oocytes was higher in the IBSA hMG (11.6 ± 6.6 and 9.7 ± 5.9, respectively). The duration of stimulation was shorter in the IBSA hMG preparation group. The safety and tolerability profiles of both preparations were similar. In conclusion, this study has demonstrated that IBSA hMG is an alternative for controlled ovarian stimulation in ART.
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