Short communication

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Human Chorionic Gonadotropin: An Old Hormone with New Potentials

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Short Commentary

Ovarian response amongst women during ovarian stimulation (COS) for in vitro fertilization (IVF) is a highly important issue and has led researchers from all over the world experiment on different protocols. The goal is to try and cope with multiple failed attempts and to try to interpret this phenomenon and come up with the ideal solution [1]. Gonadotropins and the different expression of its receptors in each patient has been the landmark of research for many years [2].

It is an established knowledge that LH is involved in follicle maturation, beginning from the antral stage. Primordial and primary preantral follicle development is considered gonadotropin independent, since both cumulus cells and theca cells lack FSH and LH receptors. However, in cumulus cells, the presence of FSH and LH receptors has been confirmed from the secondary preantral and from the antral stage onwards respectively. Regarding the theca cells, LH receptors are present from the secondary preantral stage onwards, while they are lacking FSH receptors. Gonadotropin receptor allocation in follicular cells is in line with the two-cell two-gonadotropin theory [3]. According to what we know so far, LH stimulates androgen production by the theca cells while, at the same time, FSH promotes aromatase enzyme activity and thus the utility of androgens as a substrate for estrogen biosynthesis.

FSH has a leading role in recruitment, selection and dominance of ovarian follicels, while LH contributes to dominance, maturation and ovulation. This process makes these two gonadotropins act synergistically in the process of follicular growth [4,5]. It is an established knowledge that preantral stage can be reached in the absence of LH. Nevertheless, LH is an important factor in both oocyte and follicular cells development through modification of the steroid and protein micro- and macro-environment [4,6]. These physiologic changes have a prominent role in oocyte maturation, the process of ovulation and subsequent fertilization and implantation [7]. Based on studies on non-human primates, we know that LH may act by increasing intra-ovarian androgens, which in turn promote FSH responsive granulosa cell function [8].

Human chorionic gonadotropin (hCG) has been used as a substitute for the mid-cycle LH surge because of the degree of homology between the two hormones [9]. hCG shares structural similarities with LH and binds to the same receptor, LH/CGR. However, hCG has a longer half-life of 36 hours [10] while the elimination half-life of recombinant LH is estimated to be around 10-12 hours [11]. The slower plasma metabolic clearance of hCG consists of a rapid phase in the first 5-9 hours following intramuscular (IM) administration and a slower phase in the first 1-1.3 days after administration. Moreover, hCG has stronger LH/CGR receptor binding affinity, probably due to differences in the carbohydrate moiety, which may make the molecule more sensitive to the binding receptor [12] and is much more potent than LH [13].

LH and hCG share the same α-subunits and a high cysteine content. They also present with an identical natural function; to cause ovulation and support lutein cells. Their main differences include the sequence of the β-subunit, the regulation of the secretion of the two hormones, the carbohydrate component and the pharmacokinetics of clearance of hCG as opposed to LH [14,15].

The LH/CGR has an almost ubiquitous distribution in reproductive organs, which suggests that the actions of hCG might be more extensive than once believed. It is mainly located in gonads, ovary and testis. Hence, it can be found in extragonadal reproductive organs, such as the uterus and the fallopian tubes. Nevertheless, non-reproductive tissues such as skin, breast, adrenals, thyroid, neural retina and neuroendocrine cells express LH/CGR too [16,17]. Regardless of the use of FSH, low-dose hCG can support development and maturation of larger ovarian follicles that have acquired granulosa cell LH/CGRs, possibly providing effective and safer ovulation induction regimens. In a recent study by our group, it was demonstrated that the addition of hCG to rFSH in a short GnRH-agonist protocol throughout the early follicular phase had a beneficial effect in terms of pregnancy rates, while hCG was also associated with better quality embryos [18]. This occurs probably due to the direct induction of theca cells androgen production, which is subsequently transformed to estrogen in granulosa cells through an increased aromatization rate.

It is established in a previous study by our group that hCG pre-treated women seemed to have higher E2 levels on the day of hCG administration for triggering ovulation and resumption of

meiotic division which is related to better quality embryos and increased pregnancy rates [19].

In a prospective randomized study conducted by our group, we tried to determine whether low dose hCG added to rFSH for ovarian stimulation could produce better results compared to the addition of rLH in women entering IVF-ET in a short protocol, especially in those women with previous IVF failed attempts. Our results have shown that the use of hCG led to less gonadotropin ampoules used, higher fertilization rate and a higher pregnancy rate with a tendency for a better implantation rate. In addition, the percentage of mature oocytes and the number and quality of embryos was comparable between rLH and hCG. This led us to believe that hCG, in the specific dose and way of administration, had no harmful effect on ovarian stimulation.

An explanation could be that the longer plasma half-life of hCG and its greater potency (roughly six to eight times greater than that of LH) leads to highly effective and more stable occupancy of the LH\hCG receptors. The fact that serum E2 levels in patients who received rLH were statistically significantly lower than in patients treated with hCG, shows that the occupation of the LH/hCG receptor in the rLH-administered patients is less, compared to the hCG stimulated patients [12].

Comparing the use of recombinant LH and hCG in oocyte maturation during clinical IVM (In vitro maturation) permits us to investigate the differences between the effects of these gonadotropins in a well-designed in vitro system. In the absence of the use of FSH, low-dose hCG can support development and maturation of larger ovarian follicles (≥ 15 mm in diameter) that have acquired granulosa cell LH/CGRs while, at the same time, it inhibits the demise of smaller follicles lacking these receptors, thus being dependent on FSH stimulation [16,20,21]. Dinopoulou et al., studied the effect of recombinant-LH and hCG in the absence of FSH on in vitro maturation (IVM) fertilization and early embryonic development of mouse germinal vesicle (GV)-stage oocytes. The LH/hCG receptor was expressed in all stages of in vitro matured mouse oocytes and in every stage of early embryonic development and the addition of hCG in IVM cultures of mouse GV oocytes increased maturation rates significantly [22].

Another positive effect of hCG also seems to be the improvement of uterine receptivity via the enhancement of endometrial quality and stromal fibroblast function. Moreover, through its actions on insulin-like growth factor binding protein-1 and vascular endothelial growth factor, hCG was found to stimulate endometrial angiogenesis and growth, thus extending the implantation window and increasing pregnancy rates [16,23]. Intrauterine hCG infusion seems to be associated with endometrial synchrony and reprogramming of stromal development following ovarian stimulation [24]. Another study showed that the administration of 500 IU of hCG to the endometrial cavity lead to statistically significant higher pregnancy and implantation rates compared with the control group [25]. Pre-treatment with hCG seems to have a beneficial effect on endometrial quality defines as endometrial thickness >8 mm, assessed by ultrasound scan on the day of egg collection [19].

Besides increasing production of hCG by the trophoblastic tissue soon after implantation, this hormone is also produced by the blastocyst and may contribute in a paracrine manner to the implantation process [26]. Studies have shown that hCG represents the first known human-embryo derived signal in maternal-fetal communication, through which the embryo influences the immunologic tolerance and angiogenesis at the maternal-fetal interface [27,28].

Based on that unique fetal-maternal relationship and the important role of hCG in the establishment of that connection, a new theory has been developed, according to which, hCG could be the answer in the chronic rejection in solid organ transplantation. It is well established that hCG promotes tolerance through a number of actions on the human immune system [28,29]. Recently, it was found that hCG prolongs skin allografts in mice. Moreover, women receiving hCG preconditioning prior to IVF had reduced inflammatory IL17 but increased anti-inflammatory IL27 and IL10 [30]. In addition to this effect, the improvement in the symptoms of rheumatoid arthritis during pregnancy is due in part to the hCG induced shift of Th1 mediated cellular immunity to a pro-pregnancy Th2 immunity and an increase in T regulatory cell function. Therefore, it seems that these changes are in favour of both pregnancy and reduction in pathogenic RA immune activity [31,32]. hCG has also been used with success in the management of paraneoplastic neuropathy mediated by anti-Hu antibodies [33].

Based on the fact that women feel better when pregnant while women with minimally aggressive trophoblastic neoplasia and hCG levels over 3000 mIU/ml remain generally in good health [34], it is a safe notion to say that the use of hCG lacks so far of any side effects and is both subtle and specific in its action. This is an important difference between hCG and the use of the current anti-rejection agents, such as corticosteroids, ciclosporin, tacrolimus azathioprine, mycophenolate mofetil a range of T-cell specific antibodies [35].

Normal pregnancy is the nature's way of teaching us that maybe there is a way to reduce or even prevent graft rejection, based on the effect of hCG on immune mechanisms of allo-recognition during implantation and embryo development. Apart from its now established positive effect on ovulation induction during controlled ovarian stimulation protocols and on endometrium receptivity during implantation, the effects of hCG on solid organ transplantation remain to be thoroughly tested in the future. We strongly believe that a new field of research opens ahead of us and we have still much to discover about the potential of this unique hormone.

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