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The Role of Low-Dose hCG[1] in the Late Follicular Phase of Controlled Ovarian Hyper Stimulation (COH) Protocols

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1. Introduction

Controlled ovarian hyper-stimulation (COH) is one of the most important stages in ART treatments. The main goal of COH is to achieve efficient follicle numbers without compromising oocyte quality.

During the natural ovarian cycle, different pituitary hormones are responsible for follicle recruitment and growth. In the early follicular phase, follicle stimulating hormone (FSH) is responsible for early follicular growth and development. However, in the middle or late phase, reduction in FSH levels will occur and LH gains the more important role. The more COH protocol can mimic the natural hormonal situations, the more efficacious it will be.

In most infertile women, the administration of exogenous FSH[2] alone is usually sufficient for ovarian stimulation. In these patients, dominant follicles have LH receptors in addition to FSH ones and therefore can respond to endogenous LH. However, subgroups of cases either do not respond or over-respond to FSH. These patients may benefit from LH[3] activity supplementation during their mid or late follicular phase.

Different studies have found that LH activity supplementation may lead to improved outcome in patients over the age of 35, patients with initial abnormal response to recombinant human FSH (r-hFSH), and those at risk for poor ovarian response (Alviggi et al., 2006). In patients beyond 35 years, the addition of LH in form of human menopausal gonadotropin (hMG) to r-FSH regimen may only improve the ovarian response but does not improve overall pregnancy rates (Sohrabvand et al., 2010).

On the other hand, LH components induce the local production of various molecules such as inhibin B and IGF-1[4] from granulose cells and these factors in turn promote the growth of

[1] Human Chorionic Gonadotropin
[2] Follicle Stimulating Hormone
[3] Luteinizing Hormone
[4] Insulin growth factor 1

granulose cells and regulate oocyte maturation (Alviggi et al., 2006). LH is also secreted in the theca compartment and induces androgen production. Then these theca-driving androgens are converted into estradiol by aromatize enzymes (Hillier et al., 1994). These mechanisms may have an important role in the improvement of oocyte quality and LH or hCG supplementation could be a successful method for achieving the physiologic conditions for follicle growth.

Different sources of LH activity including hMG, recombinant LH and low-dose hCG are accessible. HCG is a normal natural analogue of LH. It selectively binds to LH receptors and exerts the same actions as LH (Ross 1977). It has a longer half-life than LH (Nargand et al., 2006). HCG is able to occupy LH receptors for more than 24 hours and allow stable stimulation of the LH receptors (Damewood et al., 1989). HCG is at least six times more potent than LH (Stokman et al., 1993; The European LH Study group, 2001). In other words, 200 IU hCG is equal to 1200 IU LH. It is also less expensive than recombinant FSH or hMG (Fillicori et al., 2002; Filicori et al., 2005a).

A novel gonadotropin protocol for ovarian stimulation adds low-dose hCG (50- 200 IU) in the late follicular phase (Filicori et al., 2002a; Filicori et al., 2002b; Filicori et al., 2005a; Lee et al., 2005; Sullivan et al., 1999). This component can be used alone to complete controlled ovarian stimulation (Filicori et al., 2005a). Usage of it in the late stage of ovarian stimulation (after the follicles reach≥ 12 mm) reduces gonadotropin consumption while the fertilization outcome is comparable (Filicori et al., 2005; Ashrafi et al., 2011). Furthermore this regimen reduces the number of small pre-ovulatory follicles which could reduce the risk of OHSS[5] (Fillicori et al., 2005). Adequate ovarian hormonal levels (Fillicori et al., 2005a; Branigan et al., 2005), oocyte maturation (Branigan et al., 2005), avoidance of a premature LH surge (Fillicori et al., 2005a; Branigan et al., 2005), and increased pregnancy rate (Fillicori et al., 1999; Filicori et al., 2001) are the other benefits of this regimen. This protocol also reduces the stimulation duration and the dose of exogenous FSH administration (Filicori et al., 2005a); therefore it can minimize the patient costs. HCG might also affect endometrial function, stimulate endometrial growth and maturation and enhance the endometrial angiogenesis. These effects could extend the angiogenesis. These results could lengthen the implantation window (Fillicori et al., 2005a). Tesarik et al. (2003) showed that the administration of hCG to oocyte recipients increased the endometrial thickness on the day of embryo transfer and improved the implantation rate. Adding the low-dose hCG in ovarian stimulation regimens in PCOS patients has been associated with fewer immature oocytes (Ashrafi et al., 2011).

Compounds containing LH activity have different risks and benefits. It is believed that LH has a central role in mono-follicular selection and dominance in the physiological ovulatory cycle (Fillicori et al., 2005a; Filicori et al., 2002c). Mono-folliculogenesis is ideal for intrauterine insemination (IUI), but not for IVF/ICSI treatments. In addition, LH may exert a deleterious effect on controlled ovarian stimulation. Unnecessary elevated levels of LH during the pre-ovulatory period may also negatively influence post-ovulatory events such as conception and implantation (Chappel & Howles, 1991). In addition, because hCG is at least six times more potent than LH, there is a concern that this might result in premature luteinization of the follicle.

[5] Ovarian Hyper-stimulation Syndrome

2. Indications of LH or hCG in ovarian stimulation cycles

As mentioned before, the use of low-dose hCG leads to suitable follicle growth and prevention of OHSS by small follicle atresia. Therefore, the application of LH or low-dose hCG in the late follicular phase could be divided to two parts.

2.1 LH supplementation could be used for accelerating leading follicle development

2.1.1 In patients over 35 years of age

Women, of advanced reproductive age, have low follicular recruitment. These patients also have a low number of functional LH receptors and may have low biological activity of endogenous LH (Mitchell et al., 1995; Vihko et al., 1996). In women aged over 35 undergoing intra cytoplasmic sperm injection (ICSI), LH administration led to improved outcomes (Humaidan et al., 2004; Marrs et al., 2004).

Ovarian paracrine activity also decreases with age (Hurwitz and Santoro, 2004). These paracrine variables including growth factors and cytokines may cause adequate follicular growth and steroidogenesis even when LH concentrations are very low (Alviggi et al., 2006).

2.1.2 In poor ovarian responders with GnRH antagonist protocols

In patients treated with GnRH[6] antagonists, a dramatic decline in serum concentrations of both LH and estradiol usually occurs after administration of the drug. Therefore follicles are deprived of their LH substances (Alviggi et al., 2006). A stimulation regimen consisting of GnRH-antagonist and exogenous LH in normal responders increases estradiol production but has no significant effect on improvement of IVF outcomes (Cedrin-Durnerin et al., 2004; Griesinger et al., 2005). However, this regimen is useful for women at risk for poor ovarian response (patients with less than four follicles in prior cycles and/or with basal FSH concentrations of more than 10 IU/L) (De placido et al., 2006).

2.2 LH supplementation could be used for patients with a tendency to over-respond (hyper stimulate) with standard FSH stimulation

Some patients over-respond to FSH administration and lowering of FSH can also lead to follicular growth disruption. In these patients low-dose hCG substitution could be a useful method.

2.2.1 In patients with polycystic ovarian syndrome

Women with polycystic ovarian syndrome (PCOS) are the other group that may benefit from substituting LH for FSH in the late follicular phase. They often have multi-follicular development during ovarian stimulation and are at risk for ovarian hyper-stimulation syndrome (OHSS) or multiple pregnancy. LH activity supplementation would permit the more mature follicles to continue to develop while the less mature follicles would undergo atresia due to insufficient FSH stimulation (Zelenik & Hillier, 1984; Fillicori et al., 2002). This is because the more mature follicles have acquired the adequate amount of LH receptors during the intermediate follicular phase (Fillicori et al., 2003 a,b).

[6] Gonadotropin releasing hormone

In our research, we assessed the effect of two low-dose hCG regimens on folliculogenesis and cycle outcome in PCOS patients and these regimens were compared with r-FSH alone. Stimulation protocol for all the patients was according to the standard long protocol (Madani et al., 2009). Gonadotropin stimulation commenced 14 days following subcutaneous GnRH agonist injection with recombinant FSH (Gonal F, Serono, Switzerland), 150 IU daily. In group B, ovarian priming with r-FSH[7] was reduced to 75 IU once the lead follicle reached 14 mm in mean diameter and low-dose hCG (100 IU/day) was administered and continued until at least two to three follicles with a mean diameter of ≥17 mm were achieved. In group C, ovarian stimulation with r-FSH was discontinued and low- dose hCG (200 IU/day) was administered when the lead follicle reached 14 mm in mean diameter and continued until at least 2–3 follicles with a mean diameter of 17 mm were achieved.

We found that the substitution of hCG for r-FSH during controlled ovarian stimulation in infertile women with PCOS reduced the rates of immature oocytes and OHSS while yielding comparable fertility outcomes, since follicles in women with PCOS, as with follicles in eumenorrheic women, become LH responsive as they mature. We also observed lower gonadotropin consumption following the addition low-dose hCG in the late follicular phase in PCOS patients (Ashrafi et al., 2011).

3. Low-dose hCG starting time

Low-dose hCG supplementation could be used in most ART protocols. However, the start time of hCG administration and discontinuation or decreasing of FSH are two important issues. In most trials, the administration of low-dose hCG was started during the middle or late follicular phase or when the follicle reached a size of more than 10 mm. In these conditions receptors for LH or hCG on the granulose cells are capable of supporting continued growth of the follicles in the absence of FSH administration (Filicori et al., 2005b). Low-dose hCG has also been started at the time of beginning stimulation with r-FSH (Van horn et al. 2007).

4. Low-dose hCG administration in assisted reproductive technologies

The addition of low-dose hCG has been used in different protocols:

4.1 In patients undergoing ovarian stimulation for timed intercourse and intra uterine insemination (IUI)

The main aim of ovarian stimulation in IUI cycles is mono follicular development. Ovarian stimulation regimens containing the FSH alone or combining the FSH and LH usually cause multi-follicular development. The low-dose hCG supplementation after the FSH priming may reduce the number of developing follicles (Fillicori et al., 2002a; 2002c; 2003a).

This regimen is also useful for patients who have previously failed to ovulate with clomiphen citrate. Branigan et al. (2006) in their RCT evaluated the effect of the low dose-hCG in previously anovulatory patients on clomiphen citrate (CC) alone. These patients underwent ovarian stimulation with CC at the 100 mg dose for timed intercourse in their

[7] Recombinant FSH

previous cycles and failed to ovulate on this regimen. They found that the use of low dose-hCG (200IU) after CC in the late follicular phase resulted in good ovulation and pregnancy rates in these patients.

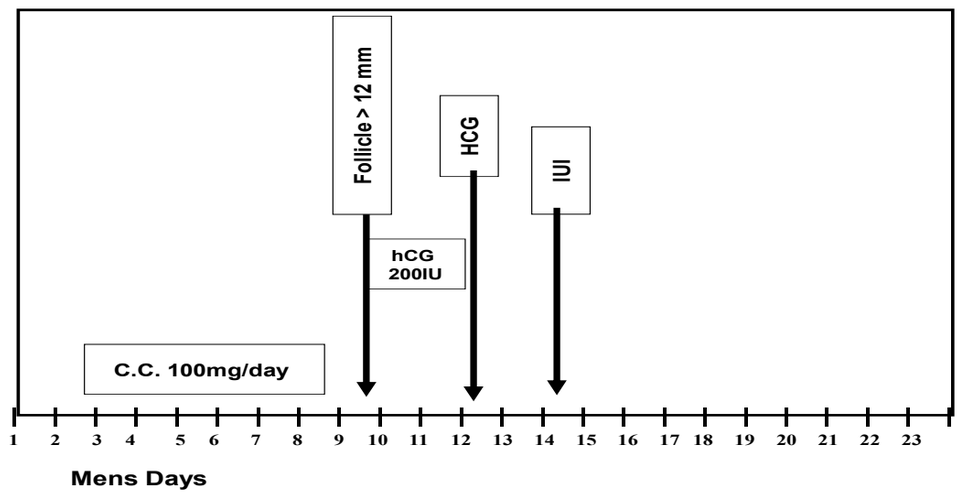

Fig. 1. Clomiphen Citrate + Low-dose hCG

4.2 Low dose hCG administration in conjunction with GnRH antagonists

The use of GnRH antagonist instead of GnRH agonist in IVF cycles has increased in recent years. Different strategies could be used for GnRh antagonist administration. A single depot maybe used on cycle stimulation day eight or nine which lasts four days and is sufficient to prevent the LH surge in 80%of women (Olivennes et al., 1998). Alternatively, multiple small doses may be used daily from cycle day six as a fixed order, or when the leading follicle has reached a 14 mm diameter in a more flexible manner, until the hCG trigger.

This protocol has some benefits. For example, it can lead to immediate pituitary suppression (Tarlatzis et al., 2006). The decreasing of OHSS, lowering the gonadotropin consumption, and avoidance of the gonadotropin flare are the other benefits of this protocol (Tarlatzis et al., 2006; Griesinger et al., 2010). However, the LH level in the GnRH antagonist protocol decreases (Duijkers et al., 1998; Griesinger et al., 2010) and this may negatively affect implantation or pregnancy rate (Esposito et al., 2001). LH secretion is necessary for appropriate follicular and endometrial development (Shoham et al., 2008; Kaufmann et al., 2007).

Adding the low-dose hCG to the GnRH antagonist protocol may compensate for its shortcomings. It can be added to all types of GnRH antagonist protocols which have been mentioned before. It may improve the implantation and live birth rates in patients with low LH levels (Propst et al., 2011). Low-dose hCG supplementation results in higher estradiol secretion of granulose cells and cumulous cell expansion that causes better oocyte maturation rates and endometrial preparation (Cedrin-Durnerin et al., 2004; Ben-Ami et al., 2009). The effect of hCG on endometrium regulation and implantation has been suggested in previous studies (Filicori et al., 2005; Cameo et al., 2006; d'Hauterive et al., 2007). LH administration can increase the LH/hCG receptors during the pre-implantation window and also prevents apoptosis of the endometrial stromal cells (Lovely et al., 2005; Jasinska et al., 2006).

Serafini et al. (2006) showed that using a low-dose hCG protocol along with a GnRH antagonist treatment in normal ovarian responders avoids premature ovulation, and OHSS. It also decreases the total dose of recombinant FSH. This protocol permitted follicles and oocytes to develop fully and aided normal fertilization along with the generation of top-quality embryos and establishment of clinical pregnancies.

Van Horne et al., (2007) also found a reduction in r-FSH requirements and an average cost saving of $600 per cycle in patients who used low-dose hCG supplementation in the GnRH antagonist cycles. These patients had similar implantation and pregnancy rates compared with GnRH antagonist cycles that used r-FSH alone.

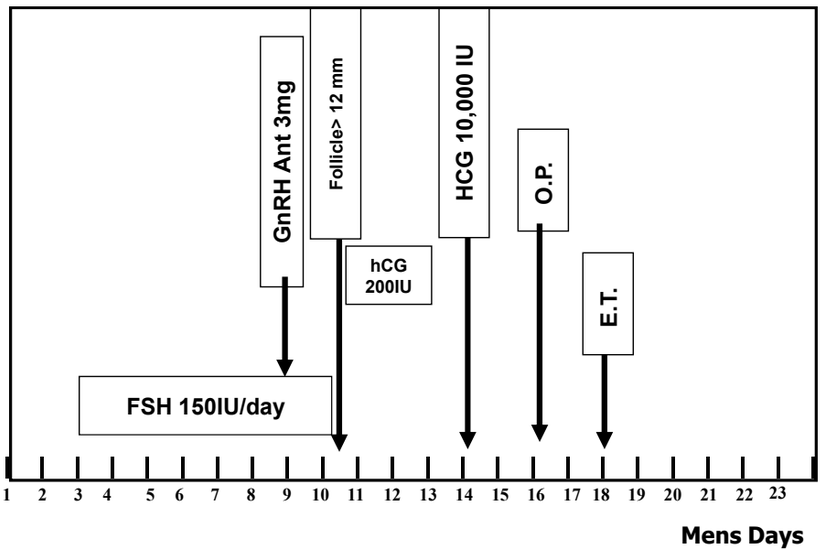

Fig. 2. GnRH antagonist (Single Dose) + Low dose hCG

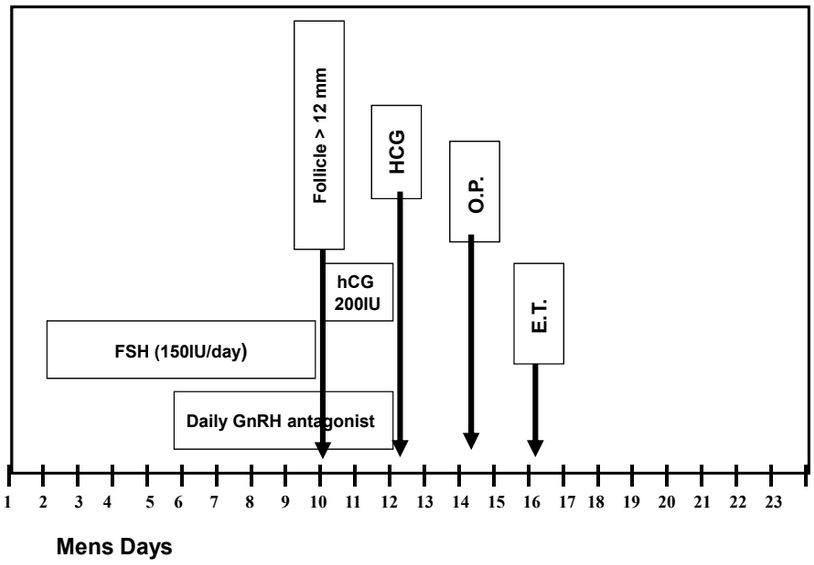

Fig. 3. GnRH antagonist (Multiple Dose) + Low dose hCG

4.3 Low-dose hCG administration in women undergoing IVF cycles down-regulated with GnRH agonists

There are two protocols for the usage of GnRH agonists in ART cycles.

1. Long protocol

For this protocol, all patients usually receive Buserelin 500 µgr (0.5 mg) via subcutaneous injection starting on day 21 of their menstrual cycles. Down-regulation is confirmed by a linear endometrium in ultrasonography (endometrium below 3 mm) and suppressed ovaries by serum estradiol concentration< 60 pg/ml. Gonadotropin stimulation commence 14 days following subcutaneous GnRH agonist injection with recombinant FSH, 150 IU daily. The dose of GnRH agonist will be decreased at this moment (to 200 µgr). The dose and duration of FSH treatment are adjusted by monitoring follicular development with ultrasound and estradiol levels. FSH administration is discontinued and low-dose hCG is added when the lead follicle reached to more than 12 mm. The goal of ovarian stimulation is to achieve at least two ovarian follicles with a mean diameter of ≥17 mm on the day of hCG administration. Then, 10,000 IU of hCG is administered and oocyte retrieval is performed 34–36 hours later.

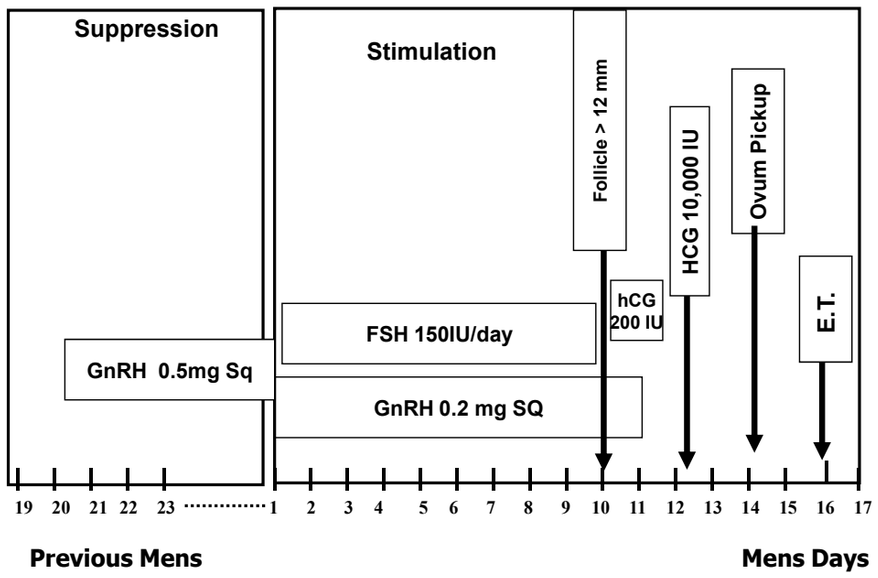

Fig. 4. GnRH Agonist Long Protocol+ 200 IU Low Dose hCG

2. Short protocol

The short or flare protocol employs the agonist-induced flare-up of endogenous FSH to stimulate the ovary in addition to exogenous FSH administration. The agonist is started on day two of the cycle with gonadotrophins on day three. Follicular growth takes 10–12 days which is adequate to down-regulate the pituitary gland and prevent a premature LH surge (Daya, 2000). The administration of recombinant FSH, 150 IU daily will be discontinued when the lead follicle reached to more than 12 mm. In this condition low dose hCG is added. The goal of ovarian stimulation is to achieve an average of two ovarian follicles with

a mean diameter of ≥17 mm on the day of hCG administration. Then, 10,000 IU of hCG is administered and oocyte retrieval is performed 34–36 h later.

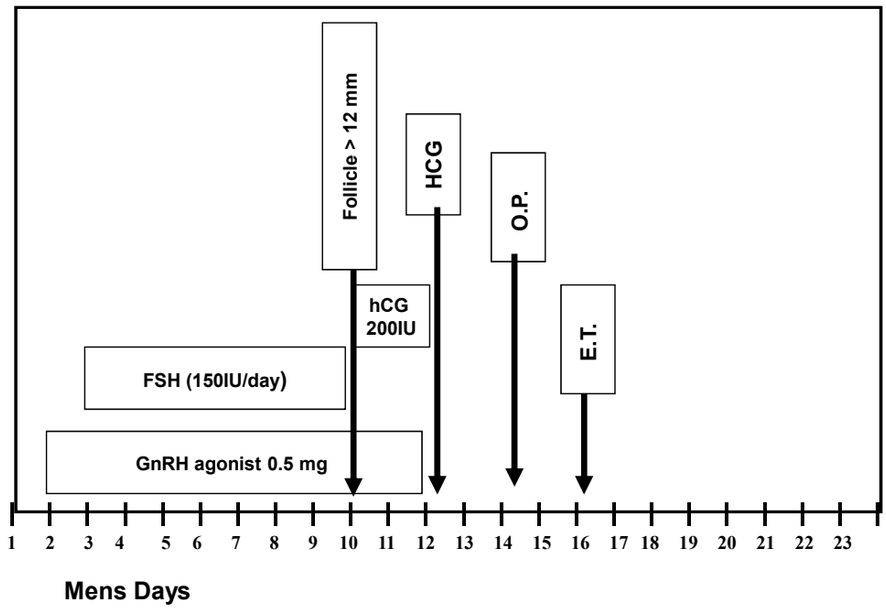

Fig. 5. GnRH Agonist Short Protocol+ 200 IU Low Dose hCG

5. Conclusion

Use of low-dose hCG in the mid to late follicular phase of COH provides these results:

1. This protocol provides adequate ovarian estradiol secretion, oocyte maturation, and acceptable fertilization rates.
2. This protocol provides significant reduction of FSH dosage and reduced cost of treatment.
3. This protocol has no adverse effects on the number of oocyte retrieved and pregnancy rate but can prevent the occurrence of OHSS with a reduced number of follicles and cancelled cycles.

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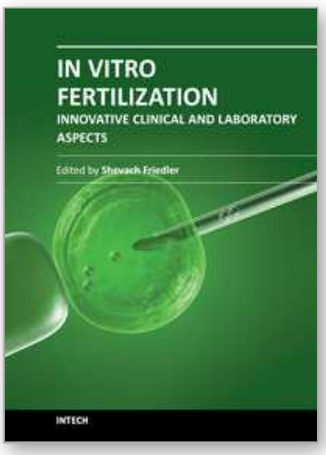

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The field of In Vitro Fertilization is a relatively new field in medicine, constantly on the move. This field is an exquisite example of the vast power in the complementary use of basic research with clinical practice and opened a new route of great basic and clinical research possibilities. The knowledge base that allowed the accomplishment of the idea of in vitro fertilization and embryo transfer has much developed since. The vast body of research pertaining to this field allowed deepening our understanding in the processes related to reproduction. In this book on in vitro fertilization we present new and interesting updated information in various aspects of this field. This work is a result of collaborative work of an international group of professionals dedicated to contribute to the advancement of our knowledge.

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