Luteal phase support after GnRH triggering in IVF cycles

Suportul fazei luteale după declanșarea ovulației cu agonist de GnRh în cadrul procedurilor de FIV

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Abstract

Introduction. *The luteal phase in IVF stimulated cycles is very different from that in natural cycles, so is very important to mimic the perfect condition for pregnancy.* ***Method.*** *Since January 2015 until December 2015, we have 88 cycles in which the triggering was done with GnRH agonist. We performed an embriotransfer in the same cycle in 84 cases. We adjusted the luteal phase support in order to compensate for the luteal phase deficiency in these cases in order to achieve a pregnancy rate similar with the classical triggering.* ***Results.*** *We had similar pregnancy rate between GnRH triggering and HCG triggering, with less complication (OHSS syndrome) and less patient discomfort.* ***Conclusion.*** *GnRH triggering is a good option for IVF cycles with similar pregnancy rates as HCG triggering and reducing almost to zero the risk of ovarian hyperstimulation syndrome.*

Keywords: *luteal phase support, GnRH agonist triggering*

Rezumat

Introducere. *În ciclurile stimulate în cadrul procedurilor de fertilizare in vitro faza lutealã este diferită față de ciclurile naturale și este foarte important să mimăm condițiile perfecte pentru dezvoltarea unei sarcini.* ***Metodă.*** *Din ianuarie 2015 până în decembrie 2015 avem 88 de cicluri de stimulare (protocol scurt cu antagonist), în care declanșarea s-a făcut cu agonist de GnRH. Am transferat embrionii în același ciclu la 84 de paciente. Am ajustat faza lutealã pentru a compensa pentru deficiența acesteia, astfel încât să avem rate de sarcini similare comparative cu declanșarea cu HCG.* ***Rezultate.*** *Avem rate de sarcini similare, mai puține complicații, iar disconfortul pacientelor este mult redus.* ***Concluzii.*** *Declanșarea cu agonist de GnRH este o bună opțiune pentru ciclurile FIV cu rate de sarcini similare cu declanșarea cu HCG și reducând până aproape de zero riscul unui sindrom de hiperstimulare ovariană.*

Cuvinte-cheie: *suportul fazei luteale, declanșarea cu agonist de GnRH*

Introduction

Since the early days of IVF it has been described that the luteal phase of stimulated IVF cycles is abnormal. Edwards and Steptoe declared that "the luteal phase of virtually all patients was shortened considerably after treatment with gonadotropins" and it was suggested that high follicular phase estrogen levels due to ovarian hyperstimulation might be involved[1].

In assisted reproductive technology (ART), is administered a bolus of HCG 5000-10000 IU to mimic the mid-cycle surge of LH. HCG and LH have structural similarities, thus they bind and activate the same receptor, the LH/HCG receptor, and exogenous HCG promotes the same biological effect as the natural mid-cycle surge of LH. There are, however, differences between them, like the one that half-life of HCG is longer (days) than that of LH (hours)[2,3]. Moreover, in the natural cycle, both LH and FSH are secreted during the mid-cycle surge of gonadotrophins, in contrast with to a bolus of HCG. On the other hand, a bolus of GnRH agonist was shown to stimulate ovulation and final oocyte maturation, by inducing a "flare-up effect", very effective in prevention of OHSS[4]. However, with the introduction of GnRH-a IVF long standard protocol, this concept was no longer applicable, but soon after that the GnRH antagonist protocol was introduced and it became feasible again to trigger ovulation with a bolus of a GnRH agonist[5,6]. The first trial revealed that triggering with GnRH agonist in patients co-treated with a GnRH antagonist had to be discontinued due to poor implantation and pregnancy rates (79%) in case of fresh embryo transfers, despite supplementation with standard luteal phase support including vaginal progesterone and estradiol[7]. It was supposed that this disruption of the luteal phase is due to a significant reduction in circulating endogenous LH induced by a single (or double) GnRH-a administration (as compared to LH surge seen in the natural cycle). Endometrial biopsies performed showed endometrial alterations that consist in a characteristic dys-syncrony between the endometrial glands and stroma. These changes haste the closure of the window of implantation, harming the fate of the slower developing embryos. Two options were developed and are currently offered for

coping with the negative effects of GnRH trigger on endometrial receptivity: freeze-all and Dec-ET and the supplementation of small amounts of HCG (most commonly 1500 IU, depending on body weight and risk of OHSS) at the time of oocyte retrieval and proceed to fresh transfer.

Shapiro et al. was the first who reported the dual trigger with a good pregnancy rate, although the study was not controlled and their higher dose of hCG may potentially increase the risk of OHSS. So, it was established that low dose of HCG should be given in patients with peak serum of E2<4000 pg/ml. For patients with peak E_2 levels >4,000 pg/mL, it is still triggering only with GnRHa, followed by the intensive luteal support protocol[8].

There have been described two luteal phase support protocols after GnRHa trigger developed over the years, i.e., the European versus the American approaches. Whereas the European concept promotes the production of endogenous steroids by the CL via exogenous hCG supplementation (Humaidan et al. propose a dose of HCG 1500 IU), the American concept relies mostly on exogenous steroids with adjuvant low-dose hCG trigger in selected cases (Shapiro et al. propose the dose of HCG depending the peak of estradiol). Both concepts facilitate fresh embryo transfer with excellent reproductive outcomes in the OHSS high-risk patient. As research continues to explore the best options for luteal phase support after GnRHa trigger, a new concept of "individualized luteal support" is beginning to emerge, where all the tools we have described in this review can be tailored to the patient's response and estimated OHSS risk[9-12].

Method

Since January 2015 until December 2015, we had 88 cases of patients in which we used antagonist short protocol and GnRH aginisttriggering.

The selection criteria for this kind of triggering were estradiol >2000 ng/ml, more than 18 folicles over 16 mm, more than 20 folicles over 14 mm. As you may observe, the criteria were not those for preventing OHSS, many patients according to literature were not candidates for that kind of complication.

The protocol was the following: in the second day of the cycle we did al ultrasound for AFC and we performed serum analysis: FSH, estradiol and progesterone. If the progesterone was higher than 0.8 ng/ml, we started a 3-day course of antagonist and only after that we started to administrate the stimulation medication. If the progesterone was less than 0.8 ng/ml, we started the stimulation using recombinant FSH if the patients were younger than 35-years-old and recombinant FSH with an adition of LH if the patients were older than 35-years-old. In the fifth day of stimulation we performed an ultrasound to evaluate the follicular growth. We used a fix protocol in which the antagonist was used from day five of stimulation. The next visit was in the 8th day of stimulation, when we did an ultrasound for measuring the follicle diameters, their number and the thickness of the endometrium. In this day we performed serum analysis: estradiol and progesterone. We had an average around 10 days of stimulation. The triggering was done with GnRH agonist when we had at least 3 follicles over 17 mm diameter.

After OPU (oocyte retrieval) (34 hours after the triggering) we used the following protocol: in the same day, the patient received between 750-1500 IU of HCG. The same dose was given in the day of the embriotransfer (day 5, blastocyst).

From the day of the triggering we gave between 1000-1200 mg intravaginal progesterone per day divided in 3 or 4 fractions.

For the luteal phase support, 6 mg of estradiol (oral) were administered on a daily basis. Other adjuvant therapy: Medrol 16 mg/day, folic acid 5 mg per day, vitamin C 1 g/day.

In the 12th day after embriotransfer patients had a pregnancy test (Beta HCG). If positive, the treatment was continued with the exception of Medrol which was slowly reduced until it was completely stopped. The progesterone was gradually reduced since the 12th week of pregnancy. The estradiol was reduced since the 8th week of pregnancy.

From the 88 patients the embriotransfer was performed in the same cycle to 84 patients. Four patients had a fragmented cycle: "freeze all" policy because the risk of OHSS was high.

Results

We studied: the pregnancy rate, the presence of signs of OHSS, the rate of misscarige.

The pregnancy rate: biochemical - 68%, confirmed by ultrasound (6 weeks) - 62%, confirmed by ultrasound (12 weeks) - 52%.

The pregnancy rate when the clinic used HCG for triggering: biochemical - 60%, confirmed by ultrasound (6 weeks) - 58%, confirmed by ultrasound (12 weeks) - 48%.

We compared similar groups regarding AFC, AMH and age. For both groups we used antagonist short protocol. The same clinicians were involved and the same embryologist with the same culture media.

We had only two cases of mild late onset OHSS in the GnRH agonist triggering group.

Discussion

The pregnancy rate is similar between the two groups (no statistical significance at this number of patients). We did not try to demonstrate that GnRH agonist-triggering is better, but simply the fact that we have a good pregnancy rate with this type of protocol and triggering with fewer side effects (OHSS). This kind of protocol gives us the chance to trigger and to not worry when the ovarian response is higher than we expected. If we consider that OHSS may occur, we simply do not transfer in that cycle. In this manner, there is no danger for the patient.

Conclusions

We believe that, in this "age of IVF", antagonist short protocol with GnRH agonist triggering is the future. It allows us to better control the stimulation cycle allowing us the chance to "fix" along the way whatever problems may occur. The worries as for the pregnancy rates (which are considered to be lower) should be a thing of the past. ■

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