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The Use of GnRH Agonist for Ovulation Induction During IVF Cycles at Risk of OHSS

1. *In what group of patients should a GnRH agonist be used to trigger ovulation?*

Patients undergoing an antagonist IVF cycle with a very high risk of OHSS:

- AMH >30, high AFC
- 15 follicles > 14mm on final scan within 24hrs of trigger **and/or**
- serum estradiol > 9 nmol/l

In country patients at high risk of OHSS (first cycle IVF with an AMH > 30 pmol or AFC > 20; past OHSS IVF cycle) the treating doctor should prescribe both a hCG and an Agonist trigger so that both are readily available for use depending on the patient's response to COH.

GnRH agonists can ***NOT*** be used to trigger ovulation when a long down regulation IVF cycle is being used. Caution with the use of GnRH agonist trigger must be taken if the patient has documented or likely pituitary dysfunction (serum LH < 1 IU/L in IVF cycle, known WHO type 1 amenorrhoea or BMI < 20 kg/m^2). In these cases a hCG trigger, possibly at a lower than usual dose (180 mcg Ovidrel, 18 "clicks" of the 25 "click" standard 250 mcg dose pen), *plus cabergoline* may be indicated (see cabergoline policy).

All patients meeting these mandated agonist trigger criteria must have a "freeze all" cycle with no fresh embryo transfer, irrespective of how well they feel or biochemistry status. As such, these high risk patients will not be given luteal support.

A GnRH agonist trigger may be used in patients at lesser risk of OHSS at the treating doctor's discretion. Equally there may be times when a decision is made not to use a GNRH agonist trigger at the discretion of the treating doctor (previous empty follicle, immature eggs, etc)

2. *What is the GnRH agonist medication protocol?*

Lucrin 2 mg s/c bolus (= 40 IU in an 0.5 ml insulin syringe) at the time of the intended trigger. Alternatively a 0.2 mg dose of decapeptyl, delivered as 2 x 0.1 mg pre-filled syringes is an acceptable alternative (6). The OPU is scheduled for 36 hours later- identical to the hCG trigger protocol.

While this GnRH agonist protocol is a very effective means of preventing late onset OHSS (3), a LH non-response with resultant "empty follicle syndrome" is seen in up to 3% of patients (1,2) and is more commonly seen in those with a low BMI and low baseline LH levels (1).

Following a successful GnRH agonist trigger serum LH and P4 levels 12 hours after trigger are on average 60 IU/L and 18 nmol respectively (2). A 12-hour serum level of LH below 15 IU/L and P4 < 10 nmol strongly suggests a failure of the pituitary to respond to the GnRH agonist and release an LHG pulse (1,2). If these failed response patients are then administered a traditional hCG trigger it has been shown that they do respond well, produce good- quality oocytes and embryos which then produce pregnancies in subsequent frozen embryo transfers (2,3). Following a recent audit of GnRH agonist triggers using these 12 hour hormone check protocols, the rate of no-response was zero in a cohort of 50 women- consistent with a rate of < 2%. As such, it is not standard practice to check serum LH and P4 levels after a GnRH agonist trigger, but it may be performed if the treating doctor feels appropriate.

If the serum LH after a GnRH agonist trigger exceeds 15 IU/L and P4 doubles from pre-trigger baseline and exceeds 10 nmol then no further action is required. However, if these criteria are not reached then the patient should be coasted to the next possible trigger time and given a traditional hCG trigger (1,2). Oocyte retrieval is then conducted 36 hours after that second hCG trigger. All patients requiring a rescue hCG trigger and delayed oocyte retrieval should be considered for cabergoline therapy, reduced dose hCG (180 mcg hCG, 18 clicks of the 25 click Ovidrel pen) and mandated freeze all embryos *irrespective of the number of oocytes collected.*

3. *What are the cost implications for a GnRH agonist trigger?*

Patients must be made aware that no fresh embryo transfer is possible if a GnRH trigger is administered.

In the event of a clinic mandated freeze all the cost of the follow up frozen embryo transfer will be limited to a net cost of no more than $250 (exact amount depending on extended safety net criteria). *This policy does not extend to planned freeze all cycles (PGS).*

4. *Rationale for Therapy*

Typically rhCG (Ovidril 250 mgm) or urinary derived hCG (Pregnyl 5000iu) has been used to create finally oocyte maturation during IVF treatment. These hCG medications behave biologically like LH, yet have a much longer half-life that the usual ovulatory LH surge. The negative consequence of this longer half-life is that hCG triggers will stimulate the ovarian follicles to continue to make steroid hormones and growth factors that predispose to the development of OHSS. In women at high risk of OHSS, studies have shown that a GnRH agonist (Lucrin or Decapeptyl) can be used to trigger the body's own production of LH, in turn producing the normal ovulation maturation changes, but with the advantage of a

substantially reducing the risk of developing clinical symptoms of OHSS. The reason for this is that a GnRH agonist induced LH surge only peaks for approximately 12 hours, before falling to sub-normal levels due to the negative feedback of high levels of estrogen typical of an IVF cycle. Without any further LH stimulation the corpus luteum can no longer survive, leading to a rapid reduction in ovarian steroid hormone and growth factor production, which in turn rapidly abolishes OHSS symptoms. By the time the embryo successfully implants and starts secreting hCG into the maternal circulation, the corpus luteum have involuted and no longer are stimulated by this endogenous hCG. This is why agonist triggers have been shown to produce a reduction in both early and late onset OHSS (1).

As would be expected from the above description, the use of a GnRH agonist trigger produces defective corpus luteum function and a marked luteal phase defect (low serum E2 and P4). In order to prevent mid-cycle bleeding and implantation loss aggressive luteal phase hormone supplementation (Crinone, Estradiol valterate) must be commenced from the day of the oocyte retrieval. Even with such aggressive steroid hormone support, many studies suggest that the pregnancy rates in GnRH triggered cycles may be inferior to those using a hCG trigger. This is postulated to be due to the need for “LH” activity in the endometrium for several days in the early luteal phase. As such some IVF units use a very low dose of hCG (1500 IU) on the day of oocyte retrieval to achieve IVF outcomes that are identical to classical hCG triggered cycles, but with a substantially reduced risk of OHSS (2). Luteal support should be extended beyond the initial day 19 pregnancy test, with most groups continuing it to 7-8 weeks gestation.

The use of a GnRH trigger does not adversely affect embryo quality as studies have shown no change in embryo morphology with the use of a GnRH agonist and the pregnancy rates using these embryos in FET cycles are identical to those seen in hCG trigger derived cycles (3).

References

1. Kummer NE, Feinn RS, Griffin DW, Nulsen JC, Benadiva CA, Engmann LL. Predicting successful induction of oocyte maturation after gonadotropin-releasing hormone agonist (GnRHa) trigger. Hum Reprod. 2013 Jan;28(1):152-9.

2. Chang FE, Beall SA, Cox JM, Richter KS, DeCherney AH, Levy MJ. Assessing the adequacy of gonadotropin-releasing hormone agonist leuprolide to trigger oocyte maturation and management of inadequate response. Fertil Steril. 2016 Oct;106(5):1093-1100
3. Iliodromiti S, Blockeel C, Tremellen KP, Fleming R, Tournaye H, Humaidan P, Nelson SM. Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study. Hum Reprod. 2013 Sep;28(9):2529-36.

4. Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Hum Reprod Update. 2006 Mar-Apr;12(2):159-68.
5. Humaidan P, Papanikolaou EG, Tarlatzis BC. GnRHa to trigger final oocyte maturation: a time to reconsider. Hum Reprod. 2009 Oct;24(10):2389-94.
6. Lainas GT, et al. Association between body mass index and oocyte maturation in patients triggered with GnRH agonist who are at high risk for severe ovarian hyperstimulation syndrome: an observational cohort study. Reprod Biomed Online. 2020 Jan;40(1):168-175.