ESHRE 2020 Virtual (5-8 July 2020)

Questions for the speakers

Session 32: Which are the optimal ovarian stimulation protocols?

Influence of the duration of GnRH-antagonist ovarian-stimulation protocol on IVF outcomes in patients with anovulation, endometriosis, premature ovarian failure (POF) and idiopathic infertility. - Judith Gómez-Martínez (Spain)

Q: Any pretreatment?

A: No, they did not receive any pretreatment prior to hormonal ovarian stimulation by GnRH-antagonists.

Q: Why D2/3 not blastocyst?

A: Because we are working in a public system where there is a high demand of patients (more than 1800 cycles per year) and, in the past, we did not have enough incubators with low oxygen levels (5%) to allow an optimal embryo culture system up to blastocyst stage. For this reason, we performed embryo transfers on day 2 or 3 instead of day 5 (blastocyst stage). Nowadays, this situation is changing because we are transferring on day 5. However, we do not have enough data yet.

Q: I would like to know if you perform egg retrieval from Monday to Sunday.

A: We perform egg retrieval from Monday to Saturday, including embryo transfers. But we do not perform any egg retrieval/embryo transfer on Sunday.

Q: Do you think the duration of stimulation affects also the endometrium? did you examen the endometrium?

A: I think the duration of ovarian stimulation could also affect the endometrium, especially in fresh cycles like in this study. But we did not consider endometrium as a studied variable because only patients with similar endometrial thickness (range between 8 to 12 mm) at time of HCG trigger day were included in the study.

Q: So essentially longer protocol is better in endometriosis and shorter in idiopathic. Correct?

A: Yes, it is correct from the point of view of live birth rate. It was the only rate that showed significant differences in both type of female infertility. Apparently, longer protocol was better for patients with endometriosis and shorter ovarian stimulation protocol for idiopathic patients.

Q: How do you explain the low abortion rate in pof in comparison to e.g. idiopatic infertility.

A: It could be related to the lower number of patients classified into each subgroup of POF (≤8 days n= 91, 9-10 days n= 240, ≥11 days n= 391) compared to idiopathic infertility (≤8 days n= 380, 9-10 days n= 878, ≥11 days n= 668). Decrease of "n" was even more accentuated when miscarriage rate was evaluated.

Q: Do you have data on cumulative live birth on your study?

A: No, this study did not include cumulative live birth because there were not frozen-embryo transfers. This study was performed only with fresh cycles to reduce variability of data.

Q: Since this is not an RCT, why did you chose the slices of <8, 8 - 10, >10

A: Because this study was based on the study of Yang et al., 2019 (https://doi.org/10.1016/j.tjog.2019.05.007) and then tried to replicated similar conditions but, including different types of female infertility. They chose four slices (≤ 6, 7-8, 9-10, ≥ 11). In our case, however, we could not split data into 4 slides as a result of low number of patients who were stimulated for less of 8 days. For this reason, we choose these three slides (≤ 8, 9-10 and ≥ 11).

Q: Should we increase the starting dose of FSH to shorten the duration of ovarian stimulation in these populations?

A: It could be an alternative, taking into account that initial dose of rFSH should always be not superior to 300 IU per day.

Q: In your study the effect could be due to diff in antagonist days rather than days of ov stimulation, have you evaluated this

A: I do not think so. Ovarian stimulation protocol by antagonist was the same in all patients. Antagonist was initially administrated when there was a follicle with a minimum size of 14mm and it lasted until day of trigger.

Q: How was the Progesterone on trigger day? How are sure that the problem is oocyte and not a bad endometrium or bad embryo with the early transfer?

A: Levels of progesterone in all patients from this study were lower than 1.5 ng/ml in order to keep homogeneity in our data.

We are not sure what the problem is. If it is the oocyte, endometrium or quality of embryo. We, therefore, kept fixed certain parameters of these variables (e.g. 8-12 mm endometrial thickness, levels of progesterone inferior to 1.5 ng/ml and same selection criteria of embryos to transfer) to reduce variability of the data. However, it is so difficult to assure the cause of this problem.

Q: Would you conclude that longer the use of antagonist, higher the miscarriage rate?

A: No, we could not conclude that. We said that the duration of ovarian stimulation protocol by antagonists could induce an increase on miscarriages but, not the duration of the use of antagonists per

se. To evaluate the influence of the duration of antagonist use we should have measured baseline levels of FSH, LH, estradiol and progesterone and study their relationship with total number of follicles and recovered oocytes at trigger day.

Q: Based on which criterias did you give the HCG trigger?

A: HCG was administrated when there were 3 or more follicles of a size of ≥ 16 mm diameter.

Q: Do you think the duration of antagonist affects also the endometrium?

A: I think so, especially in fresh cycles like in this study. However, we tried to standardize "working conditions" and reduce variability of factors involved, including only patients with similar range of endometrial thickness.

Q: Have you analyzed potential confound factors which may impact the duration of OS in each subgroup such as baseline of AFC, AMH, FSH

A: In this study, we did not take into account the effect of these possible confound factors. However, in a second analysis that we are still working on, including AFC, AMH and baseline levels of FSH and LH.

Natural micronized progesterone versus a GnRH antagonist in egg-donation cycles. An extended experience. - Juan Carlos Castillo (Spain)

Q: All patient's on P4 during stim will have to have later FET. Does this not add to the cost and time more than cost of GnRH-A?

A: Our study was focused on the use of micronized progesterone for preventing premature LH peak in oocyte donors, as the recipients are synchronically prepared in an artificial cycle a fresh embryo transfer is possible. Should the concept be applied in own-eggs cycles, a FET is required.

Q: Why do you use a depot of GnRH agonist in the mock cycle of the recipient?

A: In our protocol, the real (transfer) cycle is scheduled immediately following the mock cycle. In regularly menstruating women undergoing controlled endometrial preparation using steroid hormones, the lack of suppression of ovarian activity is associated with reduced outcome, probably due to incomplete pituitary suppression and/or undetected ovulation (El-Toukhy *et al*. 2004).

Q: Do you start the progesterone orally the same day of the FSH (on day 3) ? Do you have some premature luteinisation?

A: Micronized progesterone was started on the same day of FSH administration. Overall, signs of ovulation/premature luteinization were found in ~2% of cycles in both groups.

Q: When did you stop progesteron use in the stimulation in relation to ovulation triggering?

A: Micronized progesterone was administered until the day of triggering based on the publication by Zhu *et al.* 2017

Q: Which dose of Progeffik did you use?

A: The dose employed was 200 mg/daily oral route.

Q: Which are the PR and LBR resulting from donors that received progesterone to inhibit spontaneous ovulation?

A: Since the study included egg donation cycles performed until December 2019, we could not provide data on LBR. Data on PR is provided in the presentation.

Q: Oral MIP causes severe tiredness, a serious adverse event for donors, who are usually volunteers with a full time job. Any data?

A: Micronized progesterone was administered in the evenings in order to minimize this collateral effect.

Q: Do you think Dydrogesterone is an alternative treatment to prevent premature LH surge in egg-donor cycles?

A: Our study was focused on the use of natural micronized progesterone to prevent premature LH surge in egg donors. A recent study suggests that dydrogesterone (DYG) is as effective as progestins as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase in own eggs-cycles (Yu *et al.* Hum Rep 2018). To the best of my knowledge there are no studies exploring DYG for premature LH surge prevention in egg donation cycles.