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Author: Prof. Nalini Kaul*

PPOS Protocol Effectively Improves the IVF Outcome Without Increasing the Recurrence Rate in Early Endometrioid Endometrial Cancer and Atypical Endometrial Hyperplasia Patients After Fertility Preserving Treatment

Chen J et al., Front Med (Lausanne), 2021 Jul;27(8):581927.

Background

The prevalence of endometrial cancer is rising in women under 45 years (Cancer stats 2020). Endometroid Endometrial Cancer (EEC) and Atypical Endometrial Hyperplasia (AEH) a pre-cancerous condition, are estrogen dependent. The standard of care offered is total hysterectomy with bilateral salpingo-oophorectomy. Fertility-sparing treatment in the form of systemic or local (levonorgestrel IUD) progestin therapy is considered for patients with AEH & early EEC (grade 1, stage IA without myometrial invasion and without risk factors), wanting to preserve fertility. Due to a high recurrence risk (20-40%) within 24 months patients are encouraged to conceive as soon as complete response is achieved. ART is offered to reduce time to conception. However, pregnancy and livebirth rates remain unsatisfactory probably due to endometrial damage from disease and repeated curettage, and the associated risk factors.
High estradiol level attained during ovarian stimulation (OS) remains an area of concern as it could potentially lead to recurrence of disease. The ideal ovarian stimulation protocol in terms of safety & efficacy remains to be defined. This paper evaluates the Progesterone Primed Ovarian Stimulation (PPOS), a recently introduced pituitary downregulation regime, in endometrial cancer.

Summary of the paper

In this retrospective analysis Chen et al investigated the risk of disease recurrence (EEC & AEH) and efficacy of ovarian response with different OS protocols in 97 women (74 AEH and 23 early-stage EEC patients), who underwent IVF and FET after successful fertility preserving treatment with megestrol acetate.

- The protocols used were PPOS (37cycles), mild stimulation protocols (CC/LE+Gn) (32 cycles) and the standard regimen (28 cycles).
- FET was done in HRT cycles.
- A 2-year follow up was done for recurrence.
- Baseline characteristics were similar in the PPOS and standard regimen groups.
- Significantly lower AMH and BMI was observed in the mild stimulation group.
- Results
    - Good quality embryo rate was significantly higher in the PPOS protocol ($P = 0.034$) compared to the standard protocol indicating better response to OS. However pregnancy rates were similar.
    - Pregnancy rates were lower in the mild stimulation group (0.023) compared to PPOS.
- Recurrence rate (RR) was 18/97 (18.5%). RR was not significantly different in the three groups.
- Risk factors for recurrence
    - Univariate analysis showed significant differences in age ($P = 0.033$), treatment time of endometrial lesions ($P < 0.001$), and duration of Gn treatment ($P = 0.018$) between the recurrence and non-recurrence groups.
    - Treatment time of endometrial lesions (12.94 ± 6.93 months) in the recurrence group were significantly higher than those in the non-recurrence group (6.34 ± 4.61 months).
    - Multivariate logistic regression analysis revealed that age ($P = 0.014$) at ovulation induction and treatment time of endometrial lesions ($P < 0.001$) were significantly correlated with the recurrence of endometrial disease.

- No significant difference was observed in the 3 OS regimes for Gn dosage, duration of Gn treatment, MII oocytes rate, fertilization rate and FET cycle cancellation rate.

Critical Evaluation of paper

It is an important paper as it evaluates the safety and efficiency of the PPOS protocol in endometrial cancer patients. Theoretically, the PPOS protocol should improve safety since AEH & EEC are estrogen dependent and progesterone forms the basis for treatment.

- The study is retrospective and the patient number is low limiting the validity of its conclusion.
- The mild stimulation regime should have used letrozole exclusively rather than CC. Kawahara et al. based on experiments in a mouse model have shown that aromatase inhibitors could inhibit proliferation of endometrial cancer cells.
- The authors admit that exposure to estrogen increases the recurrence risk. Yet they use HRT cycles exclusively for FET.
- The follow up period was 24 months. A mean duration of recurrence of 20–47.9 months has been reported by Ushijima et al. 2007. A longer follow-up period might have been more prudent.
- Comparison of RR between AEH and EEC patients would have given a better perspective. Literature shows that RR is higher in EEC.
- Larger prospective studies are needed to verify results.

Conclusion

This retrospective study suggests that patients age at fertility treatment and the treatment time of endometrial lesion appear to be the two important prognostic factors for disease recurrence. Patients with EEC and AEH should therefore be encouraged to try for conception as soon as they have achieved complete response. In terms of ovarian response, pregnancy outcome and disease recurrence there was no difference between the PPOS protocol and the standard regimen in this study suggesting that it can be used safely in patients with endometrial cancer.

Current literature suggests that the PPOS protocol is patient friendly, cheaper and as effective as the standard downregulation regimes, however it does not allow for a fresh transfer thus increasing time to pregnancy and perhaps the overall cost. There is paucity of literature pertaining to the use of PPOS in fertility preservation for cancer patients particularly endometrial cancer. A recent comparative study by Zhou et al. has reported that the cumulative livebirth rate is lower in normal and high responders with this protocol. Larger prospective studies on safety and efficacy are needed to define the optimal OS protocol for endometrial cancer.

References

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*Please note: The newsletter reflects the opinion of the author and not of the ISFP.