



How Effective Is Ultra- Long Protocol In Patients Undergoing IVF For Endometriosis ?

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Introduction

Approximately 50% of infertile patients suffer from endometriosis. Endometriosis leads to subfertility by various mechanisms like disturbed pelvic anatomy, hostile peritoneal environment, diminished ovarian reserve and altered endometrial receptivity. For patients with severe endometriosis, IVF is an appropriate treatment due to grossly disturbed tubo-ovarian relationship especially if there is tubal block but patients with mild endometriosis also often end up in IVF when simpler treatments fail or other factors co-exist. Though the earlier studies reported significantly reduced pregnancy rates with endometriosis in IVF, recent ones have shown similar IVF outcomes in patients with endometriosis as compared to other factors. An evaluation of database of Society of Assisted Reproductive Technologies including 347,185 cycles concluded that endometriosis is associated with lower oocyte yield, lower implantation rates after IVF. They also mentioned that endometriosis often co-exist with other diagnoses but in minority of patients where it occurs in isolation the live birth rates maybe similar or slightly higher than other conditions. In a recently published cohort study women with endometriosis were found to have 24% less chance of livebirth in IVF as compared to patients with unexplained infertility. This effect becomes more pronounced with increasing severity of disease. Hence clinicians have explored different pre-treatment protocols to improve IVF outcomes in patients with endometriosis, most common of which is prolonged downregulation with GnRH agonist (GnRH-a).

Why Use Ultra- Long Protocol In Endometriosis ?

Prolonged downregulation might improve the clinical outcomes of women with endometriosis undergoing IVF by various mechanisms:

- GnRH-a pretreatment can improve ovarian microenvironment and hence quality of oocytes
- It may prevent the expression of endometrial 53 integrin which is the marker of endometrial receptivity and increase the number of pinopodes. It also repairs reduced implantation by increasing the apoptotic activity of endometrial cells
- Pre-treatment with GnRH-a reduces the levels of IL-1, TNF- and nitric oxide in the peritoneal fluid making it less toxic for embryos
- Prolonged treatment with GnRH-a causes pituitary desensitization leading to reduced FSH and LH secretion and hence low estradiol levels which promotes atrophy of ectopic endometrium and hence improves implantation

The Pitfalls Of Ultra-Long Protocol

Prolonged administration of GnRH-a can cause profound suppression of ovarian function leading to requirement of higher doses of gonadotropin and longer duration of ovarian stimulation. In patients of endometriosis where the ovarian reserve is already compromised prolonged downregulation can even end up in cycle cancellation. Repeated doses of GnRH-a depots may also cause hypoestrogenic symptoms in women like hot flushes, vaginal dryness and increased bone loss.

Current Status Of Ultra-Long Protocol In Mild Endometriosis

A recently published RCT (2020) addressed the question of efficacy of ultra-long administration of GnRH-a in patients with mild endometriosis. 200 women with laparoscopically proven mild endometriosis received 3 doses of GnRH-a depot every 28 days before IVF while another 200 with laparoscopically proven mild endometriosis went ahead for standard long protocol (midluteal start). Besides clinical parameters, follicular fluid levels of cytokines (IL-1, IL-6, IL-8, TNF-) were also measured in both the groups. It was found that follicular fluid cytokines level were significantly lower in women who received prolonged down regulation. The fertilization rate in the group who received GnRH-a depots was also found to be significantly higher than the group which did not. But embryo quality, implantation rate and clinical pregnancy rate were similar in both groups. The authors concluded that since prolonged administration of GnRH-a did not improve fertility outcomes in mild endometriosis these women may directly proceed for IVF after laparoscopy. In a latest meta-analysis published in 2020 which included 7 RCTs and 14 cohort studies, it was found that the ultra-long protocol was not associated with any significant differences in clinical pregnancy rates as compared to long protocol in women with ASRM stage I-II endometriosis. It could be due to the fact that pelvic anatomy distortion, the level of inflammatory response in pelvic cavity and local micro-environment imbalance in endometrium is less pronounced in mild endometriosis. The authors suggested that in mild endometriosis conventional long protocol might be more cost effective and less time consuming than prolonged down regulation.

Current Status Of Ultra-Long Protocol In Severe Endometriosis

Lee Houwen et al in 2014 published a retrospective study of 113 laparoscopically proven severe endometriosis (ASRM stage III and IV) wherein 68 had received prolonged downregulation while 45 did not before their first IVF cycle. They reported similar i.e. 13 (19.1%) ongoing pregnancies in fresh cycles in longterm down regulation group vs. 9 (20%) in control group (adjusted OR 0.58 95% CI (0.18- 1.86). When both fresh and frozen transfers were taken into account patients with downregulation fared better i.e. 24(25.3%) ongoing pregnancies vs 10(22.2%) in control group, adjusted OR 1.62 95% CI 0.6- 4.38. They also found that the ongoing pregnancy rates after fresh transfer in IVF in severe endometriosis was lower than all patients who had undergone IVF during the same period. They proposed that long term downregulation improves oocyte quality and hence may have long term positive effect seen in cryopreserved cycle but may have short term negative effect on implantation when transfer is done in the fresh cycle. The recent Cochrane review (2019) which took into account 8 RCTs, also did not support the role of prolonged downregulation with GnRH-a before IVF in women with endometriosis. They concluded that it is uncertain if long term GnRH-a therapy before IVF in endometriosis improve live birth rate or complication rate as compared to conventional IVF. But they also mentioned that the evidence is very low quality and more high-quality studies required. The systematic meta-analysis done by Cao et al (2020) where both RCTs and non-RCT studies were analysed it was found that in subgroup of type III and IV endometriosis the ultra-long protocol group had significantly higher pregnancy rates as compared to conventional long protocol in RCTs (RR 2.04, 95% CI: 1.37-3.04, p<0.05). On the other hand no significant difference was found in the non-RCT studies between ultra-long protocol and conventional protocol in terms of pregnancy rates in patients with severe endometriosis (RR 1.05, 95% CI: 0.93-1.33, p>0.05). The authors concluded that though RCTs are more reliable the observation of non-RCT studies cannot be neglected.

Prolonged Down Regulation Prior To Frozen Embryo Transfers

A major deterrent to the use of ultra-long protocol during IVF in endometriosis has been the reduced ovarian response to gonadotropins seen in patients, particularly those with compromised ovarian reserve which may lead to cycle cancellation also. Hence if IVF is done using standard protocol, embryos are frozen (freeze-all) and then transferred after prolonged downregulation, the patient may benefit from the positive impact of this protocol on implantation without its negative effect on ovarian response. Surrey et al published a retrospective pilot study in 2017 wherein GnRH agonist administration prior to embryo transfer in freeze all cycles of patients with endometriosis and aberrant endometrial integrin expression was studied. Patients were administered two doses of GnRH-a depots 28 days apart before starting HRT for endometrial preparation. The authors demonstrated that prolonged administration of GnRH-a after vitrification of all embryos in IVF in patients of endometriosis or aberrant endometrial integrin expression led to high implantation and pregnancy rates even after previous IVF failures which was comparable to general population. Prospective randomized controlled trials are required to more definitely address this issue

Conclusion

It was believed for a long time that prolonged administration of GnRH-a by virtue of its positive effect on ovarian micro-environment and endometrial integrin expression improved the outcomes of IVF in patients with endometriosis. The recent studies failed to demonstrate this and hence there is an ongoing debate on the efficacy of ultra-long protocol in endometriosis. In patients with mild endometriosis there doesn't seem to be any benefit of prolonged down regulation and it proves to more time consuming and less cost effective. The role of prolonged downregulation before IVF in severe endometriosis on the other hand, is still not clear. Emerging interest is seen in segmentation of IVF, freeze-all and prolonged down regulation before cryo- embryo transfer in patients with endometriosis

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