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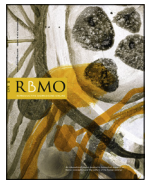

COMMENTARY

Long-term pituitary down-regulation pretreatment for endometriosis – chronicles of guidelines and recommendations

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ABSTRACT

It was suggested in the 1980s that long-term pituitary down-regulation by a gonadotrophin-releasing hormone agonist, termed the ultra-long protocol, inducing a hypo-oestrogenic state, might improve reproductive outcomes in women with endometriosis. Subsequently, international guidelines strongly supported the long-term pituitary down-regulation protocol in women with endometriosis based on a Cochrane review from 2006. The recently published European Society for Human Reproduction and Embryology guideline, based on the updated Cochrane review from 2019 and newer evidence, has reversed this recommendation. This paper explores the past and current evidence that led to these recommendations and calls for a consideration of refinement of the international guidelines to include additional factors and evaluate whether a paradigm shift is needed in the approach to endometriosis-related infertility. We believe that this can optimize evidence-based patient-centred care and benefit women worldwide and improve the design of future studies.

INTERNATIONAL GUIDELINES AND THEIR SUPPORTING EVIDENCE

The Society of Obstetricians and Gynaecologists of Canada guideline of 2010 states that if a woman with known endometriosis is to undergo IVF, gonadotrophin-releasing hormone (GnRH) agonist suppression with hormone therapy add-back for 3–6 months before IVF is associated with an improved pregnancy rate. The American Society for Reproductive Medicine guideline of 2012 cites that a summary of three randomized controlled trials (RCT) concluded that the administration of a GnRH agonist for a period of 3–6 months before IVF or intracytoplasmic sperm injection (ICSI) in women with endometriosis increases the odds of clinical pregnancy; this guideline also questions the applicability of these studies to other populations and various disease stages. The Israeli Fertility Association guidelines of 2014 recommend treatment with the ultra-long protocol for 3–6 months in women with moderate to severe endometriosis. In addition, the European Society for Human Reproduction and Embryology (ESHRE) guideline of 2014 states that clinicians can prescribe a GnRH agonist for a period of 3–6 months prior to treatment with assisted reproductive technology (ART) to improve clinical pregnancy rates in women with endometriosis. This guideline was recently revised, and now the extended administration of a GnRH agonist prior to ART treatment to improve the live birth rate in infertile women with endometriosis is not recommended (*Becker et al., 2022*).

Let's explore the evidence that leads to a unanimous agreement across all of

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these international guidelines to support the use of the ultra-long protocol of long-term pituitary down-regulation prior to hormonal stimulation in ART cycles. All these international guidelines cite the same Cochrane review that was published in 2006, which showed a remarkable positive effect on the live birth rate (odds ratio [OR] 9.19, 95% confidence interval [CI] 1.08–78.22), clinical pregnancy rate (OR 4.28, 95% CI 2.0–9.15) and number of oocytes retrieved in ovarian stimulation (OR 2.05, 95% CI 1.27–2.84) (*Sallam et al., 2006*).

However, a critical second look into this review raises some important questions. This 2006 Cochrane review included only three RCT. First, Dicker and colleagues in 1992 randomized 67 women with surgically diagnosed severe endometriosis into groups for conventional ovarian stimulation for oocyte retrieval (protocol A, 32 patients) and 6 months of hormonal suppression with a GnRH agonist prior to ovarian stimulation (protocol B, 35 patients). This study found a significantly higher clinical pregnancy rate in group B pretreated with the ultra-long protocol ($P < 0.0001$). (*Dicker et al., 1992*).

In the second study, Rickes and collaborators in 2002 randomized 110 women with video-laparoscopically staged stage II–IV endometriosis into two treatment groups, of 55 patients each, for surgical treatment of endometriosis alone or surgery followed by GnRH agonist treatment for 5–6 months before being assigned to fertility treatment with either intrauterine insemination or IVF/ICSI (28 participants treated with surgery followed by a GnRH agonist, and 19 participants who did not have GnRH agonist pre-treatment prior to IVF). Of note, because of the small sample size, the participants were not randomized according to the stage of endometriosis before being allocated to the intrauterine insemination versus IVF/ICSI groups. This study reports significantly higher pregnancy rates among GnRH-pretreated patients ($P < 0.05$) (*Rickes et al., 2002*).

Finally, Surrey and co-workers in 2002 conducted a multicentre RCT that randomized 51 women with surgically staged endometriosis to receive injections of GnRH agonist for 3 months prior to starting ovarian stimulation for IVF (25 patients) or be given no pretreatment before IVF (26 patients). This study found a higher ongoing pregnancy rate in the GnRH agonist pretreated group ($P < 0.05$).

These studies date back almost 20–30 years ago and reveal some methodological flaws. First, the small number of participants in each study does not meet power analysis calculations for such a common condition as endometriosis and hence does not allow conclusions to be drawn. Only the outcome of clinical pregnancy rate was included in all three studies, with only 88 patients in the ultra-long protocol group and 77 in the control group, while other outcomes included only one or two studies with a small number of participants.

Second, there are some areas in the review that warrant investigation. The outcome of live birth rate was not reported in any of the studies, yet one study was included and presented in the review with eight live births in 35 women in the ultra-long protocol group and one live birth in 32 women in the control group. Looking carefully into Dicker and colleagues' original study, the term used was 'reached viability', which presumably refers to pregnancy after 24 weeks, which is not the exact definition of live birth rate. An additional issue in Dicker and colleagues' study is the outcome of the number of retrieved oocytes. The review miscited the number of patients in the study and confused it with the number of cycles, as appears in Table 2 in the original study (*Dicker et al., 1992*). This led the reviewers to allocate the entire weight of this outcome to Dicker and colleagues' study (96.56%) and conclude that the ultra-long protocol increases the number of retrieved oocytes two-fold (OR 2.05). Although this is statistically significant, 5 versus 3 oocytes is hardly clinically relevant, as both results reflect a very poor response to ovarian stimulation, and the conclusion drawn from these data is both inaccurate and misleading.

Third, the outcomes of the studies reported in the 2006 Cochrane review are very different from current IVF standards and practice, thus challenging their applicability nowadays. Dicker and colleagues' study in 1992 reports only a 3.9% pregnancy rate in the control group but 25% in the ultra-long protocol arm. This extremely low pregnancy rate in the control group raises many questions and makes it hard to conclude that the ultra-long protocol is indeed superior to the control. Similarly, the extremely high pregnancy rates reported in the ultra-long protocol arm by Rickes and collaborators in 2002 (82% versus 40% in patients with stage 3 and 4 endometriosis; *Rickes et al., 2002*) and by Surrey and co-workers in 2002 (80% versus 53.85%; *Surrey et al., 2002*) make the data hard to interpret: why do these complex patients have such high pregnancy rates, especially considering that Rickes and collaborators report that the overall pregnancy rate in their centre was less than half at that time (34.7% after IVF and 35.1% after ICSI). Was there a selection bias in favour of better-prognosis patients? As previously mentioned, in Rickes collaborators' study, once participants had undergone the initial randomization before surgery they were not randomized further before assignment to ART. How can we explain these numbers? And most importantly, how can we base our international guidelines on these findings?

Finally, the length of prolonged GnRH agonist down-regulation before IVF varied among the studies, ranging between 3 (*Surrey et al., 2002*), 5 or 6 (*Rickes et al., 2002*) and 6 (*Dicker et al., 1992*) months. This also contributes to the lack of homogeneity in the methodology and suggests no standard definition of the ultra-long protocol.

RECENT EVIDENCE AND SIGNS OF PARADIGM SHIFT

The newest ESHRE guideline (*Becker et al., 2022*) is based on a more recent Cochrane review that was published in 2019 (*Georgiou et al., 2019*). This review included six studies for the outcome of clinical pregnancy rate and only one study for the outcome of live birth rate. For the outcome of clinical pregnancy rate, the three studies from the previous Cochrane review were included in addition to three newer studies (of the three new studies, two were clinical trials that were published later, in 2020). Interestingly, none of the recent studies has shown any benefit of the ultra-long protocol (Risk ratio, RR 1.13, 0.91–1.14 is 95% CI). The 2019 Cochrane review on long-term pituitary down-regulation prior to ART cycles in women with endometriosis is very cautious and hesitant in making a statement against

the previous conclusions, made in 2006, stressing the paucity and low quality of existing data.

Two RCT from Spain and Greece that were already included in the 2019 Cochrane review were recently published. Rodríguez-Tárrega and collaborators have conducted a single-blind, placebo-controlled RCT that included 91 women with endometriosis in the GnRH agonist down-regulation arm and 92 in the placebo arm. Both groups were treated for 80 days prior to proceeding with gonadotrophin stimulation in a GnRH antagonist protocol. This study found no statistically significant difference in the cumulative birth rate (22% versus 33.7%, $P = 0.077$) and cumulative clinical pregnancy rate (27.5% versus 40.2%, $P = 0.144$), with lower values noted in the GnRH down-regulation group. Moreover, participants in the ultra-long arm required a higher gonadotrophin dose (3027 ± 974 IU versus 2339 ± 673 IU, $P < 0.001$) and longer stimulation (10.4 ± 2.6 days versus 9 ± 1.7 days, $P < 0.001$) (*Rodríguez-Tárrega et al., 2020*). In the other study, Kaponis and co-workers randomized 400 women with endometriosis to GnRH down-regulation or no down-regulation prior to proceeding with gonadotrophin stimulation with a long GnRH agonist protocol; the outcomes were then compared with those of an additional control group of women with tubal factor infertility. This study also found no statistical difference in clinical pregnancy rate between the three groups (*Kaponis et al., 2020*).

As these publications used current stimulation protocols, randomized a large number of participants and were better designed (using a placebo as a control or comparing women with endometriosis with women who had other infertility aetiologies), we find them superior to other older publications. The findings of those studies may better reflect practice nowadays and are more applicable to the modern endometriosis patient population that is often diagnosed by a combination of clinical diagnosis and imaging rather than by laparoscopy (*Bazot and Daraï, 2017*).

Tomassetti and colleagues published an RCT comparing clinical pregnancy rates in 21 women with endometriosis pretreated with an ultra-long GnRH protocol and compared with 21 women with endometriosis in the control group (*Tomassetti et al., 2001*). Similar to the other recent studies, this study also found no difference in cumulative clinical pregnancy rates in the ultra-long versus control group (30% versus 40%, $P = 0.7411$, RR1.33, 95% CI 0.57–3.19). Furthermore, they reported a shorter duration of stimulation, a lower total dose of gonadotrophins used, and a higher serum oestradiol concentration at the end of ovarian stimulation on the day of ovulation triggering or cycle cancellation, suggesting a better ovarian response in the control group.

This study was, however, prematurely stopped as it did not reach the targeted sample size due to strong patient preference against the ultra-long protocol. Although it was small and underpowered, we find that this study stresses the limitations of GnRH agonist treatment that must be addressed when consulting patients or formulating recommendations. First, the importance of patient satisfaction should be strongly considered, considering the severe hypo-oestrogenic symptoms associated with long-term GnRH agonist treatment. This calls for well-designed qualitative studies in the field of endometriosis-related infertility and associated treatment. Second, the ultra-long protocol may have deleterious consequences on cycle characteristics: higher gonadotrophin doses and longer stimulation may lead to significant patient inconvenience and higher costs. Third, the delay in hormonal stimulation required for a prolonged pituitary down-regulation that affects the time to achieve pregnancy should also be taken into account.

Alternatively, as it is clear that superficial and deep endometriosis are separate entities with variable clinical presentations that affect fertility to different extents, it is still possible that a yet to be better defined subpopulation of endometriosis patients may benefit from the ultra-long protocol.

CONCLUSION

We conclude that current data do not support recommending the use of the ultra-long protocol for all women with endometriosis, as clinical pregnancy rates appear similar for the ultra-long protocol and control groups. Nevertheless, we propose that additional considerations must be included in clinical decision-making. It is now the appropriate time to update and upgrade the international guidelines regarding the preferred stimulation protocol for treating endometriosis-related infertility.

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