Endometriosis, Endometrial Disorders, and Infertility: From Bench to Bedside

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SPOTLIGHTING endometriosis, a session at the European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting, 2024, held in Amsterdam, the Netherlands, considered the latest advancements in the clinical management of patients with this condition who are trying to conceive. Chaired by Stacey Missmer, Michigan State University, East Lansing, USA, and Noortje van den Boogaard, Flevo Hospital, Almere, the Netherlands, six presentations were delivered to a packed auditorium.

SERUM PROGESTERONE LEVELS IN ENDOMETRIOSIS

The session began with a presentation from Chloé Maignien, Cochin University Hospital, France, reporting that serum progesterone levels do not differ between patients with and without endometriosis who conceived after hormone replacement therapy-frozen embryo transfer (HRT-FET) cycles.[1] It is well established that there is a correlation between serum progesterone levels around the time of HRT-FET and live birth rate. Interestingly, when considering endometriosis, which frequently causes infertility, progesterone resistance in the endometrium is common. Subsequently, it is hypothesised that these women require higher progesterone levels to achieve a live birth. Given the absence of evidence of this from controlled studies, Maignien's research team sought to compare progesterone levels on the day of HRT-FET in patients with endometriosis/adenomyosis to controls who achieved a live birth.

> **Serum progesterone levels do not differ between patients with and without endometriosis who conceived after hormone replacement therapy-frozen embryo transfer (HRT-FET) cycles**

The observational cohort study was conducted between January 2019–December 2021.[1] Patients undergoing single autologous blastocyst FET using HRT with exogenous oestrogen and micronised vaginal progesterone were included. Oestrogen treatment commenced on Day 1 of menstruation and continued for approximately 14 days, following which a transvaginal ultrasound and blood testing were performed. If endometrial thickness was above 6 mm and progesterone level was below 1.5 ng/mL, FET was scheduled, with progesterone supplementation commencing 5 days prior. Blastocysts were transferred by senior gynaecologists and if the patient became pregnant, they continued the same luteal phase support until 12 weeks of gestation.

In total, 1,784 patients were included, with 31.4% having endometriosis.[1] Mean progesterone levels on the day of FET was 13.2 ng/mL (standard deviation: 4.8).[1] The overall live birth rate was 31.4%, and 32% of these patients who achieved a successful live birth had a diagnosis of endometriosis.[1] Among women who conceived, there was no significant difference between the mean progesterone levels on the day of FET when comparing patients with endometriosis to those without. Finally, considering patient characteristics and progesterone levels,

neither the presence of endometriosis nor adenomyosis were related with a significant difference. However, factors such as BMI, duration of infertility, and geographic origin significantly affected progesterone levels.

Thus, Maignien concluded that they found no difference between progesterone levels in patients with endometriosis and controls on the day of FET, and therefore, patients with endometriosis do not require higher progesterone levels to achieve a pregnancy.

SUBCUTANEOUS PROGESTERONE SUPPLEMENTATION IN FROZEN EMBRYO TRANSFER

The second talk, delivered by Noémie Sachs-Guedj, Dexeus University Hospital, Barcelona, Spain, also considered serum progesterone in patients with endometriosis, but focused on artificial cycle FET (AC-FET).[1] She began by highlighting that several studies report on the best preparation protocol for patients with endometriosis, noting that recent studies suggest AC-FET is the most appropriate protocol, as it may help prevent endometrial alterations by inducing ovarian suppression and reducing inflammation. Due to the absence of a corpus luteum, preparing the endometrium is crucial in these patients. The standard procedure for this is 2 mg oestrogen taken three times per day. If an ultrasound indicates an endometrial thickness of over 7 mm, 200 mg of micronised vaginal progesterone is delivered three times per day. Despite this, recent studies suggest serum progesterone levels of less than 10 ng/mL are linked to poorer outcomes. To combat this, Sachs-Guedj outlined a new protocol that uses subcutaneous progesterone supplementation of 25 mg/day if the serum progesterone level is not above 10.6 ng/mL the day prior to embryo transfer.[2] Specifically considering patients with endometriosis, this protocol may require adjustment as the condition disrupts the balance between progesterone and oestrogen.

Investigating this further, Sachs-Guedj and team sought to consider progesterone levels in patients with endometriosis and whether subcutaneous progesterone would aid those below the progesterone cutoff achieve similar live birth rates to those without endometriosis. A retrospective cohort study between January 2019–December 2022 suggested that mean progesterone levels on the day of transfer were comparable between patients with and without endometriosis.[2]

Additional analysis of the study data, using a multivariable logistic regression including 985 AC-FET cycles, specifically investigated the effect of subcutaneous progesterone supplementation. Patients with endometriosis and progesterone levels below 10.6 ng/mL receiving subcutaneous supplementation were the reference group. Results showed comparable live birth rates between the reference group and all other test groups, with and without endometriosis, with progesterone levels above or below 10.6 ng/mL, receiving or not receiving supplementation.

Overall, Sachs-Guedj concluded AC-FET cycles in patients with endometriosis requiring subcutaneous progesterone achieve live birth rates comparable to both endometriosis and non-endometriosis cycles with the correct progesterone levels before FET. Thus, supplementation does not need to be altered when delivered to patients with endometriosis and the protocol allows cost-effective and convenient luteal phase individualisation.

DOES ENDOMETRIOSIS AFFECT OOCYTE MORPHOLOGY?

Ipek Nur Balın Duzguner, Istanbul Memorial Hospital, Türkiye, delivered the third research presentation of the session, focusing on whether endometriosis affects oocyte morphology.[3] Previous conflicting evidence meant the research team aimed to investigate this relationship using a retrospective, single-centre study between August 2011–March 2023.[3]

Overall, 29,130 assisted reproductive technology cycles were included in the study.[3] There were 4,602 cycles originating from patients with endometriosis and 24,528 cycles from patients without endometriosis, permitting the study of 27,204 oocytes and 178,774 oocytes, respectively.[3] Various parameters, such as presence of vacuole(s) and zona pellucida defects, were assessed individually to identify abnormal oocyte morphology.

Following statistical analysis, the number of previous unsuccessful cycles, duration of infertility, and anti-mullerian hormone levels were significantly different between the two test groups.[3] The oocyte morphological abnormalities evaluated were cytoplasmic granulation, large perivitelline space, zona abnormalities, and polar body defects.[3] These were significantly increased in patients with endometriosis.

However, when considering the effect size, there was no significant difference between the two groups, due to the large number of oocytes.[3] Further analysis focused on pregnancy results, specifically single blastocyst FET cycles (n=11,116).[3] Clinical and total pregnancy loss was significantly higher in patients with endometriosis, but again, the effect size suggested this result was negligible.

Overall, no significant differences were found between the endometriosis and non-endometriosis groups when oocyte morphological abnormalities were evaluated using effect size.

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THE ENDOMETRIOSIS LONGITUDINAL FERTILITY STUDY

Vanessa Ross, Royal Women's Hospital, Melbourne, Australia, delivered the fourth talk, which outlined the outcomes and interim data of the Endometriosis Longitudinal Fertility Study (ELFS) study, specifically focusing on outcomes for women with moderate or severe endometriosis trying to conceive.[4] After reminding the audience that endometriosis is associated with reduced natural and assisted conception rates, she stressed that there is still limited data available to advise treatment recommendations, as studies are commonly retrospective cohort studies thatlack a control group. Whilst laparoscopic surgery has been explored as a treatment option, due to the increased risks associated with surgical intervention robust evidence is required regarding its effectiveness in improving fertility in patients with endometriosis.

> **Endometriosis is associated with reduced natural and assisted conception rates**

Therefore, the research group aimed to explore the role of surgery for infertility in patients with moderate or severe endometriosis, as well as the use of pre-emptive surgical treatment. The ELFS study,

a multi-site longitudinal cohort study, is currently recruiting women <38 years of age, and aims to assess clinical pregnancy and live birth rates in those with evidence of moderate to severe endometriosis.[4]

Following enrolment, participants complete a baseline questionnaire, before downloading a smart phone app that delivers periodic cyclical questionnaires. Finally, pregnancy outcome data is collected.[4]

In total, 868 completed cycles from 151 participants have been captured so far. The majority of participants (70%) elected to undergo surgical treatment during the study period.[4] Furthermore, 54 participants have recorded that they are trying to conceive, with 193 attempted conception cycles recorded (53 of these through *in vitro* fertilisation).[4] In total, 33 pregnancies were recorded, with a fecundity of 17%, which Ross noted was surprising due to the low average age of the cohort.[4] Seven miscarriages and one termination were also recorded.[4]

Ross concluded by addressing the study limitations. Namely, as it is not a prospective randomised control trial, cofounders are not accounted for. Furthermore, in the absence of robust data regarding management, clinician scope and practice, and pain symptoms may influence recommendations for patient management.

CONCLUDING REMARKS

In conclusion, the session provided valuable insights into the complexities of endometriosis, endometrial disorders, and infertility. Through a series of detailed presentations, researchers highlighted key findings and advancements in the clinical management of these conditions. Notably, studies on serum progesterone levels revealed no significant differences in patients with endometriosis, challenging the assumption that higher progesterone levels are necessary for successful conception. Overall, there was an emphasis on the need for continued research and individualised treatment approaches to improve fertility outcomes for women with endometriosis and other endometrial disorders.

References

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