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How Should We Assess the Endometrium of Infertile Patients? What Does the Future Look Like?

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ABSTRACT

Attempts at assessing endometrial receptivity through its transcriptomic signature have unfortunately failed. On the contrary, RCTs have indicated that the period of receptivity is fairly wide, lasting 48–72 hours. Today, the ultimate challenge is to optimize hormonal preparation for frozen embryo transfers (FETs). Recent data have provided compelling evidence that vaginal progesterone provides insufficient plasma levels of progesterone in a large fraction of patients, which leads to lower live birth rates and increased risks of miscarriage. The most efficient option consists in delivering injectable progesterone, or opting for a combo approach associating vaginal and injectable progesterone.

Keywords: Assisted Reproductive Technologies (ART); In Vitro Fertilization (IVF); Endometrium; Endometrial Receptivity; ERA Test; Implantation Failure.

ABSTRACT
[IN NATIVE LANGUAGE – KHMER]

សេចក្តីសង្ខេប៖ គេបានព្យាយាមសិក្សាពិសោធន៍ជាច្រើនដងតាមរយៈការសិក្សាពី Transcriptomic ដើម្បីកំណត់ សមត្ថភាពស្រទាប់រដូវដែលទទួលអំប្រ៊ីយ៉ុង ប៉ុន្តែការព្យាយាមកន្លងមកមិនទទួលបានជោគជ័យទេ ។ ផ្ទុយមកវិញ ការសិក្សាស្រាវជ្រាវ (តាម RCTs) បានបង្ហាញថារយៈពេលនៃសមត្ថភាពស្រទាប់រដូវអាចទទួលយកអំប្រ៊ីយ៉ុងនោះ អាចមានរយៈពេលវែងបង្ហូរពោលគឺចន្លោះពី ៤៨ ទៅ ៧២ ម៉ោង ។ នាពេលបច្ចុប្បន្ននេះនីតិវិធីដាក់បញ្ចូលក្នុងស្បូននូវអំប្រ៊ីយ៉ុងដែលបានបង្កកទុកមានឧបសគ្គចម្បងមួយគឺការគ្រប់គ្រងអ័រម៉ូនរបស់ស្ត្រីឲ្យមានកម្រិតអំណោយផលល្អបំផុតសម្រាប់តោងជាប់។លទ្ធផលដែលត្រូវបានចងក្រងកន្លងមក បង្ហាញថាការប្រើប្រាស់អ័រម៉ូនប្រូហ្សេស្តេរ៉ូនស៊ិលតាមទ្វារមាសសម្រាប់អ្នកជំងឺភាគច្រើនមិនអាចជួយបង្កើននូវកម្រិតអ័រម៉ូនប្រូហ្សេស្តេរ៉ូននៅក្នុងឈាមគ្រប់គ្រាន់បានឡើយ។កត្តានេះនាំឲ្យអត្រាកំណើតថយចុះនិងហានិភ័យរលូតកូនកើនឡើងទៅវិញ។ វិធីសាស្ត្រដែលជំរុញលទ្ធផលល្អបំផុតគឺការបញ្ចូលអ័រម៉ូនប្រូហ្សេស្តេរ៉ូន ដោយប្រើថ្នាំចាក់ ឬជម្រើសសំយោគចូលគ្នាទាំងការប្រើថ្នាំចាក់ផង និងការប្រើថ្នាំស៊ិលតាមទ្វារមាសផង។

ពាក្យគន្លឹះ៖ បច្ចេកវិទ្យាជំនួយការបង្កកំណើត; ការបង្កកំណើតក្រៅ; ស្រទាប់រដូវ; សមត្ថភាពស្រទាប់រដូវដើម្បីភ្ជាប់អំប្រ៊ីយ៉ុង; តេស្តវាយតំលៃសមត្ថភាពស្រទាប់រដូវដើម្បីភ្ជាប់អំប្រ៊ីយ៉ុង; ការមិនតោងជាប់របស់អំប្រ៊ីយ៉ុងនឹងស្រទាប់ស្បូន

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INTRODUCTION

The concept of personalized medicine has gained momentum in the recent years. Personalized medicine implies that a treatment is adjusted according to certain patient characteristics that are different than just age, weight, and other parameters known to affect pharmacokinetic and pharmacodynamic. This has been notably the case in cancer therapy at the forefront of which stands the individualization approaches chosen in immunotherapy for treating melanoma (Curti and Faries, 2021). Indeed, molecular evaluation allows to identify mutations that are different antigens, which predict the response to immunotherapy and allow to adjust therapy accordingly (Jiang et al., 2020). From there, the belief that personalized medicine could improve outcome caught several domains of medicine like brushfire, including our field of assisted reproductive technologies (ART). For example, one pharmaceutical company proposed that gonadotropin doses selected by an algorithm could outperform classically chosen ovarian stimulation doses (OS) in terms of both safety and efficacy (Andersen et al., 2017; Blockeel et al., 2022).

Assessing and managing endometrial receptivity has been no exception to this quest for individualization of treatment—notably, the timing of embryo transfers (ET)—based on novel assessments. Here, however, as we will see, facts have not validated an early enthusiasm that lasted nearly two decades. In the meantime, a new dilemma has arisen with new challenges for optimizing hormone preparations for frozen embryo transfers (FETs).

What the Future Is Not: Endometrial Receptivity Assays

DNA microarray technology allows measuring thousands of genes simultaneously. This permits to determine the level of gene transcription or transcriptome, which identifies genes that are expressed or suppressed at mRNA levels. The results provide the transcriptomic signature of a given organ at a given time. In studies relevant to implantation, transcriptomic data have amounted to assess the endometrium at the time of the expected period of receptivity to embryo implantation. This was, however, conducted in mock cycles taking place prior to the actual transfer cycle. The transcriptomic signature was meant to characterize endometrial function, which is known to fluctuate throughout the luteal phase and determine whether the time chosen for transfer is adequate. Microarray technology led notably to develop a test—the endometrial receptivity array (ERA)—which was claimed to provide the transcriptomic signature of endometrial receptivity (Díaz-Gimeno et al., 2011).

In the early years of the ERA test, it was noted that ovarian stimulation (OS) induces a functional delay of endometrial changes—progesterone induced—with potential clinical implications (Horcajadas et al., 2008). In later reports, however, no mention was made anymore of such differences and ERA results were merged in OS, natural cycle, and E2- and progesterone-programed cycles (Blesa et al., 2014). Indeed, results of the ERA test now simply indicate whether the endometrium is receptive, pre-receptive, or post-receptive. This leads to making recommendation to adjust the duration of progesterone administration before the transfer according to the biopsy results. Using this simple concept, the ERA test has been heavily marketed worldwide for many years (Fig. 1). According to Blesa et al. (2014), results of the ERA test allow the personalization of ET, despite the fact that the test itself is conducted in a biopsy performed in a different cycle.

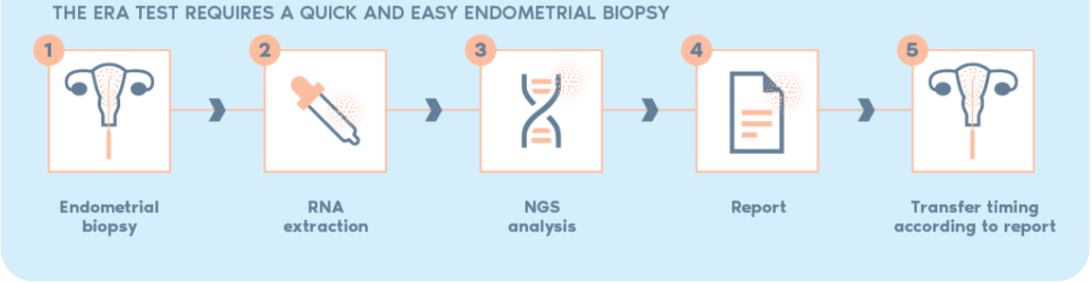
Recently, however, a wealth of publications have started to question the clinical pertinence of ERA data and their efficacy for improving ART outcome. In 2022, Cozzolino et al. (2022) reported that after a failed transfer, applying the so-called "*personalized ET Approach*" recommendation based on ERA results was associated with lower live birth rates in donor and autologous cycles. In a different single-center retrospective study, Bassil et al. (2018) concluded that the ERA test done in a mock cycle prior to FET does not improve ART outcome. In a still different retrospective study, Doyle et al. (2022a) compared ART outcome in women who had ERA-timed FETs to those who had a standard FET protocol without ERA. ART outcome was compared between nonreceptive and receptive results for subjects who underwent an ERA-timed FET or a standard protocol FET (Doyle et al., 2022a). There were no differences in LBR between ERA-receptive and ERA-nonreceptive results (48.8% and 41.7%, respectively; OR 1.17; 95% CI, 0.97–1.40) and no difference in LBR between ERA tested and untested patients (Doyle et al., 2022a).

The final word regarding ERA testing came from a recent RCT published in *JAMA* again by Doyle et al. (2022b), which included 381 ERA-timed and 386 standard FETs. LBRs were identical in the ERA-timed and standard FETs at 58.5% and 61.9%, respectively (Doyle et al., 2022b). Finally, a post hoc analyses of these data (Richter and Richter, 2023) revealed that (i) there are no differences in ART outcome between women whose ERA biopsy is receptive or nonreceptive, and (ii) women whose biopsy is nonreceptive and FET ultimately timed as recommended by ERA had inferior results compared to those whose FET protocol was standard (control group and receptive biopsies) (Richter and Richter, 2023).

Taken together, these results have put an end to any justification for using ERA as marker of endometrial receptivity. It, thus, also explains that Human Fertilization and Embryology Authority (HFEA) in the United Kingdom (https://www.hfea.gov.uk) gave a red symbol—no evidence of efficacy—to the ERA test.

Other endometrial receptivity tests have been proposed. Lessey's group who longed worked on endometriosis reported that B-cell lymphoma 6 (BCL-6) expression in the endometrium is a marker of endometriosis (Evans-Hoeker et al., 2016) and a predictor of poor

Fig. 1. The ERA test as marketed worldwide.
(https://www.igenomix.eu/our-services/era-endometrial-receptivity-analysis/)



ART outcome (Almquist et al., 2017). While the ability of BCL-6 measurement to detect endometriosis—offered as the Receptiva® test—is not questioned here, its capacity to predict receptivity is seriously challenged. Indeed, in a recent trial, BCL-6 levels were not associated with LBR in normal ART responders undergoing euploid blastocyst transfers in E2 and i.m. progesterone cycles (Klimczak et al., 2022). Finally, other markers of endometrial receptivity have been proposed, but never assessed by proper RCTs (Cheloufi et al., 2021; Haouzi et al., 2021). Considering that very existence of receptivity issues in women whose uterus is normal on ultrasound is probably extremely rare [article on RIF in Fert n Reproduction], it is likely that these latter two receptivity tests are likewise not practically useful.

Certain have claimed that chronic endometritis (CE), a pauci-symptomatic inflammatory disorder of the endometrium—could impair endometrial receptivity (Moreno et al., 2018). The diagnosis of CE is best based on histological evidence of increased plasmocytes—identified by CD-138 staining on immunocytochemistry—in endometrial biopsies (Moreno et al., 2018). Richard Scott's group, however, reported that the presence of CD-138 marked cells in approximately 50% of infertile women, with no correlation between CD-138 concentration and ART outcome (Herlihy et al., 2022). The incidence of CE, however, is markedly increased in endometriosis (Cicinelli et al., 2017), which suggests that CE could play a role in the pathophysiology of this frequent disease encountered in 20%–40% of infertile women. Yet, a recent review on endometrial receptivity in women affected with endometriosis indicated that all recent reports concluded that in ART, outcome (LBR) is not affected in case of endometriosis (Pirtea et al., 2021a). Under the circumstances, therefore, the use the Alice® test for diagnosing CE (https://www.igenomix.eu/our-services/alice-analysis-of-infectious-chronic-endometritis/) does not appear to be justified in infertility treatment until more is known.

Recent data have suggested that the endometrial microbiome might affect endometrial receptivity (Punzón-Jiménez and Labarta, 2021). Salliss et al. (2021) have reported a possible link between the gut and genital microbiota (Salliss et al., 2021). Furthermore, these authors mention possible links between alterations of the reproductive microbiota and endometriosis and/or pelvic pain (Salliss et al., 2021). Pursuing its quest for developing endometrial receptivity assay, Igenomix has developed a test—EMMA®—based on microbial DNA sequences (16S rRNA gene and/or metagenome analyses) (https://www.igenomix.net/our-services/emma-patients/). The EMMA® test performed on an endometrial biopsy obtained in a cycle before the actual ET is aimed at helping to determine endometrial receptivity. Here again, however, the practical use of the test has been seriously challenged, mainly because of methodological issues. Indeed, 16S rRNA gene analysis provides knowledge of the possible taxa present, but a microbial DNA sequence does not equate to the presence of an alive microorganism. DNA sequences could originate from microbial breakdown (e.g., DNA from dead microorganisms) (Kliman, 2014). DNA fragments may persist for decades (Glassing et al., 2016) or may result from background DNA contamination (de Goffau et al., 2018; Kim et al., 2017). In a recent article, Gonçalo et al. indicated that one should strive toward functional analysis of the microbiome by non-sequencing-based methods (Correia et al., 2023). In line with this view, Sola-Leyva et al. (2021) reported a mapping of the entire functionally active endometrial microbiota. In these authors' results, the lactobacillus—the marker of endometrial receptivity according to EMMA®—was not present in either the follicular or luteal phase of healthy normally ovulating women (Sola-Leyva et al., 2021). For the time being, we are, therefore, left to conclude that more research is necessary and that endometrial receptivity assessment based on the microbiome is not ready for prime time.

The lack of biological marker that effectively assess endometrial receptivity goes along with the fact that the very existence of endometrial receptivity impairment is questioned today (Pirtea et al., 2021b). Indeed, the 2022 Lugano Recurrent Implantation Failure (RIF) Workshop concluded that endometrial alterations causing RIF may exist, but is very rare, being estimated at less than or equal to 5% in women whose uterus is normal on ultrasound (Pirtea et al., 2023).

Return to the Future

The lack of usable data for assessing endometrial receptivity based on genetic profiling of the endometrium has left us with our understanding of hormonal effects established by the pioneers of donor-egg ART (Lütjen et al., 1985; Navot et al., 1986). From these early data, we learned that the timing of endometrial receptivity for scheduling ETs in E2 and progesterone cycles is determined by the duration of progesterone exposure, not by the actual progesterone levels (Bergh and Navot, 1992; Navot et al., 1991). In two RCTs, it was demonstrated that cleaving stage and blastocyst embryos could be transferred between the third and fifth day (van de Vijver et al., 2016) and fifth and seventh day of progesterone (Roelens et al., 2020), respectively, without affecting ART outcome. We also know from the early egg donation work that the luteal phase endometrium is not affected by the E2 to progesterone serum ratio (de Ziegler et al., 1992), as baselessly affirmed before.

Donor-egg ART results were remarkable right from inception, to the point that it rapidly led to using the same E2 and progesterone regimens for timing FETs. In a prospective RCT, Groenewoud et al. (2016) observed that programmed E2 and progesterone cycles and FET timed in the natural cycle provided similar results. This was recently confirmed in a 6,682-cycle study conducted by the Boston-IVF group, showing no difference in LBR between transfers scheduled in E2 and i.m. progesterone substitution and modified natural cycles (Wolfe et al., 2023). The issue that embryo cryopreservation might increase certain obstetrical risks, such as the incidence large babies at birth and hypertensive disorders remains open (Maheshwari et al., 2018). This increased risk is, however, limited compared to incidences reported in same age—advanced age—mothers after natural conception (Pettersson et al., 2022).

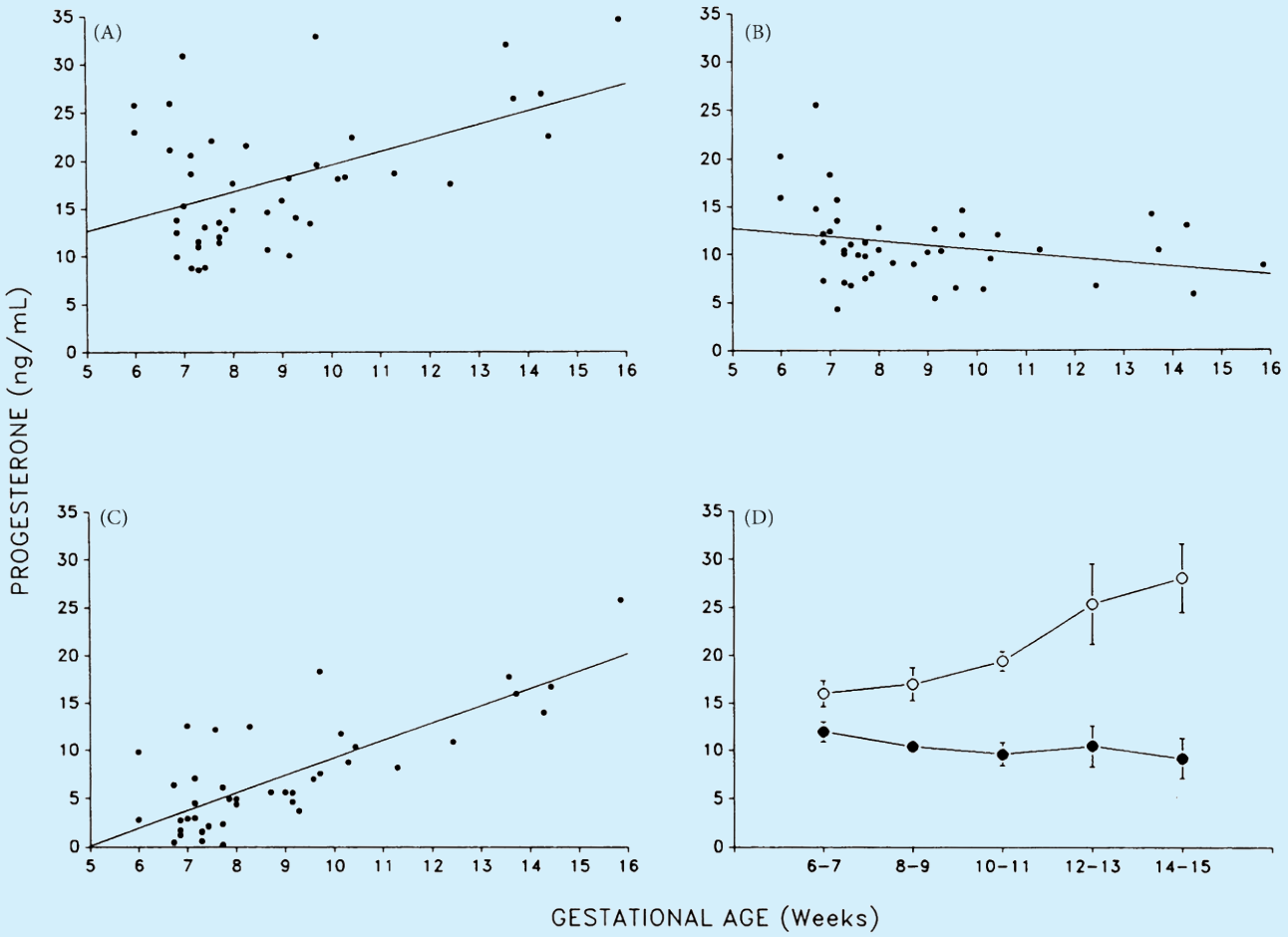
The New Challenge: Priming Receptivity for Frozen Embryo Transfers

The advent of embryo vitrification has tremendously increased the number of FETs performed worldwide, which commonly exceeds that of fresh transfers. Classically, these were scheduled in E2 and progesterone cycles, or HRT cycles, as it allows to limit the number of clinical controls and blood measurements to just one in principle. FETs performed in programmed E2 and progesterone cycles have, however, raised new issues regarding the adequacy of progesterone supplementation when administered vaginally.

All progesterone preparations approved for luteal support in the world—Utrogestan®, Endometrin®, and so on—have been formally tested and approved by regulatory agencies in fresh ART cycles only. Hence, the use of these products in FET is practically speaking off-label. There is one exception the vaginal progesterone gel Crinone®, which has been tested in a small cohort of egg donation recipients, but at the double recommended dose (Gibbons et al., 1998). In fresh ART cycles, progesterone support is strictly necessary only until the positive pregnancy test is achieved. Indeed, several studies have indicated that progesterone supplementation can be stopped after pregnancy is established (Schmidt et al., 2001). This is in agreement with the fact that in fresh ART, the only pathophysiological disturbance is an inadequacy of LH production by the anterior hypophysis impairing

Fig. 2. Progesterone levels at baseline (A), 3 hours after abortion (B), and the decline in levels from baseline to 3 hours after abortion (C). Composite of mean (±SE) *P* levels (D) at baseline (0) and 3 hours after abortion, by 2-week gestational age intervals ($n = 44$) (Nakajima et al., 1991).

Adapted from: Nakajima et al. (1991)



corpus luteum (CL) support. Once pregnancy is achieved, however, hCG exerts its proper support of the CL(s). But, as most clinicians continue their luteal phase support for 8–10 more weeks (yet, for no good reason), commercial products approved for luteal phase support have been tested for the same duration of treatment.

The situation prevailing in FET timed in E2 and progesterone supplementation cycles is totally different, however. Indeed, ancient data have indicated that in naturally occurring pregnancies, progesterone production increases in the first weeks of pregnancy (Fig. 2) (Nakajima et al., 1991). The question, therefore, is to determine whether duplicating this increase in progesterone is necessary in FET timed in E2 and progesterone cycles and whether issues of progesterone levels may exist.

In the United States and countries where the first donor-egg pregnancies were conducted, that is, Australia and Israel, progesterone was originally administered by i.m. injections, generally using 50 mg/day. This regimen assures progesterone levels in the 50 ng/mL range, which has been judged sufficient in donor-egg recipients and FETs scheduled in E2 and progesterone regimens. However, no i.m. progesterone preparation has been approved for luteal phase support in ART, either in the United States or elsewhere. Most i.m. progesterone preparations used in the United States notably are for multiple use and, therefore, contain preservatives, as mandated by regulatory authorities. The presence of conservatives, which causes irritation. As i.m. injections of progesterone are painful and require the help of the spouse or a nurse, efforts have been deployed for finding replacement options. Oral progesterone is not effective because of intense hepatic metabolism and transdermal is not possible because of the amounts needed (two orders of magnitude larger than for E2). Hence, the vaginal route has been seen as a valid alternative for the painful i.m. injections of progesterone. For example, the vaginal progesterone preparation, Endometrin®, has been formally tested in fresh ART cycles. Likewise, the soft gelatin vaginal capsules Utrogestan® and Cyclogest® have been tested in fresh ART and approved by EMA, the European regulatory agency.

Using nonnaturally existing products, such as dydrogesterone, is not recommended during organogenesis. A recent report presented at the ESHRE meeting in Copenhagen indeed calls for caution regarding the prescription of this drug for luteal phase support. Indeed, Henry et al. report a significant disproportionate reporting of birth defects was found with dydrogesterone when compared to any other drug (ROR 5.4, 95%CI 3.9–7.6) and to any other ART agent (ROR 5.4, 95%CI 3.9–7.6). In the head-to-head comparison to progesterone, the authors report an increased reporting of birth defect with dydrogesterone (ROR 5.4, 95%CI 3.7–7.9) (https://uioxr.app.link/?event=642175959f55a

322c3b0bae2&object=64525e1e2969c17a887123d6). These recent data presented at the 2023 meeting of ESHRE need to be further assessed when presented in full in a peer review journal. Indeed, these data are in contradiction with previously published reports on dydrogesterone (Katalinic et al., 2022).

In FET timed in E2 and progesterone cycles, it progressively became evident that vaginal progesterone as prescribed in fresh ART is insufficient in certain women. In 2012 already, Kaser et al. (2012) reported in a retrospective analysis that vaginal progesterone provided lower outcome compared to i.m. progesterone in FETs. Subsequently, an RCT conducted by Devine et al. (2021) formally revealed lower pregnancy and higher miscarriage rates in women receiving exclusively vaginal progesterone as compared i.m. or a combination of vaginal and i.m. progesterone.

Labarta et al. (2021) were first to attribute the insufficiency of vaginal progesterone to low blood levels of progesterone encountered in certain women. This shortcoming could be overcome by supplementing subcutaneous progesterone (25 mg/day), starting on the day of transfer or the day before in women whose progesterone levels are insufficient (Alvarez et al., 2021). Certain ART teams, however, prefer to routinely supplement all women undergoing FRT in a programed cycle using vaginal progesterone with subcutaneous progesterone (25 mg/day) (Ramos et al., 2021). Hence, there is now evidence that vaginal progesterone alone is insufficient for providing efficient luteal phase support in FET timed in E2 and progesterone cycles.

CONCLUSIONS

The recent two decades have seen many changes in how the endometrium is being assessed and treatment optimized for best ART outcome. The enthusiasm for assessing the endometrium with microarray techniques has, however, ended with a deception. Indeed, the proposed deciphering of results—notably, the ERA test—failed to predict actual receptivity and the proposed interpretation of results have been proved detrimental. Unfortunately, the ALICE® and EMMA® are probably equally ineffective at predicting endometrial receptivity.

We are, therefore, left with the understanding of endometrial receptivity originally laid out by the pioneers in donor-egg ART (Lütjen et al., 1985; Navot et al., 1986). The challenge today concerns priming receptivity for FET. In programmed cycles, knowing that vaginal progesterone is insufficient for a large fraction of patients. This has led to either use injectable progesterone for all or opt for a combo approach mixing vaginal and injectable progesterone. We also need to further assess the respective safety of all methods used for timing FETs in either, programmed, natural, or modified natural cycles.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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