LISTER FERTILITY CLINIC
part of HCAHealthcare UK

Endometrial Receptivity Testing

What is the endometrium?

The interior of the uterus is lined with a tissue called endometrium, which is prepared each month for the arrival of an embryo and is the place where the embryo implants and resides during gestation. When this does not occur, menstruation begins the shedding of the endometrial lining.

Endometrial receptivity

Sometimes embryo implantation in the endometrium does not develop successfully. This failure can occur for different reasons. A particularly important factor is endometrial receptivity. The endometrium is receptive when it is ready for embryo implantation to occur. This period of receptivity is called the window of implantation (WOI). In a hormone replacement therapy (HRT) cycle, this WOI is understood to occur after 5 full days of progesterone exposure.
Data from over 60,000 ERA tests shows that 3 in 10 women with recurrent implantation failure have a window of implantation that is displaced from this 'standard' timing. Thus, the synchronisation of the embryo and WOI being lost leading to failure of implantation. WOI is abnormal in approximately 25% of couples with recurrent implantation failure.

Endometrial Receptivity Array (ERA)

The Endometrial Receptivity Array (ERA) is a pioneering test developed in 2009 after more than 10 years of research. ERA is designed to evaluate endometrial receptivity and determine the ideal time for embryo transfer. An 'explainer' video for ERA can be viewed online:
https://www.youtube.com/watch?v=RHr2CBNJPxI

A small sample from the womb lining is taken on the day an embryo would normally be transferred and is analysed to assess the expression of 248 genes that are key to implantation. The result of this analysis establishes whether the endometrium is receptive during this 'standard' timing and detects a shift in the window of implantation. . The endometrium will be categorised as either receptive, pre-receptive, or post-receptive.

In subsequent cycles of treatment, the patient will then have what is termed a 'personalised embryo transfer', taking place at the optimal time for her specific window of implantation. This would theoretically increase the chances of the embryo implanting successfully and the patient having a baby.

However, there are questions over whether the test is accurate at predicting the optimal window of implantation, and whether a patient has the same window of implantation for each of their cycles of treatment. If the test is inaccurate or the window of implantation varies for each cycle then the test may actually reduce the chances of having a baby.

Are there any risks?

As this procedure requires obtaining a biopsy of the endometrium patients can experience cramping and there is a small risk of infection and bleeding. There is also a very small chance of uterine perforation. The biopsy may need to be repeated in the rare event that either the results are inconclusive, or the biopsy fails to obtain a sufficient quantity or quality of tissue for testing.
Endometrial receptivity testing requires patients to undergo a freeze-all cycle which carries a small risk that any frozen embryos would not survive the thawing process.
Endometrial receptivity testing does not carry any additional known risks for the child born as a result of fertility treatment.

What's the evidence for ERA?

A number of publications (M. Ruiz Alonson, 2013 Fertil Steril) and our Lister data does demonstrate an improved outcome in these couples.

The largest trial done so far is a 5- year multicentre randomised controlled trial involving 458 patients, published in 2020[1]. It looked at all women ≤37 years and undergoing blastocyst transfer to see if ERA would be of benefit by comparing those randomised to fresh transfer, frozen transfer and frozen transfer with ERA.

Although live birth rates at the first embryo transfer and cumulative live birth rates were much higher with frozen embryo transfer with ERA compared to frozen embryo transfer without ERA or fresh transfer, the trial has some limitations that leaves the data open to criticism.

Lister opinion:

There is conflicting evidence from studies on the effectiveness of ERA testing. However, a recent study analysed 2256 patients and found a significantly improved outcome in patients who underwent an ERA and had a subsequent personalised embryo transfer, compared to those who did not (Enciso et al, 2021).

We acknowledge that it is a new and growing field with limited evidence. However, lack of evidence is not a proof of lack of effectiveness. We have therefore been offering this technique cautiously in selected patients, mainly those with repeated implantation failure despite transferring good quality embryos. We have analysed our own data for patients with implantation failure who had an ERA and subsequent personalised embryo transfer, compared to a control group who did not have the ERA test. The live birth rate was 38.1% in the ERA group compared to 31% in the non-ERA group. This difference was not statistically significant; however our data is trending towards ERA improving reproductive outcomes.

The HFEA "traffic light rating" for the use of ERA is "red", suggesting that moderate/high quality evidence shows that this add-on may reduce treatment effectiveness. This is because, patients undergoing ERA would need to freeze all their embryos and do a frozen embryo transfer after getting the results for ERA. There is a small risk that embryos might not survive the thawing process, which can reduce their chances of success.

You can read more about the HFEA traffic light system on fertility "add ons" in the following link: https://www.hfea.gov.uk/treatments/treatment-add-ons/endometrial-receptivity-testing/

A fertility "add-on" is an "optional extras that you may be offered on top of your normal fertility treatment, often at an additional cost. They're typically emerging techniques that may have shown some promising results in initial studies but haven't necessarily been proven to improve pregnancy or birth rates."

Endometrial Microbiome

In addition to receptivity, investigations suggest that the endometrial microbiome – the bacteria present in the lining of the uterus – can have an impact on fertility. Assessment of this microbiome is broken down into two categories:

1. Ensuring that the endometrium is host to sufficient 'good' bacteria (e.g. Lactobacillus); low abundance of which is associated with poor reproductive IVF outcomes

2. Detection of harmful infections, called chronic endometritis, which may affect up to 30% of patients with fertility problems

The **EMMA** test from Igenomix includes full analysis of both of these factors. This test of the endometrial microbiome can be performed on the same sample that is used for ERA testing – the combined **EndomeTRIO** test provides a complete view of endometrial health or alone at Day 15 – 25 of a cycle.

What's the evidence for the Microbiome:

Since these are new developments, we have limited evidence. The largest study so far is a multicentre prospective observational study involving 342 women showing endometrial microbiota composition before embryo transfer to be a useful biomarker to predict reproductive outcome[2]. No RCT are available as yet. Further studies with large patient cohorts are required to establish the sensitivity and specificity of microbial biomarkers.

EMMA test is still not in the HFEA traffic light system. At Lister, we perform a test of the endometrial microbiome (EMMA) and test for chronic endometritis (ALICE) in conjunction with ERA testing (as the ENDOMETRIO test) and also separately (as decided by the clinician) in those with recurrent failures of top-quality embryos. If any abnormal bacteria are sequenced then an antibiotic regime followed by probiotics is prescribed prior to any further embryo transfer.

We have analysed our own data for patients with implantation failure who had an EMMA/ ALICE test, compared to a control group who did not have the EMMA/ ALICE test. The live birth rate was 40.9% in the EMMA/ ALICE group compared to 30.9% in the non-EMMA/ ALICE group, which was a statistically significant difference.

A further information sheet on the ERA and ENDOMTRIO (ERA test is available)

How is it done?

ERA is only done in medicated frozen embryo transfers (FET) at Lister. You will have endometrium prepared with oestrogen and progesterone exactly the same way as for a medicated FET cycle. On the day an embryo would normally be transferred, you would have endometrial biopsy instead. It is very similar to an embryo transfer procedure which you would have previously have had. However, in contrast to the transfer (where we do not want to disturb the lining) we will be gently moving the instrument within the uterus for a few seconds and take a biopsy.

If you are doing EMMA/ALICE only, then you can do the test in your natural cycle on day 15-21.

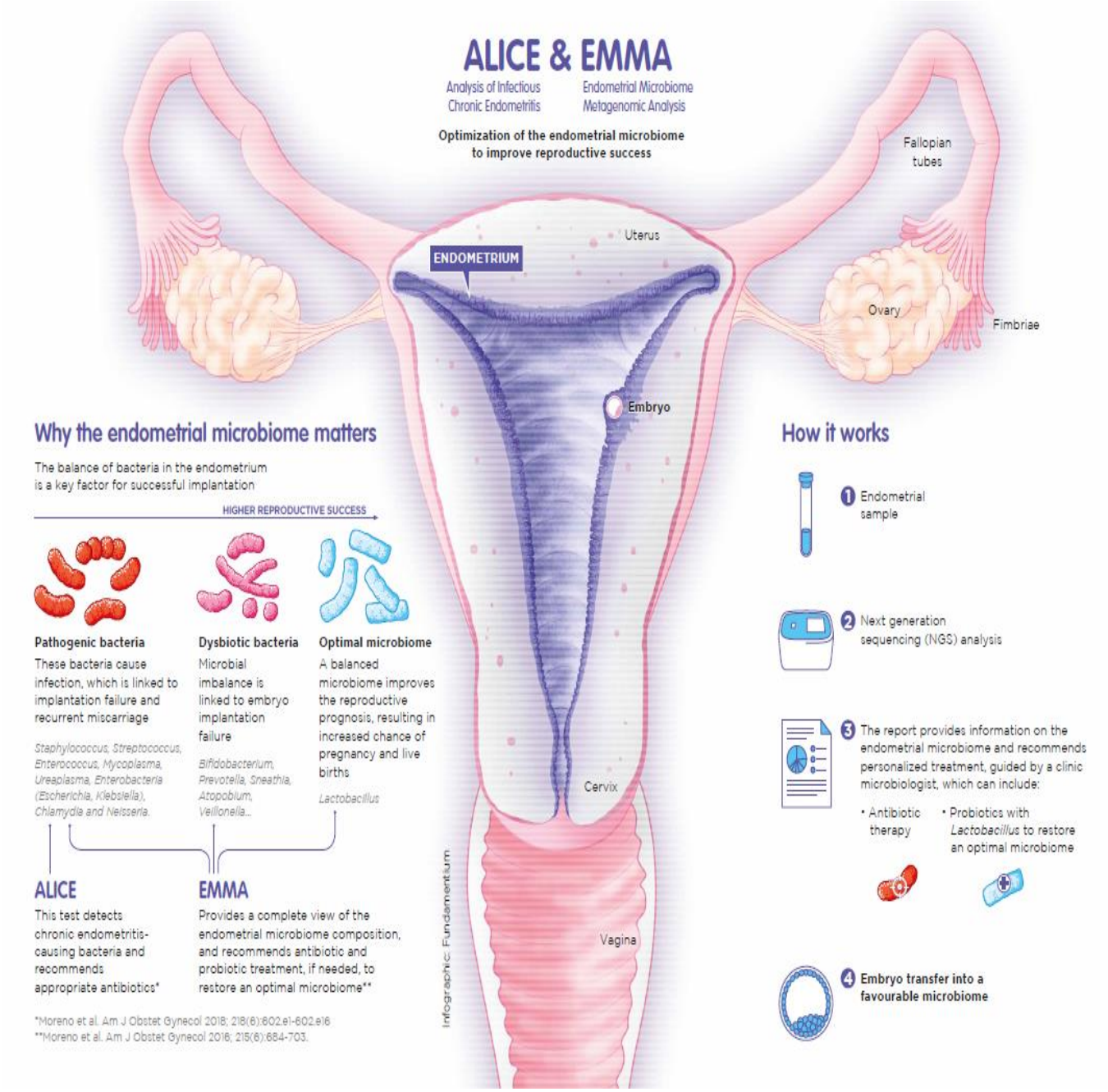
- You should come with a **partially full bladder**.
- If no recent Chlamydia result you will need **prophylactic Antibiotics**.
- Consider taking some simple analgesia such as ibuprofen beforehand (or Paracetamol if contraindicated) as can cause period-like cramps on occasion.

Rarely, the biopsy would need to be repeated if the results are inconclusive or biopsy fails to obtain sufficient quality of sample for ERA testing. In addition, if the EMMA result detects pathogenic bacteria, then biopsy would need to be repeated after completing the course of antibiotics.

Could this affect the chances of getting pregnant naturally in that month?

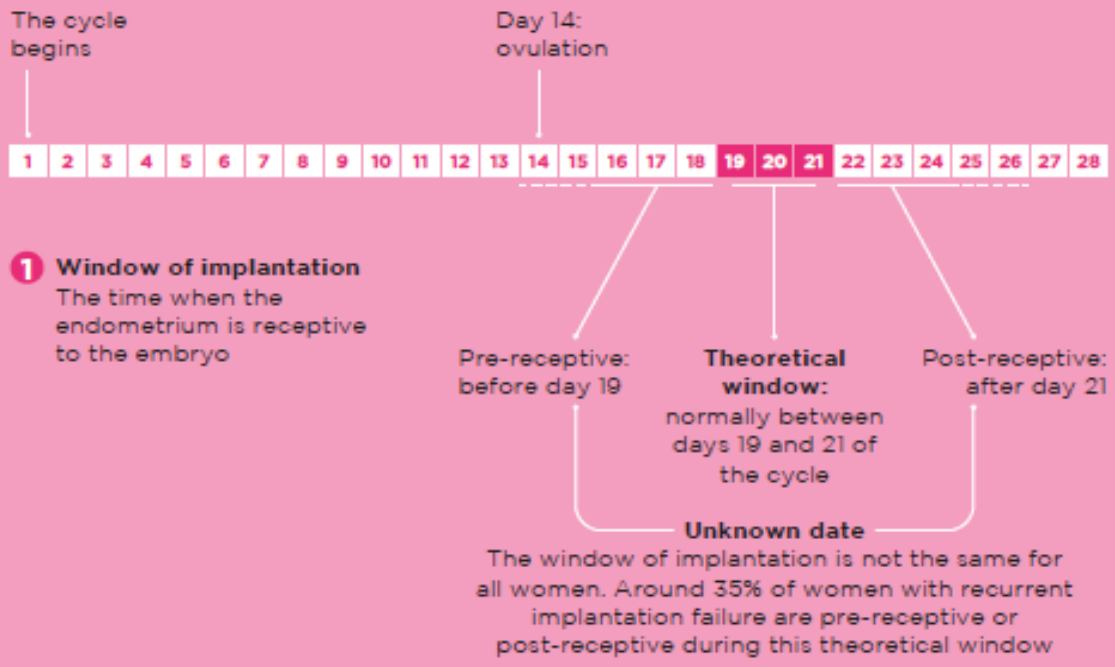
In cases of EMMA/ALICE, which is performed in a natural cycle, we would advise avoiding trying for pregnancy that cycle. In most women the chances of natural conception are very small. However, in the unlikely event of a fertilised egg naturally having implanted that could lead to a pregnancy, the biopsy may stop this occurring. We ideally recommend avoiding intercourse from your period to test or have protection during intercourse.

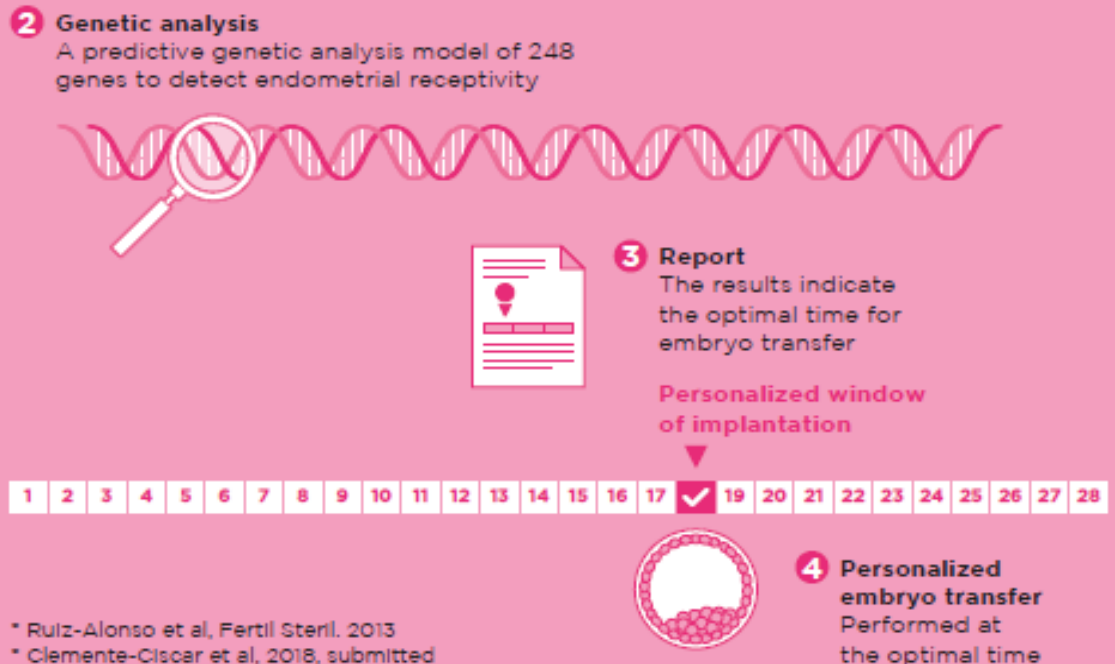
Further information from the developers of the test as below


ALICE & EMMA
Analysis of Infectious Chronic Endometritis
Endometrial Microbiome Metagenomic Analysis
Optimization of the endometrial microbiome to improve reproductive success
Fallopian tubes
Uterus
ENDOMETRIUM
Ovary
Fimbriae
Embryo
Cervix
Vagina
Why the endometrial microbiome matters
The balance of bacteria in the endometrium is a key factor for successful implantation
HIGHER REPRODUCTIVE SUCCESS
Pathogenic bacteria
These bacteria cause infection, which is linked to implantation failure and recurrent miscarriage
Staphylococcus, Streptococcus, Enterococcus, Mycoplasma, Ureaplasma, Enterobacteria (Escherichia, Klebsiella), Chlamydia and Neisseria.
Dysbiotic bacteria
Microbial imbalance is linked to embryo implantation failure
Bifidobacterium, Prevotella, Sneathia, Atopobium, Veillonella...
Optimal microbiome
A balanced microbiome improves the reproductive prognosis, resulting in increased chance of pregnancy and live births
Lactobacillus
ALICE
This test detects chronic endometritis-causing bacteria and recommends appropriate antibiotics*
EMMA
Provides a complete view of the endometrial microbiome composition, and recommends antibiotic and probiotic treatment, if needed, to restore an optimal microbiome**
*Moreno et al. Am J Obstet Gynecol 2018; 218(6):602.e1-602.e16
**Moreno et al. Am J Obstet Gynecol 2016; 215(6):684-703.
How it works
1 Endometrial sample
2 Next generation sequencing (NGS) analysis
3 The report provides information on the endometrial microbiome and recommends personalized treatment, guided by a clinic microbiologist, which can include:
• Antibiotic therapy
• Probiotics with Lactobacillus to restore an optimal microbiome
4 Embryo transfer into a favourable microbiome
Infographic: Fundamentum

ERA
Endometrial Receptivity Analysis

More than 32,000 women in 70 countries have been tested by ERA. This test determines the window of implantation - the precise time when the endometrium is receptive. The ERA test resulted in a **73%** pregnancy rate in patients with implantation failure.





* Ruiz-Alonso et al, Fertil Steril. 2013
* Clemente-Ciscar et al, 2018, submitted

1. Simón C, Gómez C, Cabanillas S, Vladimirov I, Castillón G, Giles J, Boynukalin K, Findikli N, Bahçeci M, Ortega I, Vidal C, Funabiki M, Izquierdo A, López L, Portela S, Frantz N, Kulmann M, Taguchi S, Labarta E, Colucci F, Mackens S, Santamaría X, Muñoz E, Barrera S, García-Velasco JA, Fernández M, Ferrando M, Ruiz M, Mol BW, Valbuena D; ERA-RCT Study Consortium Group. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reprod Biomed Online. 2020 Sep;41(3):402-415. doi: 10.1016/j.rbmo.2020.06.002. Epub 2020 Jun 15. PMID: 32723696.
2 . Moreno I, Garcia-Grau I, Perez-Villaroya D, Gonzalez-Monfort M, Bahçeci M, Barrionuevo MJ, Taguchi S, Puente E, Dimattina M, Lim MW, Meneghini G, Aubuchon M, Leondires M, Izquierdo A, Perez-Olgiati M, Chavez A, Seethram K, Bau D, Gomez C, Valbuena D, Vilella F, Simon C. Endometrial microbiota composition is associated with reproductive outcome in infertile patients. Microbiome. 2022 Jan 4;10(1):1. doi: 10.1186/s40168-021-01184-w. PMID: 34980280; PMCID: PMC8725275.