ora

Non-Invasive Endometrial Receptivity Test

inti LABS

ora™: A Revolution in Endometrial Receptivity Testing

What is ora™

ora™ is the world's first non-invasive endometrial receptivity test for identifying a patient's optimal window of implantation (WOI). It assesses a combination of microRNA (miRNA) biomarkers in the bloodstream and physiological conditions to determine the status of a patient's endometrium, providing information that can be used to optimize the timing of implantation.

Who is ora™ for?

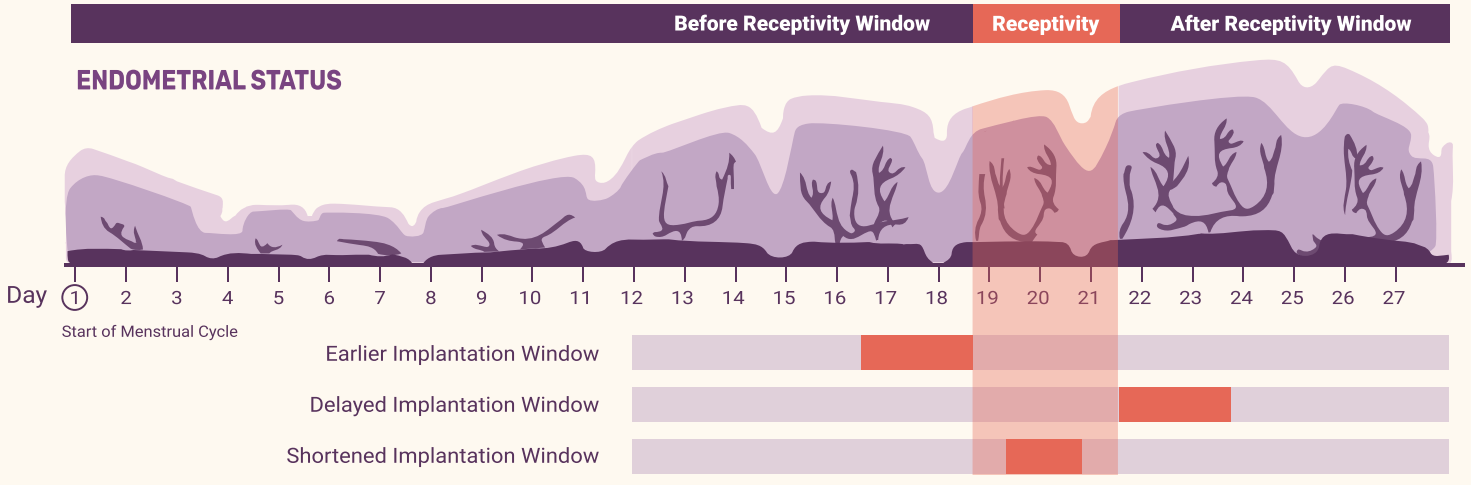
If any of the following situations apply to your patients, ora™ may be able to help:

- A history of implantation failure or miscarriage
- Few remaining high-quality embryos
- A lower or higher BMI
- Age 35 or older*

* While all ages have the possibility of having a displaced WOI, recent data has shown that this is an increased possibility for patients 35 or older.

Window of Implantation

The average WOI is between days 19 and 21 of the menstrual cycle. However, this can vary among individuals. Among women who have trouble conceiving, around 30% have been found to have a displaced WOI – one that occurs earlier or later than average.



Why choose ora™ ?

ora™ uses novel miRNA biomarkers present in the blood to accurately identify a patient's WOI, all with simple blood samples taken on day 4 and day 5 of a mock cycle*. This unique endometrial receptivity test delivers fast and reliable results, helping increase the successful pregnancy rate for IVF patients with a history of implantation failure.

* We recommend drawing blood on both day 4 and day 5 to account for the possibility of a shortened WOI post-receptive result. However healthcare providers may choose to do only a single blood draw on day 5.

NON-INVASIVE

ora™ analyzes miRNA biomarkers in the blood, removing the need for an invasive and uncomfortable endometrial biopsy procedure.

SINGLE MOCK CYCLE

By drawing blood on day 4 and day 5, ora™ is able to account for both average and shortened post-receptive windows, meaning patients only require one mock cycle regardless of what stage their endometrium is in.

HIGH ACCURACY

ora™ as been shown to have > 95% accuracy in predicting endometrial receptivity, offering a stable solution with a more comfortable testing procedure. Further, the need to re-test on account of inconclusive results or invalid/insufficient RNA occurs in <1% of cases.

COMPREHENSIVE ANALYSIS

ora™ analyzes close to 300 miRNA biomarkers that target over 1,000 endometrial receptivity-related genes to accurately identify the optimal time for embryo transfer.

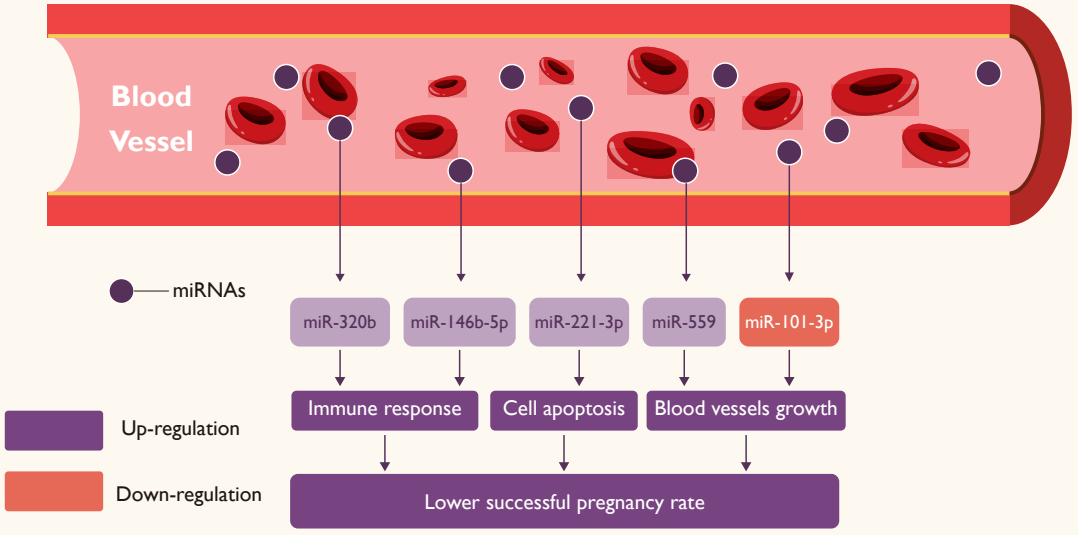
Why use miRNA biomarkers?

MiRNAs have been shown to have over 90% accuracy in predicting displaced window of implantation as cause for implantation failure (1).

- ✓ **microRNAs (miRNAs) are enclosed and protected by proteins, making them more stable than mRNAs, facilitating analysis of lower-quality endometrial tissue samples.**
- ✓ **miRNA exhibits a high correlation with the protein level, as miRNAs regulate mRNAs to suppress protein translation and/or induce mRNA degradation.**
- ✓ **Numerous scientific publications have indicated that miRNAs play a role in the embryo implantation process, including regulating the endometrium to prepare for an embryo.**

miRNAs in tissue and blood

Endometrial receptivity tests were originally performed using endometrial tissue samples. microRNA (miRNA) biomarkers in the bloodstream can identify those same endometrial conditions.



These miRNAs in the bloodstream have been found to regulate a number of immune mechanisms during pregnancy, and are critical physiological factors for cell growth and angiogenesis. Through the regulation of these mechanisms, miRNAs can affect the endometrium's environment, growth process, and, by extension, pregnancy results.

Inti Labs was able to identify blood-based miRNA biomarkers that accurately reflect the endometrium's status, similar to the traditional method of analyzing endometrial tissue samples, but without the invasive biopsy needed for sample collection.

What can ora™ tell you?

ora™ uses these miRNA biomarkers to accurately analyze the endometrium's status, providing healthcare providers with a more precise recommendation for the optimal time for embryo transfer.

Receptive

The day 5 blood draw was found to be within the window of implantation (WOI), and is the optimal time for embryo transfer.

Pre-Receptive

The blood was drawn before the WOI, and the endometrium was not yet ready for embryo transfer. It is recommended to delay the embryo transfer cycle by 24 hours.

Post-Receptive (short)

The blood was drawn after the WOI, and the endometrium had passed the optimal time for embryo implantation. Based on the day 4 and day 5 blood draw results, it is recommended to move the embryo transfer time forward by **12 hours**.

Post-Receptive (average)

The blood was drawn after the WOI, and the endometrium has passed the optimal time for embryo implantation. Based on the day 4 and day 5 blood draw results, it is recommended to move the embryo transfer time forward by **24 hours**.

Inconclusive:

The resulting data could not be analyzed by ora™'s algorithm. This may be due to an exceptionally low-quality sample or complicated physiological conditions that are affecting the sample. An ora™ representative will follow up with the healthcare provider to discuss performing the blood draw(s) again.

Invalid/insufficient RNA:

Results cannot be obtained due to the low quality or low concentration of the blood sample. The blood draw should be performed again to obtain a higher quality or higher concentration sample. An ora™ representative will follow up with the healthcare provider to discuss re-performing the blood draw.

Sample Submission Process

Step1

Complete the Sample Submission and Consent Form

Fill out the Sample Submission and Consent Form with your patient (included in the kit).

Step2

Schedule the Blood Draws

Schedule the blood draws based on either natural cycles or hormone replacement therapy cycles*.

Step3

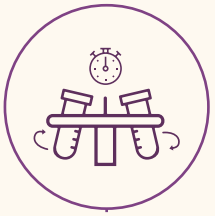
Obtain the Blood Samples

Use the blood sample collection tubes provided in the kit. Invert the tube 5-10 times immediately after the blood sample has been collected.

Step4

Process the Blood Samples

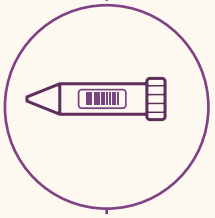
The blood samples will be processed into plasma samples onsite within three hours of sample collection according to ora™'s laboratory instructions.



Step5

Store the Sample

Label the processed blood samples (plasma samples) with the unique sample barcode provided in the kit. Store the tube at -20°C for at least 12 hours.



Step6

Ship the Sample

Ship the package at low temperature or on icepacks to the designated shipping address using priority or next day shipping.

* Blood samples should be taken:
4 days (96 hours) and 5 days (120 hours) after starting progesterone administration in an HRT cycle or 6 days (144 hours) and 7 days (168 hours) after LH surge is detected or 6 days (144 hours) and 7 days (168 hours) after hCG administration in a natural cycle.

Inti Labs is the brainchild of embryologist Dr. Barry Behr and microRNA researcher Dr. Eric Pok Yang, focused on developing less-invasive tests for improving IVF outcomes.

ASSISTING HEALTHCARE PROFESSIONALS

Inti Labs collaborates with clinics, service providers, and distributors worldwide to deliver impactful solutions to fertility specialists and their patients.

IMPROVING IVF SUCCESS RATES

Our tests are designed to offer more accurate, less-invasive solutions, reducing the likelihood of additional treatment cycles while enhancing the overall patient experience.

REFINING THE FERTILITY JOURNEY

Inti Labs continues to progress the reproductive healthcare landscape for professionals and families, empowering each to make the most informed decisions regarding their treatment plan.

References

For Tissue miRNA

Chen CH, Lu F, Yang WJ, Yang PE, Chen WM, Kang ST, Huang YS, Kao YC, Feng CT, Chang PC, Wang T, Hsieh CA Lin YC, Jen Huang JY, Wang LH. A novel platform for discovery of differentially expressed microRNAs in patients with repeated implantation failure. Fertil Steril. 2021 Apr 3:S0015-0282(21)00088-1. doi: 10.1016/j.fertnstert.2021.01.055. Epub ahead of print. PMID: 33823989.

For Blood miRNA

Cretoiu D, Xu J, Xiao J, Suciu N, Cretoiu SM. Circulating MicroRNAs as Potential Molecular Biomarkers in Pathophysiological Evolution of Pregnancy. Dis Markers. 2016;2016:3851054. doi:10.1155/2016/3851054

Qin W, Tang Y, Yang N, Wei X, Wu J. Potential role of circulating microRNAs as a biomarker for unexplained recurrent spontaneous abortion. Fertil Steril. 2016 May;105(5):1247-1254.e3. doi: 10.1016/j.fertnstert.2016.01.028. Epub 2016 Feb 8. PMID: 26868995.

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Non-Invasive Endometrial Receptivity Test

Analysis Report

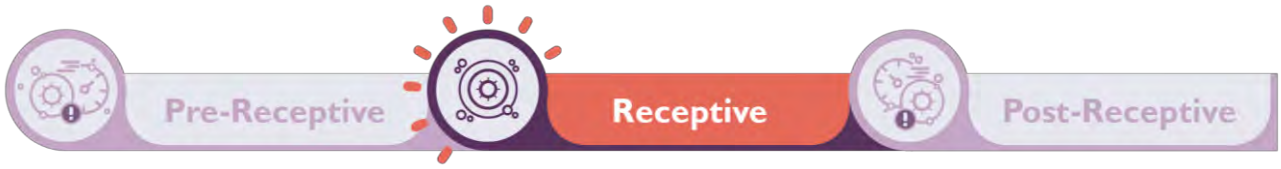
Basic Information

Patient Name	Patient
Date of Birth (dd/mm/yyyy)	01/01/1990
Medical Record No.	MRN
Clinical Center	Fertility Clinic
Physician Name	Doctor
Clinic Address	Fertility Clinic
Clinic Phone Number	Phone Number

Test Information

Treatment Date (dd/mm/yyyy)	01/11/2021 9:00 AM	**Blood Draw Date(s)**	06/11/2021 9:00 AM
Sample Received Date	07/11/2021	**Treatment Cycle**	HRT, P+5 (120 hrs)
Report Date	12/11/2021	**Sample Type**	Blood
Report ID	MIRA20211112001		

Endometrial Receptivity Status:



Test Result	**WOI (Receptive)**	
Recommended pET Time	**Day 5 Embryo/s: 120±3 hours**	**Day 3 Embryo/s: 72±3 hours**

Interpretation Based on ORA™ Analysis:

The results of ORA™ indicate that day-5 embryo(s) transfer can be performed at the time at which the blood draw was performed 121±3 hours when undergoing Hormone Replacement Therapy (HRT) cycle.

For day-3 embryo(s), the embryo transfer should be performed two days earlier than the recommended time above at 73±3 hours when undergoing Hormone Replacement Therapy (HRT) cycle.

＊This analysis result is only applicable for the same treatment cycle type and dose as the one used for this endometrial tissue biopsy.

Anson Huang, PhD
Service Laboratory Manager

An Hsu, PhD
Director of Research & Development

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Appendix: ORA™'s results are mainly reported as receptive, pre-receptive, post-receptive (additional mock cycle), post-receptive (short), or post-receptive (average). Less than 1% of samples have resulted in an inconclusive or invalid/insufficient RNA result.

Receptive : The day 5 blood draw was found to be within the window of implantation (WOI), and is the optimal time for embryo transfer.

Pre-Receptive: The blood was drawn before the WOI, and the endometrium was not yet ready for embryo transfer. It is recommended to delay the embryo transfer cycle by 24 hours.

Post-Receptive (additional mock cycle): The blood was drawn after the WOI, and the endometrium had already passed the ideal time for embryo transfer. In the case where your initial mock cycle only had a single blood draw performed on day 5 of an HRT cycle or day 7 of a natural cycle, an additional mock cycle is recommended to confirm if embryo transfer time should be moved forward by 12 hours or 24 hours.

Post-Receptive (short): The blood was drawn after the WOI, and the endometrium had passed the optimal time for embryo implantation. Based on the day 4 and day 5 blood draw results, it is recommended to move the embryo transfer time forward by **12 hours**.

Post-Receptive (average): The blood was drawn after the WOI, and the endometrium has passed the optimal time for embryo implantation. Based on the day 4 and day 5 blood draw results, it is recommended to move the embryo transfer time forward by **24 hours**.

Inconclusive: The resulting data could not be analyzed by ORA™'s algorithm. This may be due to an exceptionally low-quality sample or complicated physiological conditions that are affecting the sample. An ORA™ representative will follow up with the healthcare provider to discuss performing the blood draw(s) again.

Invalid/insufficient RNA: Results cannot be obtained due to the low quality or low concentration of the blood sample. The blood draw should be performed again to obtain a higher quality or higher concentration sample. An ORA™ representative will follow up with the healthcare provider to discuss re-performing the blood draw.

Test Method

ORA™ was developed by Inti Labs and runs on next generation sequencing (NGS) technology. Close to 300 microRNA (miRNA) biomarkers in the blood sample are analyzed by ORA™'s algorithm to pinpoint the optimal time for embryo transfer. A series of quality control steps throughout sample processing (Such as extracted miRNA amount is greater than 10 ng and analysis ensure the highest quality results are provided.)

Limitation

Your healthcare provider may use the results of this ORA™ analysis to alter the time of personalized embryo transfer during the IVF treatment cycle. Following the results of ORA™ does not guarantee successful implantation as there may be a variety of factors that affect the success or failure, such as poor embryo quality or other healthcare-related issues.

Declaration

This report is released only when a completed and signed ORA™ Sample Submission and Consent Form is received. The services and analysis carried out are intended to be interpreted only by qualified healthcare professionals. This report and any information derived from it cannot act as a substitute for medical treatment or counselling by a qualified healthcare professional.

References:

For Tissue miRNA:

Chen CH, Lu F, Yang WJ, Yang PE, Chen WM, Kang ST, Huang YS, Kao YC, Feng CT, Chang PC, Wang T, Hsieh CA, Lin YC, Jen Huang JY, Wang LH. A novel platform for discovery of differentially expressed microRNAs in patients with repeated implantation failure. Fertil Steril. 2021 Jul;116(1):181-188. doi: 10.1016/j.fertnstert.2021.01.055. Epub 2021 Apr 3. PMID: 33823989.

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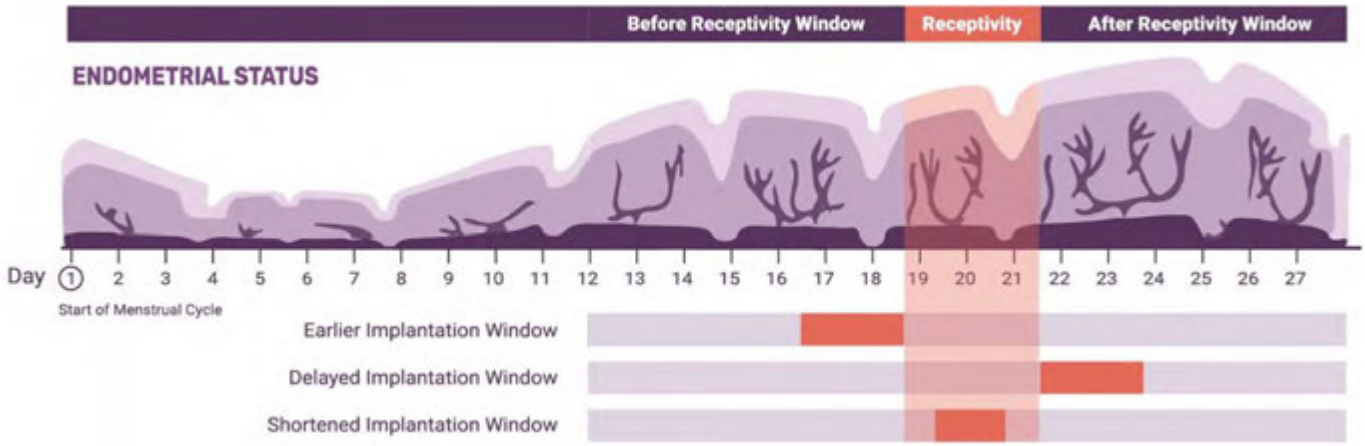
What is endometrial receptivity and why is it important?

Endometrial receptivity refers to the status of the endometrium in relation to its ability to accept an embryo for implantation. This interval of receptivity is commonly called the window of implantation (WOI).



Studies have shown that at least 30% of infertility patients have a displaced WOI. This means that embryo implantation failure occurs due to the lack of synchronization between embryo and endometrium. This is why is it important to utilize ORA™ to assess the endometrium's status and determine the optimal time for embryo transfer.

What is ORA™?

ORA™ is the first and only **non-invasive** endometrial receptivity test, utilizing microRNA (miRNA) biomarkers to evaluate the receptivity status of a patient undergoing IVF treatment.

Non-invasive

ORA™ analyses miRNA biomarkers in the blood, removing the need for an invasive and uncomfortable endometrial biopsy procedure.

High Accuracy

ORA™ as been shown to have > 95% accuracy in predicting endometrial receptivity, offering a stable solution with a more comfortable testing procedure. Further, the need to re-test on account of inconclusive results or invalid/insufficient RNA occurs in <1% of cases.

Comprehensive Analysis

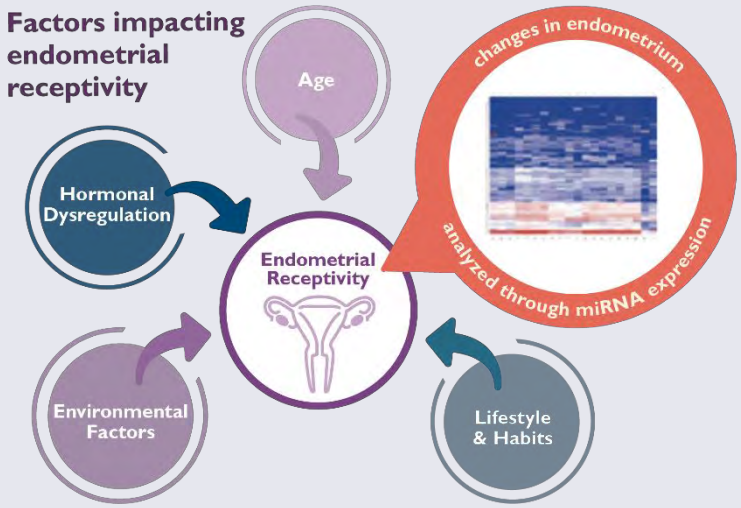
ORA™ analyzes close to 300 miRNA biomarkers that target over 1,000 endometrial receptivity-related genes to accurately identify the optimal time for embryo transfer.

What are microRNAs (miRNAs)?

DNA is made up of genes that carry all the necessary information to build a human body. So why is it that the same genetic information can be reflected differently throughout different parts of our body?

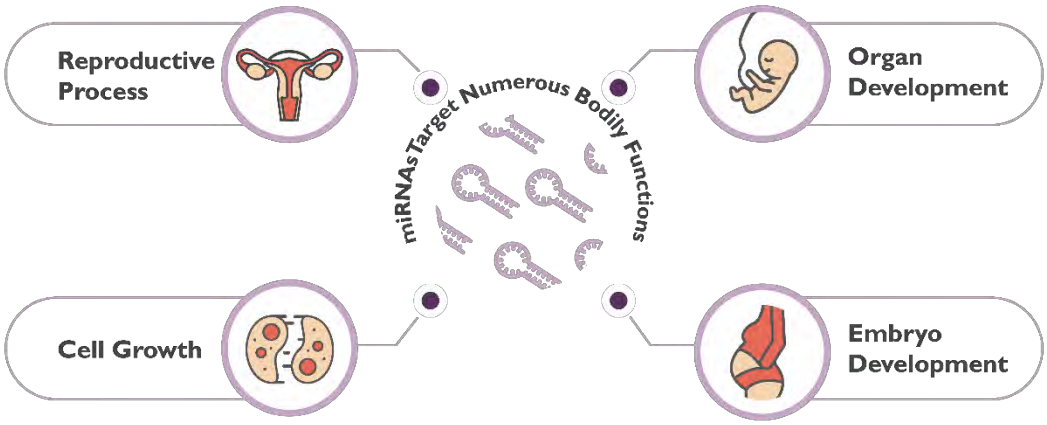
This is due to "gene expression and regulation". While the human DNA remains unchanged, your body's gene expression is constantly changing to reflect different statuses of the human body.

These genes are regulated through a special kind of molecules present in our body called miRNAs, which influence various processes and reactions in our body, such as cell growth, development, and metabolism.



Various factors such as environment, age, BMI, and lifestyle can contribute to the changing endometrium, affecting endometrial receptivity and causing a displaced window of implantation in patients undergoing IVF treatment. Changes in the endometrium can be reflected through the miRNA expression.

The expression signatures of miRNAs can reflect the different physiological states of the endometrium in response to changes. miRNAs have regulatory functions throughout the entire embryo implantation and pregnancy process, including tissue development, embryo attachment and growth, pre-eclampsia, and more.



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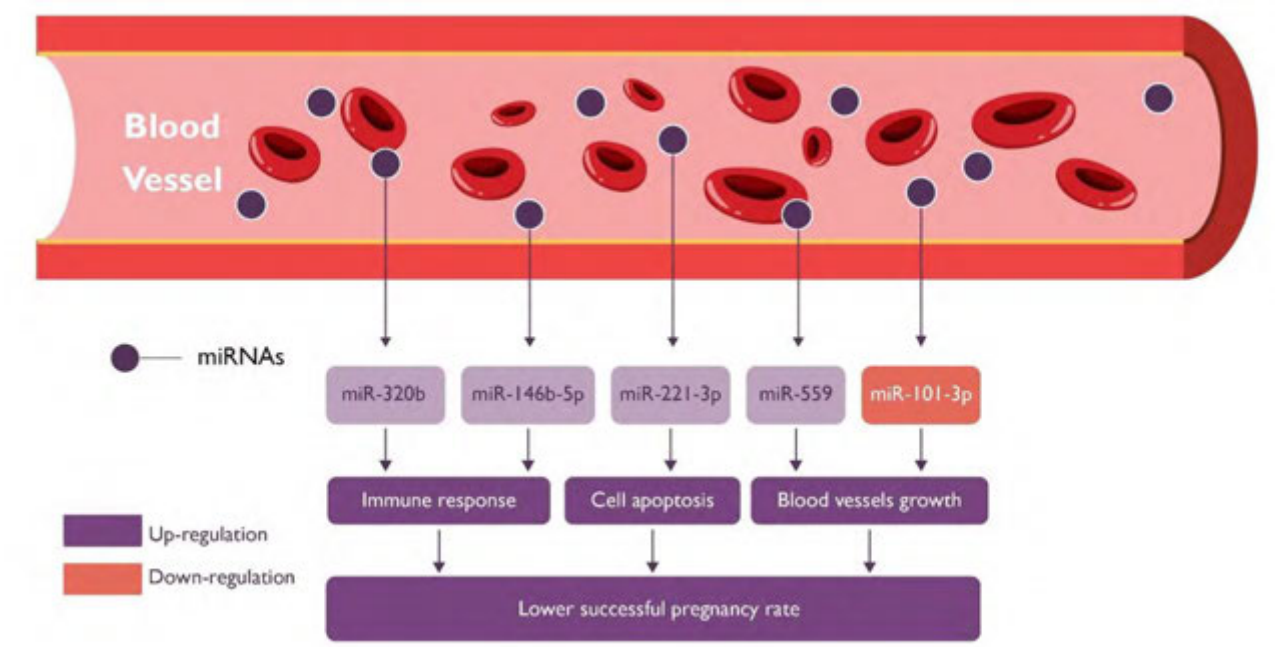

These miRNAs in the bloodstream have been found to regulate a number of immune mechanisms during pregnancy, and are critical physiological factors for cell growth and the formation of new blood vessels (angiogenesis). Through the regulation of these mechanisms, miRNAs can affect the endometrium's environment, growth process, and, by extension, pregnancy results.

Inti Labs was able to identify blood-based miRNA biomarkers that accurately reflect the endometrium's status, similar to the traditional method of analyzing endometrial tissue samples, but without the invasive biopsy needed for sample collection.

ORA™ uses these miRNA biomarkers to analyze the endometrium's status, providing doctors with a more precise recommendation for the optimal time for embryo transfer.