Recent Developments on the Transmission of Human Life

19 to 21 January 2023

Berlin, Germany

Welcome to all Participants

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Recent Developments on the Transmission of Human Life

Luteal phase deficiency:
Does it exist?
Does progesterone play a role in RIF?

Jason Franasiak, MD, HCLD/ALD

Luteal phase deficiency: Does it exist? Does progesterone play a role in Recurrent Implantation Failure?

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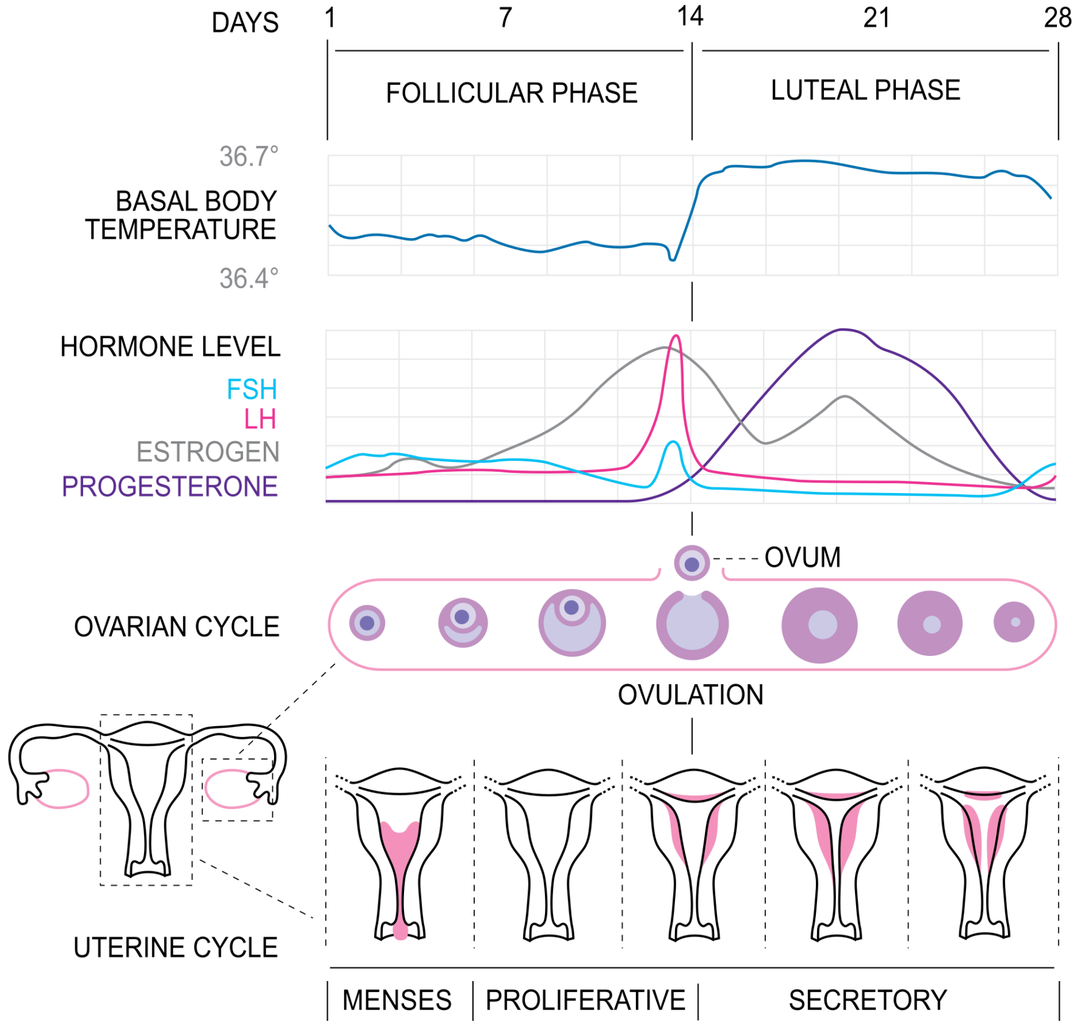
Faculty Disclosure

I have no potential conflict of interest to declare related to this talk

PHYSIOLOGY OF NORMAL LUTEAL FUNCTION

- A typical luteal phase length is 12–14 days but may range from 11–17 days
- Progesterone levels peak in nonpregnancy cycles 6–8 days after ovulation and is secreted in pulses under the control of LH
- Once implantation occurs, progesterone secretion by the corpus luteum depends on rising hCG levels
- Failure of hCG levels to increase results directly in corpus luteum failure and a decline in progesterone levels



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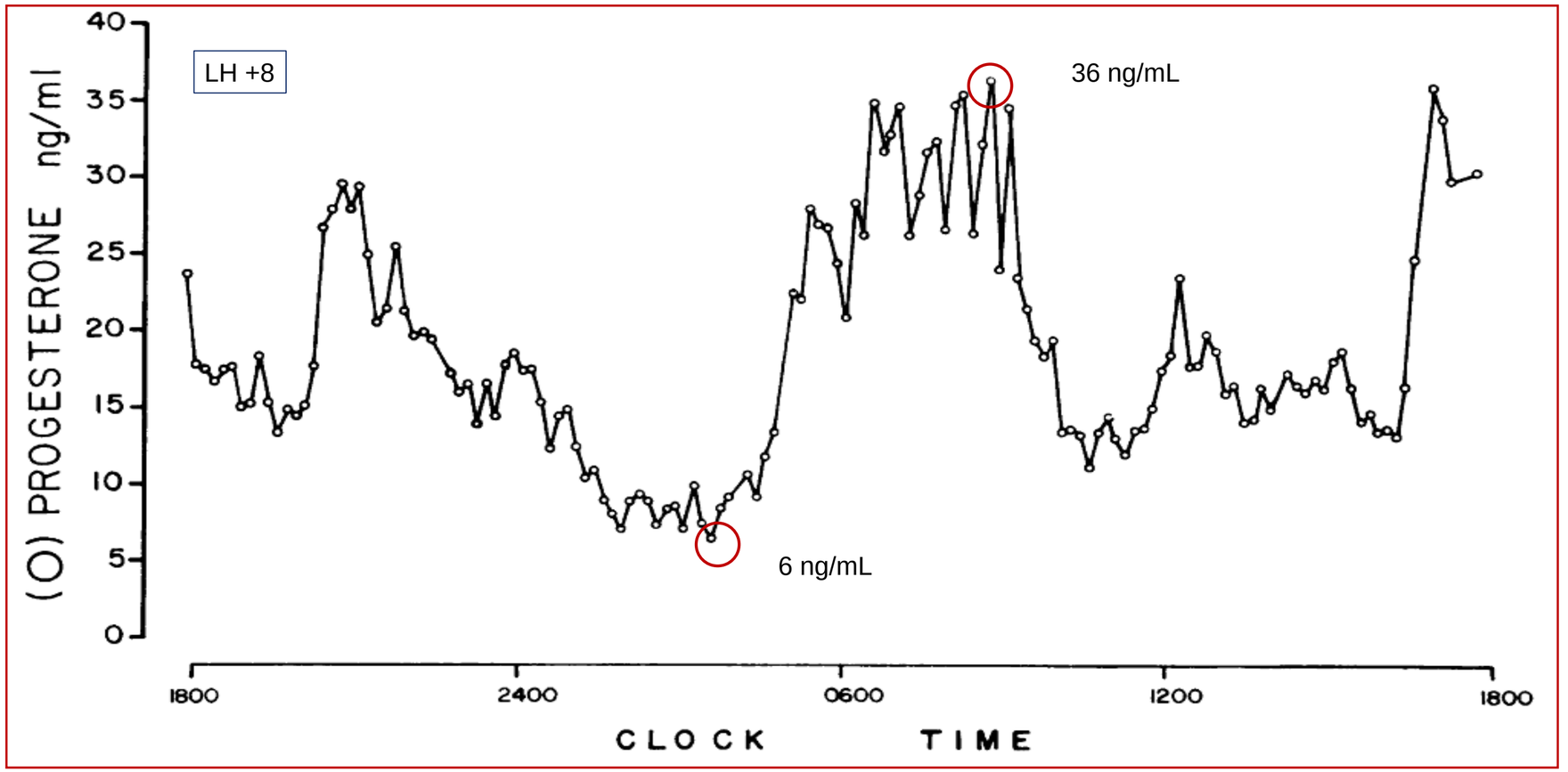
Serum Progesterone Levels...



- Natural cycle
- Different in stimulated cycle with hCG present
- Demonstrates tolerance for varying levels of P
- May explain limited predictive value of serum P monitoring

Filicori *et al*
J Clin Invest 1984;73:1638-47

DEFINITION OF LUTEAL PHASE DEFICIENCY

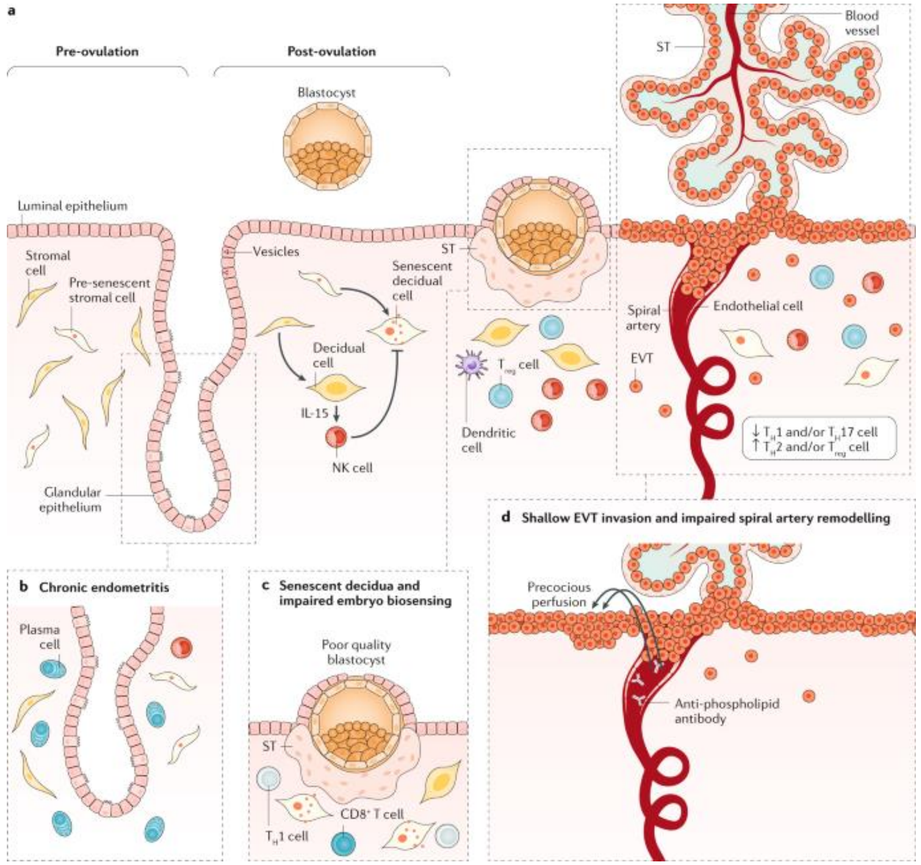
- LPD was first described in 1949 and broadly refers to an abnormal luteal phase
- Given the importance of the luteal phase in the establishment of a normal pregnancy, LPD has been suggested as a cause of RPL
- Classically, clinically detected LPD refers to a luteal phase of <=10 days but alternate definitions include <=11 days and <=9 days
- Clinical and biochemical tests have been proposed to diagnose LPD

Jones, JAMA 1949.

POTENTIAL CLINICAL IMPLICATIONS OF LPD

- LPD has also purportedly been associated with infertility and subfertility (1-2), first-trimester pregnancy loss (3), short menstrual cycles (4), and premenstrual spotting (5)

- Overall, it is unclear if abnormal luteal function is an independent cause of implantation failure or early pregnancy loss in natural cycles (6).



1. Blacker et al. Fert Stert. 1997.
2. Mesen et al. Obstet Gyncol Clin North Am. 2015.
3. Swyer et al. BMJ. 1953.
4. Strott et al. JCEM. 1970.
5. Muechler et al. Int J Fertil. 1987.
6. Dimitradis et al. Nat Rev Dis Prim. 2020.

PATHOPHYSIOLOGIC BASIS FOR LPD

- Inadequate ovarian hormone production
  - A short luteal phase has been associated with low follicular phase FSH levels, low follicular phase E2 levels, altered follicular phase FSH/LH ratios, and abnormal FSH and LH pulsatility (1)

- Inadequate endometrial response to adequate hormone levels
  - For example, it has been proposed that some patients demonstrate an endometrium that has progesterone resistance (2-3)

- Idiopathic LPD

Note: because of the pulsatile nature of serum progesterone, it has not been possible to define a normal threshold peak, trough, or average concentration for progesterone in natural cycles.

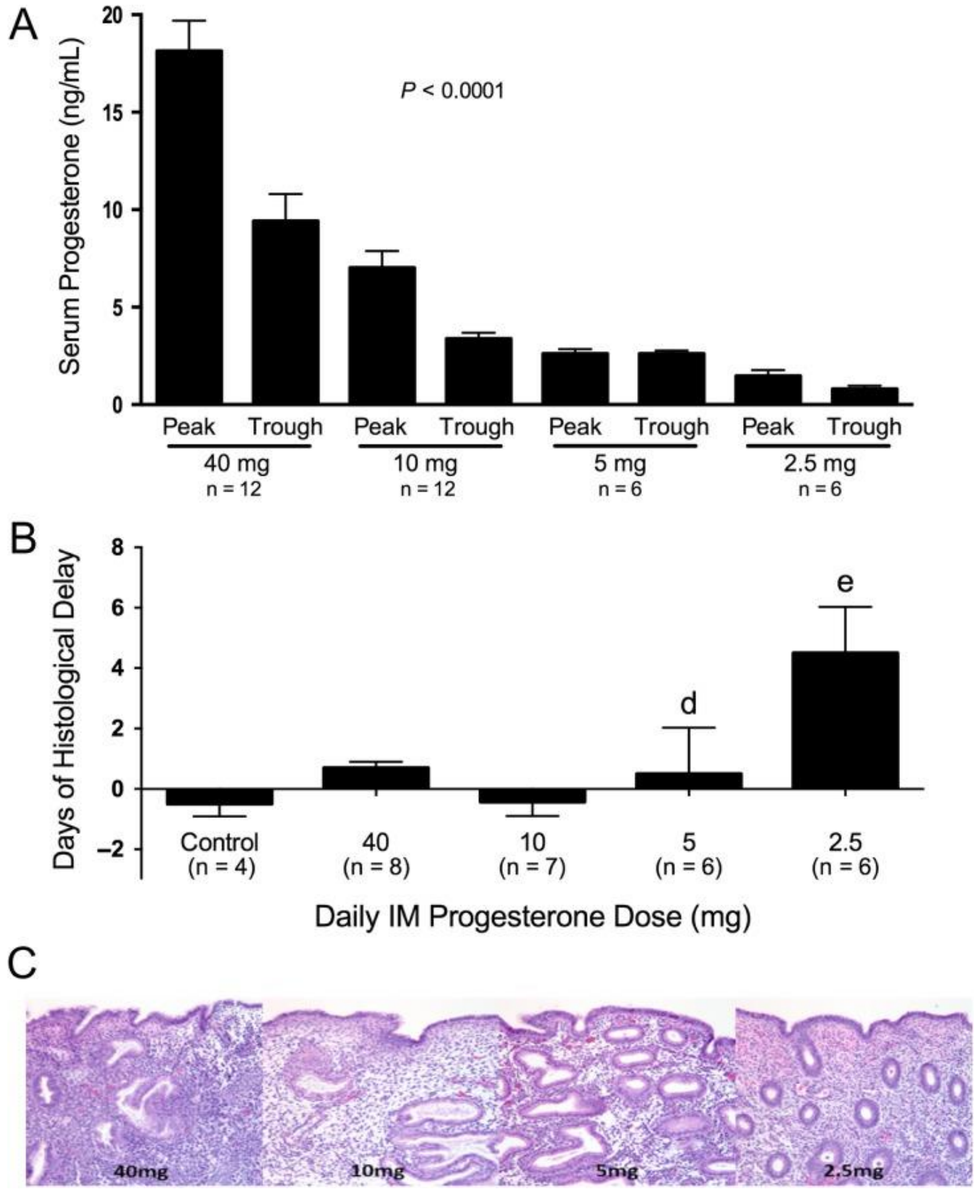
*Programmed cycles have suggested that the threshold serum progesterone levels for a normal endometrial histology may be as low as 2.5 ng/mL, but that normal gene expression may require a peak threshold between 8 and 18 ng/mL (4)

1. Schliep et al. JCEM 2014.
2. Burney et al. Endocrinology. 2007.
3. Bulum et al. JCEM 2006.
4. Young et al. Hum Repro. 2017.

- 46 healthy volunteers
- GnRH down-regulation cycles with transdermal estradiol for 10 days and PIO at varying doses for 10 days
- EMB on the 10th day of PIO of LH +10 for controls
- Histologic dating
- Microarray analysis of whole genome
- RT-PCR analysis
- Western blot analysis

- Results:

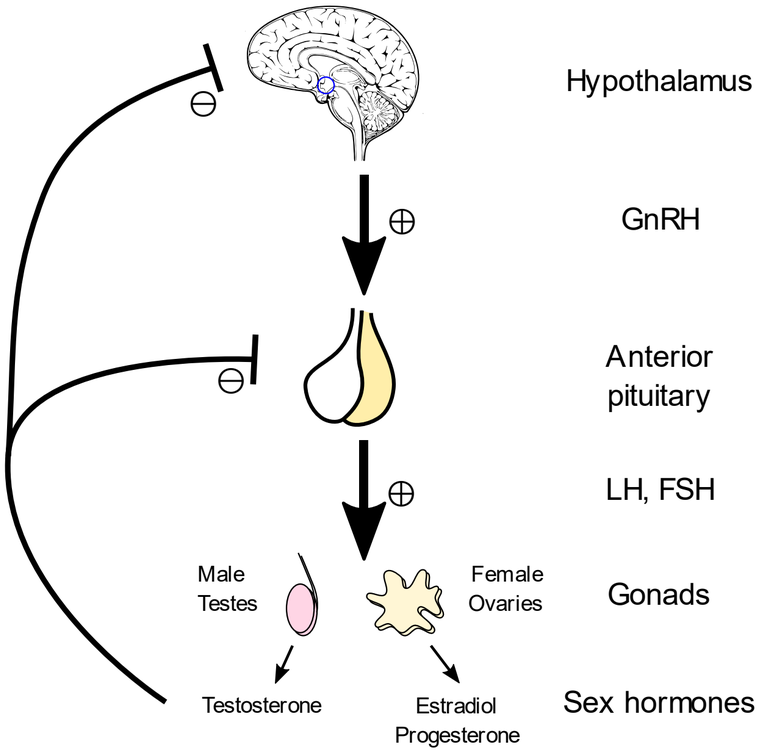
-Morphologic delay in the 2.5 mg/day P group
-Normal histology but abnormal microarray analysis at both 2.5 mg/day and 5 mg/day doses



Young et al. Hum Repro. 2017

CONDITIONS THAT ALTER THE LUTEAL PHASE

- Many conditions are proposed due to the disruption of GnRH*
  - Hypothalamic amenorrhea
  - Eating disorders
  - Significant weight loss
  - Stress
  - Obesity
  - PCOS
  - Aging
  - Thyroid dysfunction
  - Hyperprolactinemia



- An evaluation of the underlying medical causes should be initiated in any woman with clinical evidence of LPD

* Whether LPD which may result contributes to the lower pregnancy and higher loss rates is unclear

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PROPOSED DIAGNOSTIC TESTS FOR LPD

- Diagnosis of LPD is made clinically
- Multiple diagnostic tests have been proposed, including clinical, biochemical, and histologic tests, but none have been able to reliably differentiate between fertile and infertile women (1-2)
- Shortened luteal phase based on:

Menstrual cycle length → BBT charting or urinary LH surge detection kits → measurement of progesterone levels → EMB

1. Jordan et al. Fertil Steril. 1994.
2. Murry et al. Fertil Steril. 2004.

Menstrual Cycle Length

- The average luteal phase length is 14 days, with a normal variation of 11–17 days (1-2)
- A short luteal phase is an interval of less than 9–11 days from the LH peak to the onset of menstrual flow (1-2).
- Short luteal phases have also been diagnosed in non-infertile women with regular menstrual cycles
  - 13% of ovulatory menstrual cycles were associated with a luteal length <10 days (3)
  - 18% of menstrual cycles had a luteal phase length <12 days (4)
- These findings suggest that a shortened luteal phase length is relatively common and not associated with decreased fecundity over 12 months
- Assessing LPD is complicated further by the fact that the luteal phase length cannot be measured in cycles that result in pregnancy, but only in cycles that do not result in pregnancy

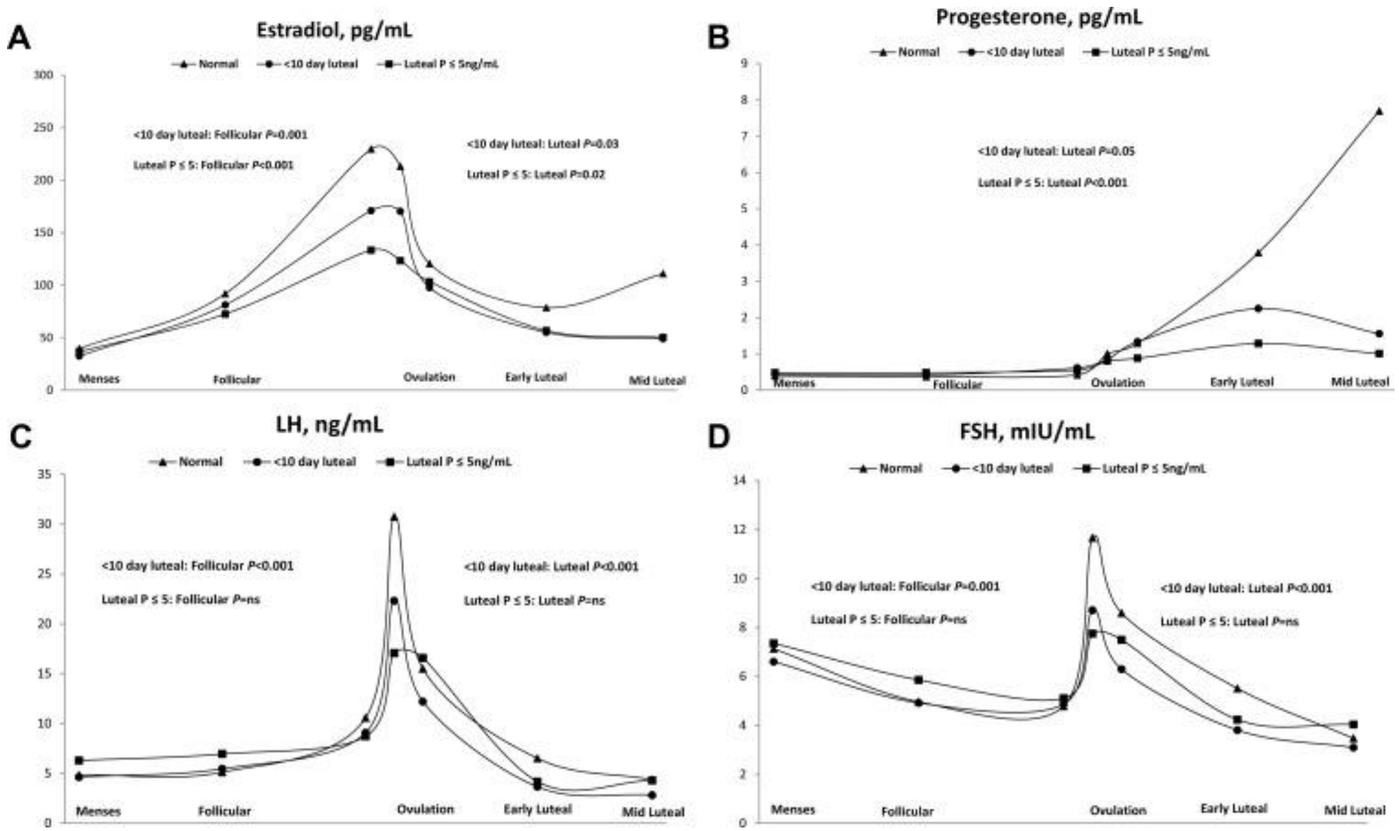
1. Strott et al. JCEM. 1970.
2. Lenton et al. Br J Obstet Gynecol. 1984.
3. Schliep et al. JCEM. 2014.
4. Crawford et al. Fertil Steril. 2017.

LPD Based on Short Luteal Phase and/or Low Progesterone

- **Objective**: assess the prevalence of two established LPD diagnostic criteria

- **Participants**: 259 healthy participants over 463 menstrual cycles in women with regular menses (infertile patients excluded)

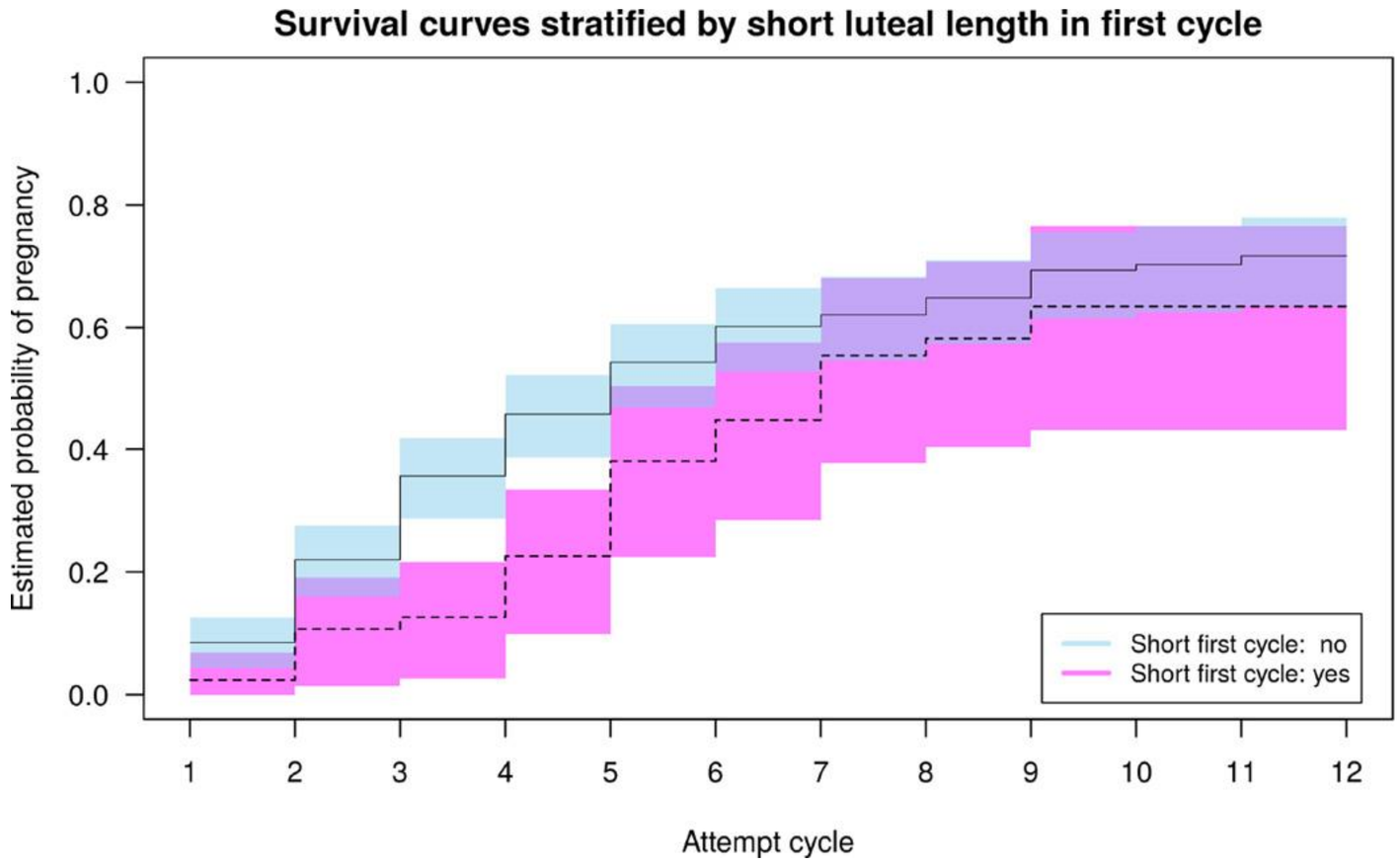
- **Results**: 41 cycles (8.9%) with clinical LPD (<10 d), 39 cycles (8.4%) with biochemical LPD (<5 ng/mL), and 20 cycles (4.3%) meeting both criteria



Schliep et al, JCEM. 2014.

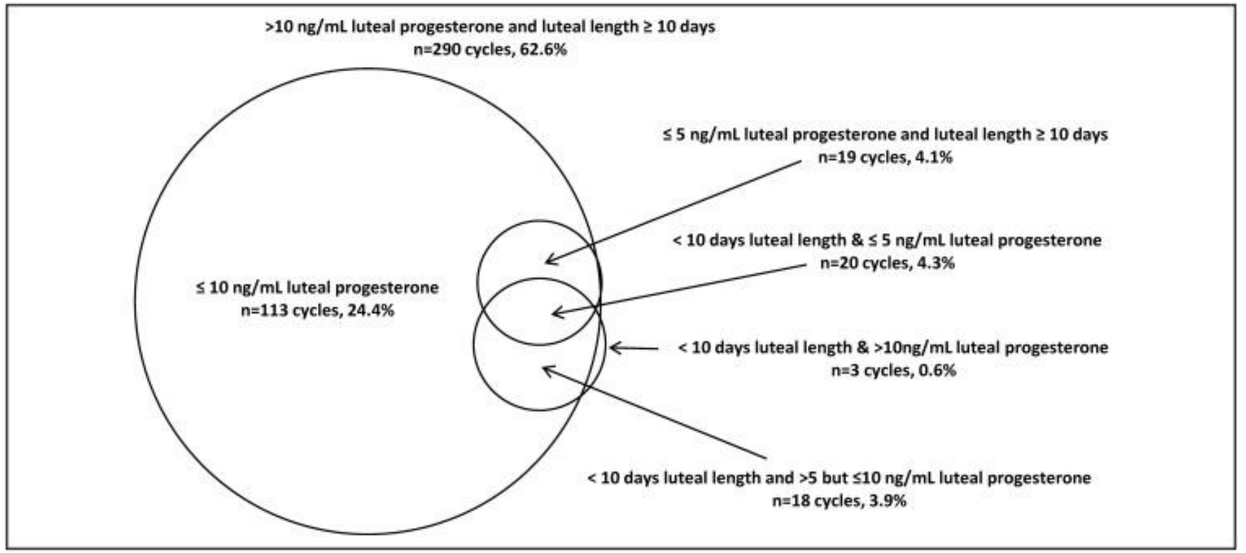
LPD Based on Short Luteal Phase

- **Objective**: to evaluate the impact of a short luteal phase on fecundability
- **Participants**: 284 women trying to conceive without fertility interventions
- **Results**: Short luteal phase (=<11 days) occurred in 18% of cycles. Women with a short luteal length in the first observed cycle had lower fertility after 6 months but no difference at 12 months.



Crawford et al, Fertil Steril. 2017.

Progesterone Levels



- A luteal progesterone value of >3 ng/mL is considered indicative of ovulation

- No minimum serum progesterone concentration defines normal or fertile luteal function

- Progesterone is secreted in response to LH pulses, with progesterone values oscillating between 5 and 40 ng/mL over short periods of time in normally ovulatory women, making a single random measurement difficult to interpret (1).

- In ovulatory cycles, luteal progesterone values of <5 ng/ml occur 8.4% of the time, and values of <10 ng/mL occur 31.3% of the time (2)

- Proposed: integrated progesterone values obtained daily or over 3 days (3)
  - Not clinically validated
  - May not be clinically practical

1. Filicori et al. J Clin Invest. 1984.
2. Schliep et al. JCEM 2014.
3. Jordan et al. Fertil Steril. 1994.

Endometrial Biopsy

- Abnormalities of endometrial maturation have been viewed historically as the gold standard to diagnose LPD however it is imprecise (1)
- Further, EMB is a poor tool for differentiating fertile from infertile women
- In a multicenter RCT of 847 women with regular menstrual cycles, 49% of midluteal and 35% of late luteal biopsies were ‘‘out of phase,’’ and there was no difference when comparing fertile and infertile women (2)
- Consistent with these findings are studies which show normal endometrial histology was seen with peak serum progesterone levels as low as 2.5 ng/mL, but completely normal gene expression required a peak serum threshold >8–18 ng/mL (3)

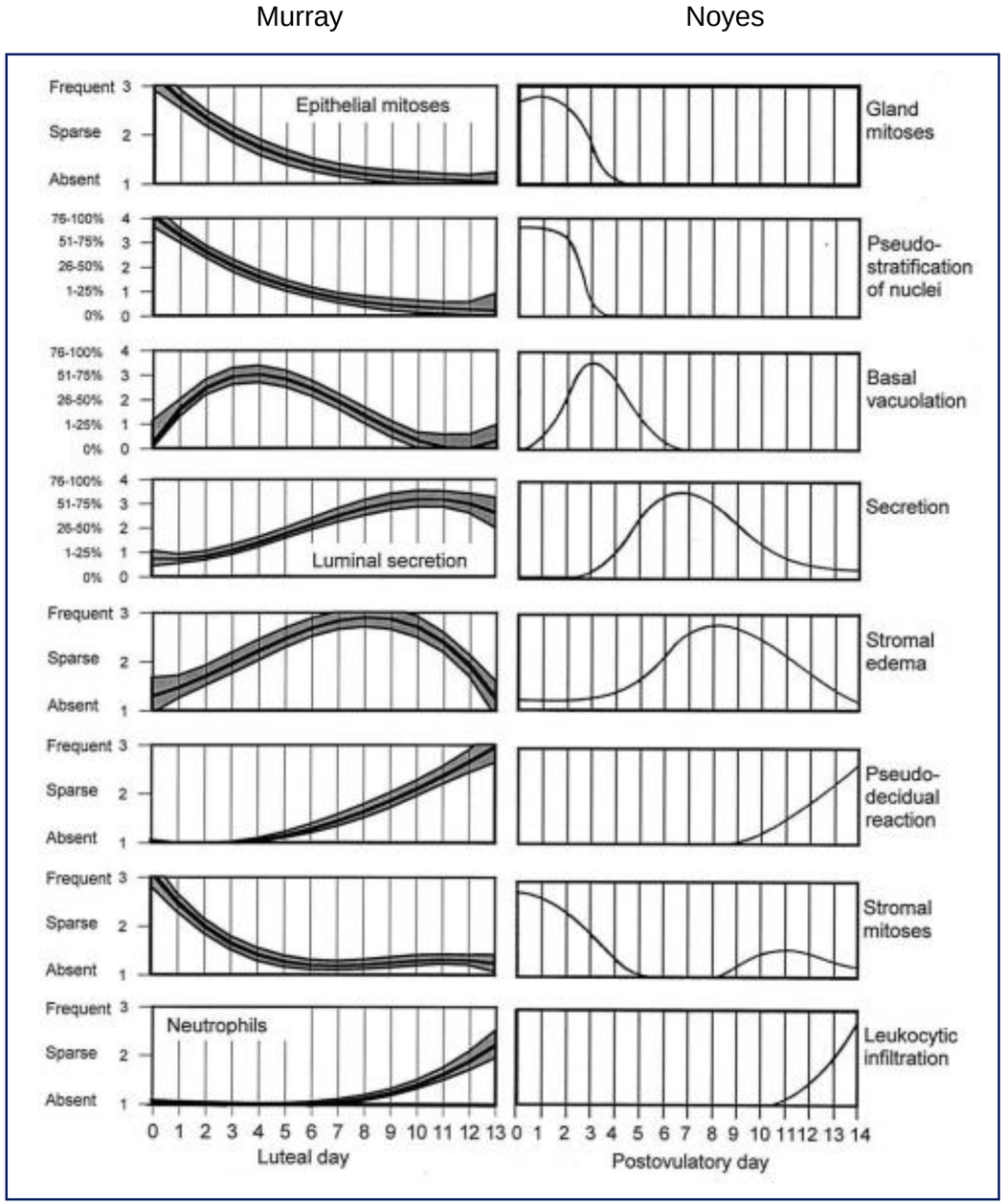
1. Murray et al. Fertil Steril. 2004.
2. Coutifaris et al. Fertil Steril. 2004.
3. Young et al. Hum Repro. 2017.

Endometrial Biopsy is Imprecise

- 130 healthy, regularly cycling fertile volunteers
- 32 features evaluated

Results:

- The traditional endometrial histologic dating criteria are much less temporally distinct and discriminating than originally described
- This is due to considerable intersubject, intrasubject, and interobserver variability
- Traditional dating criteria could not reliably distinguish any specific cycle day or narrow interval of days



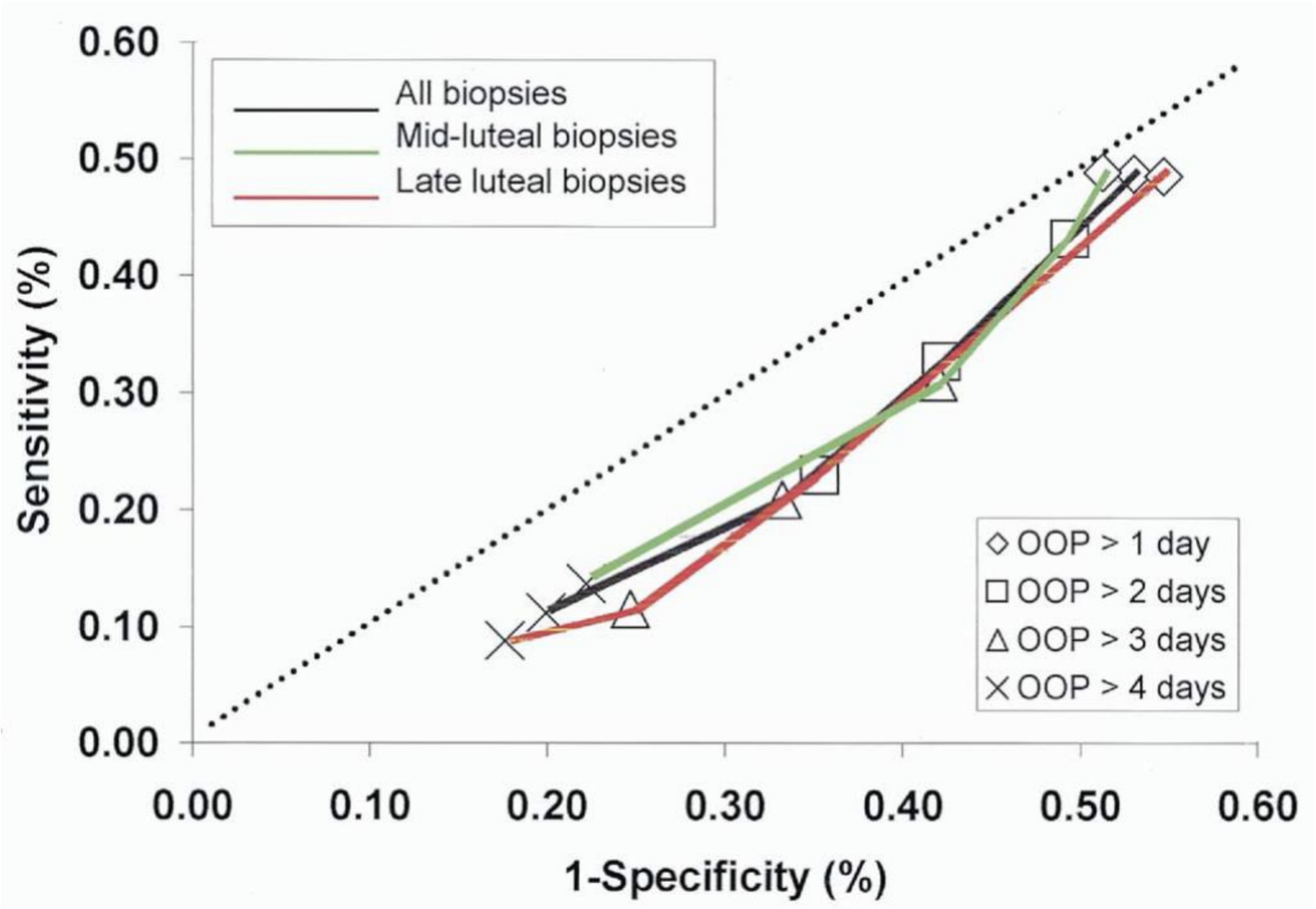
Murray *et al Fertil Steril* 2004; 81:1333

Endometrial Biopsy Cannot Distinguish Fertile from Infertile

- 847 subjects at 12 clinical sites in the RMN
- Biopsy in the mid-luteal and late luteal phase

Results:

- Out-of-phase biopsy results poorly discriminated between fertile and infertile

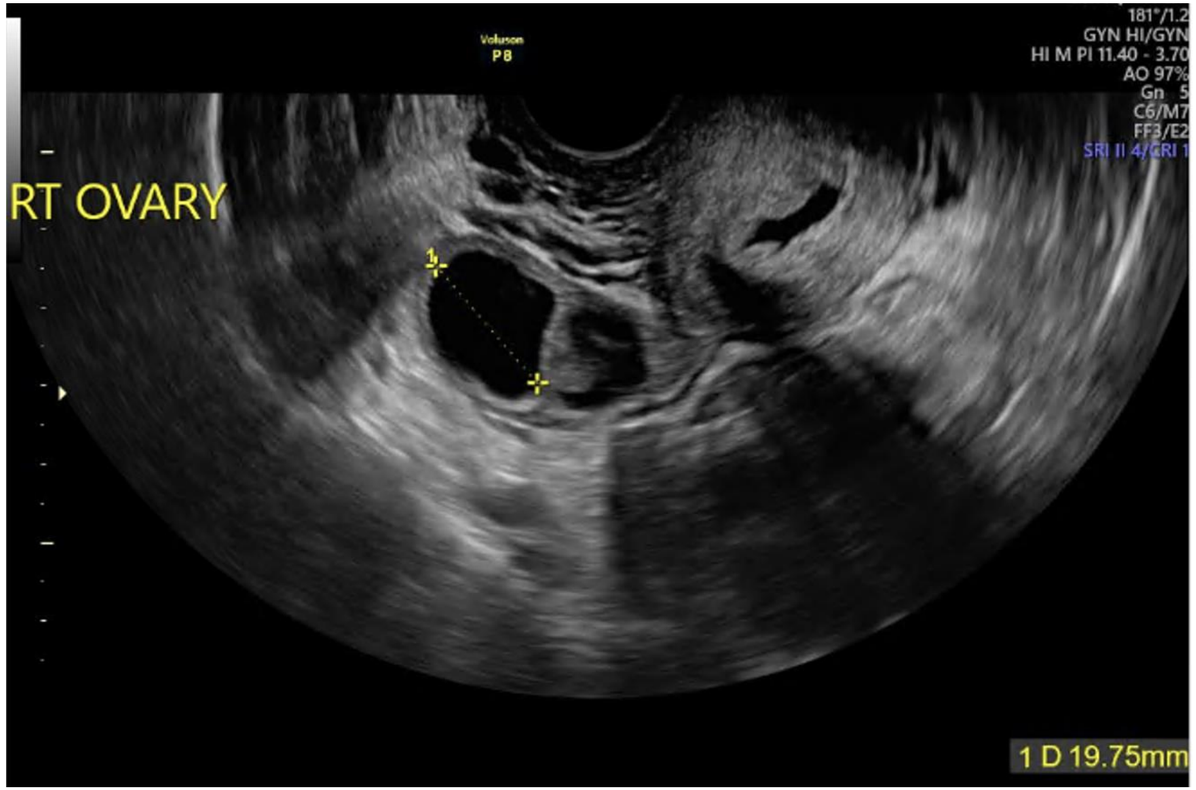


Coutifaris et al. Fertil Steril. 2004.

PROPOSED TREATMENTS FOR LPD

- Given the lack of clear diagnostic criteria for LPD and the overlapping results in most tests between fertile and infertile women, quality data are lacking for treating LPD.
- The first approach to the treatment of potential LPD is the correction of any underlying condition, such as hypothalamic or thyroid dysfunction, or hyperprolactinemia.
- If no underlying abnormality is identified, then treatment becomes empiric and is not generally recommended.
- The aim of empiric treatment has historically been to improve ovulatory function, promote endometrial maturation, enhance endometrial receptivity, and support implantation and development of an early pregnancy.

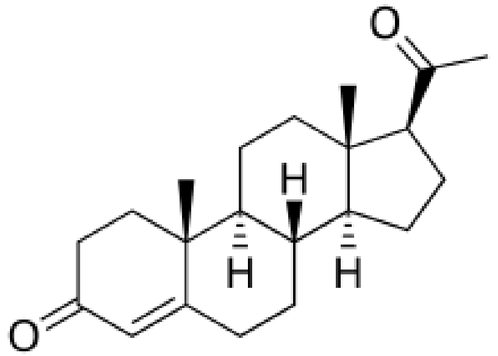
Ovarian Stimulation



- The use of agents to stimulate the ovaries may improve the fertility of subfertile women.
- The biologic plausibility of this treatment strategy is based on the physiologic continuity between the developing follicle and the corpus luteum – improved preovulatory follicular dynamics should improve corpus luteum function.
- However, attempts to link poor fertility outcomes to these surrogate endpoints have been unsuccessful and ovulation induction has not been demonstrated to treat LPD (1-2).

1. Wentz et al. AJOG. 1990.
2. Balasch et al. Hum Reprod. 1992.

Progesterone



- Although progesterone is beneficial after various therapeutic infertility treatments, there is no evidence that progesterone is beneficial for fertility in natural cycles or is beneficial for treating LPD
- There are no RCTs investigating progesterone supplementation for women with LPD
- Studies have investigated progesterone supplementation for recurrent pregnancy loss, which theoretically may overlap with LPD due to inadequate progesterone support for early pregnancy
- A systematic review and meta-analysis also suggested that progestogen supplementation reduced the miscarriage rate in women with unexplained recurrent miscarriage (1)
- Progesterone supplementation initiated after a positive pregnancy test was not shown to decrease miscarriage risk (2)

1. Haas et al. Cochrane Database. 2019.
2. Coomarasamy et al. NEJM. 2015.

SUMMARY LPD

- LPD is a clinical diagnosis and may be present with a luteal phase <=10 days in length
- Abnormal luteal function may occur as the result of several medical conditions
- True isolated LPD implies an underlying pathologic abnormality of the luteal phase in the absence of an identifiable disease process negatively affecting normal LH support of the corpus luteum
- No diagnostic test for LPD has proven to be reliable in the clinical setting or in differentiating fertile from infertile women
- Endometrial biopsies only have the precision to distinguish the early luteal, midluteal, and late luteal phases, and have been shown to not discriminate between fertile and infertile women
- No treatment for LPD has been shown to improve pregnancy rates in natural, unstimulated cycles

CONCLUSION LPD

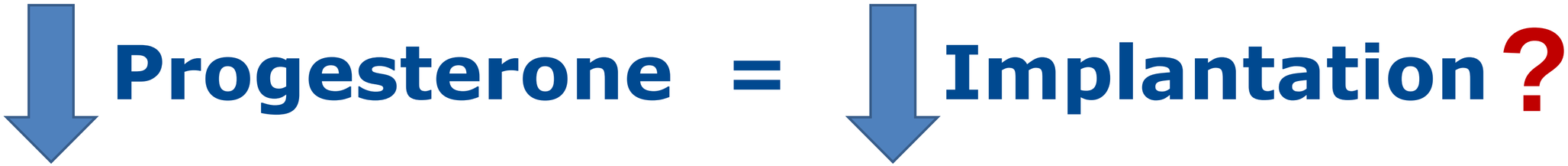
- Infertile women suspected of having abnormal luteal function due to an underlying medical condition should be evaluated and appropriately treated for an identified abnormality.

- Histologic dating of the endometrium with endometrial biopsies is not recommended.

- Additional research is needed to determine if testing modalities, such as combined testing (i.e., luteal progesterone measurement and luteal phase length <10 days), identifies a subgroup of patients with poorer reproductive outcomes and, if so, whether treatment improves outcomes.

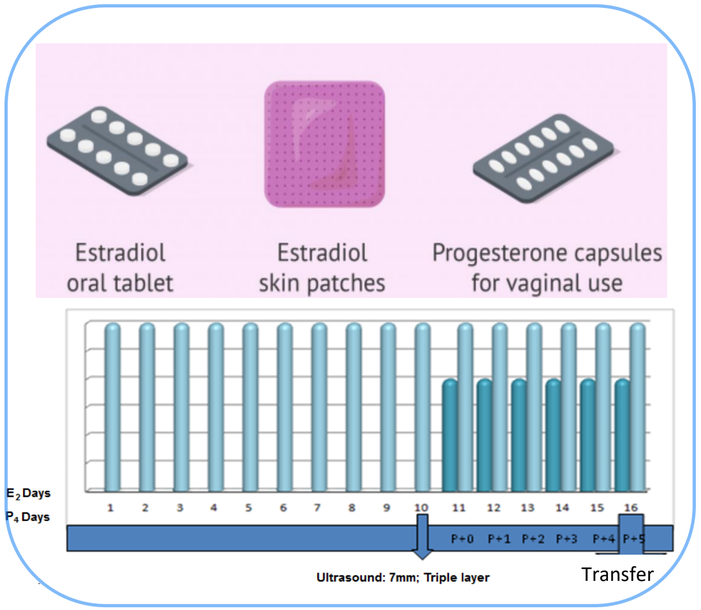
PROGESTERONE IN RECURRENT IMPLANTATION FAILURE

*Several slides were presented by Dr. Elena Labarta at the Recurrent Implantation Failure Summit in Lugano, Switzerland prior to the 2022 ESHRE Congress

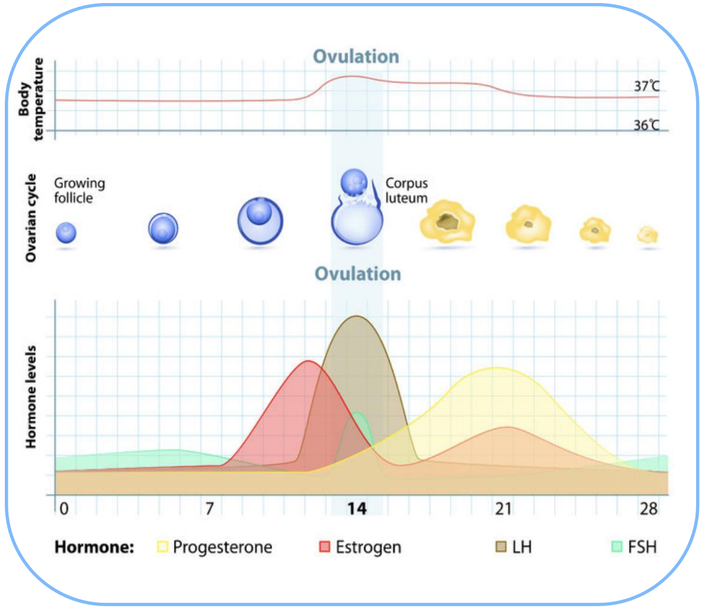

Progesterone = Implantation ?

Progesterone in Recurrent Implantation Failure

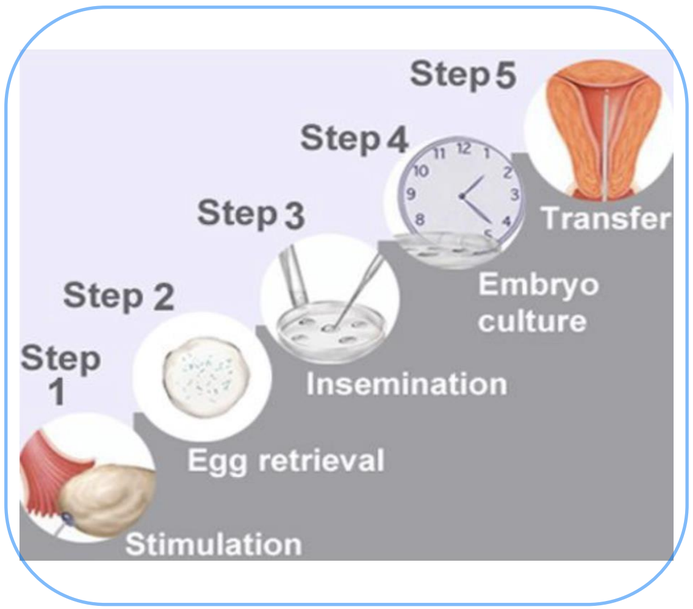
ARTIFICIAL CYCLE



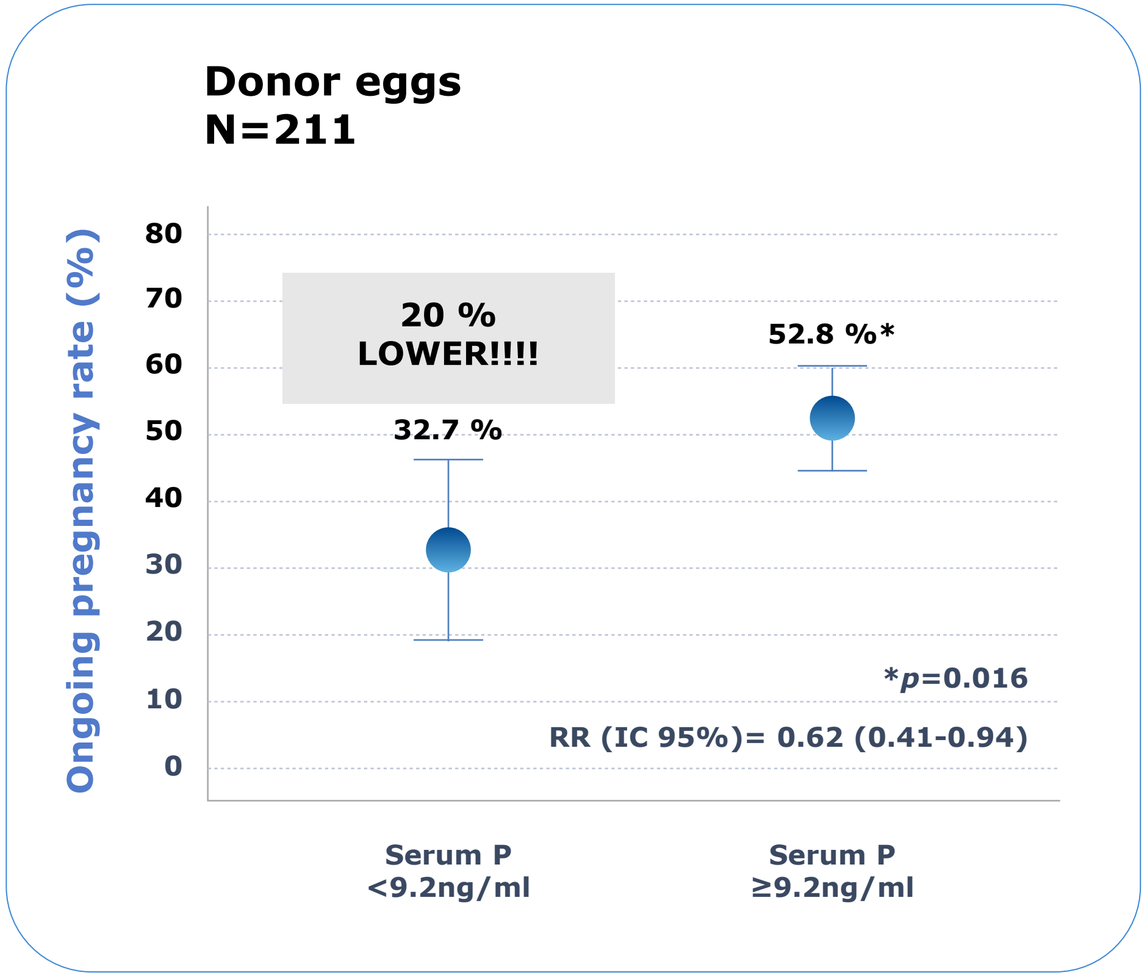
NATURAL CYCLE

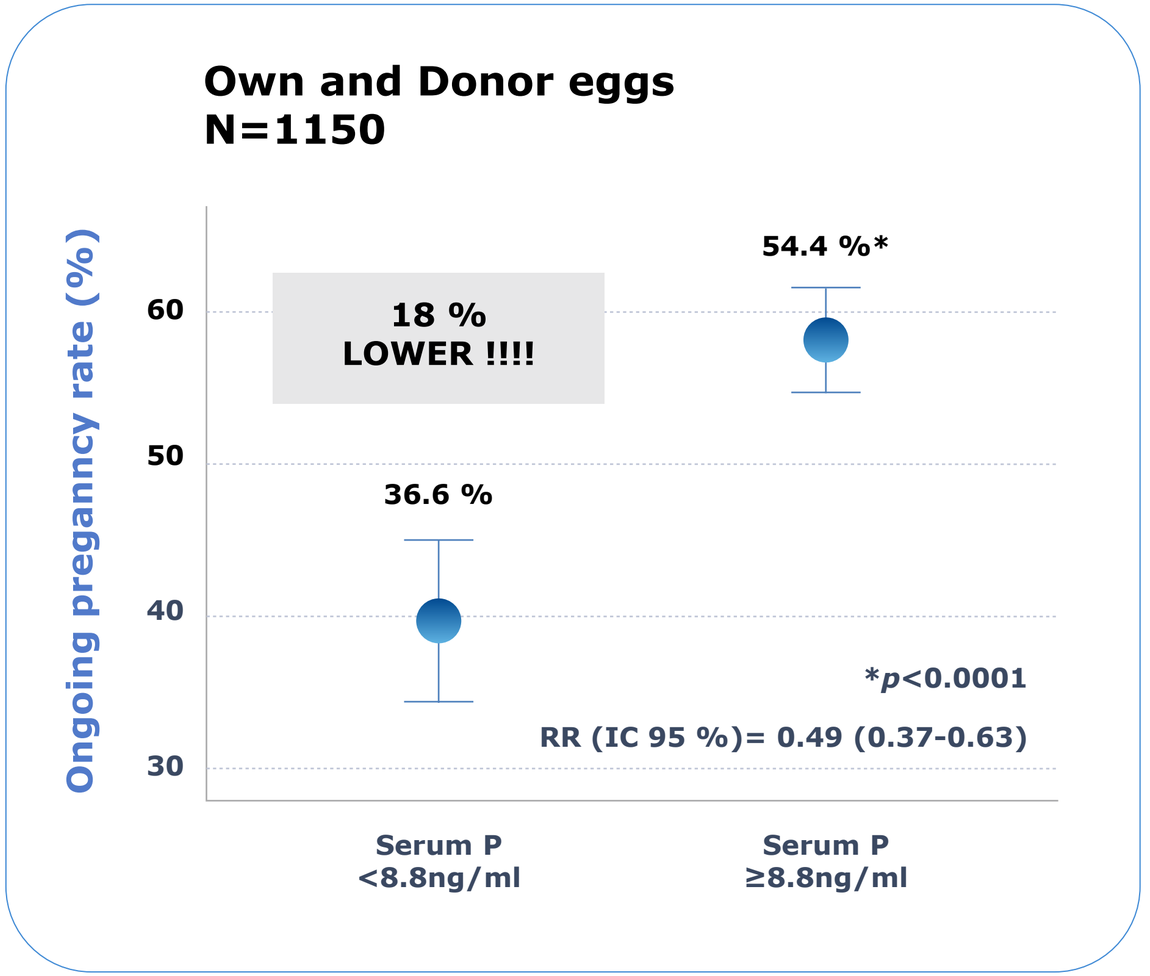


STIMULATED CYCLE



What do the data tell us? Artificial cycle





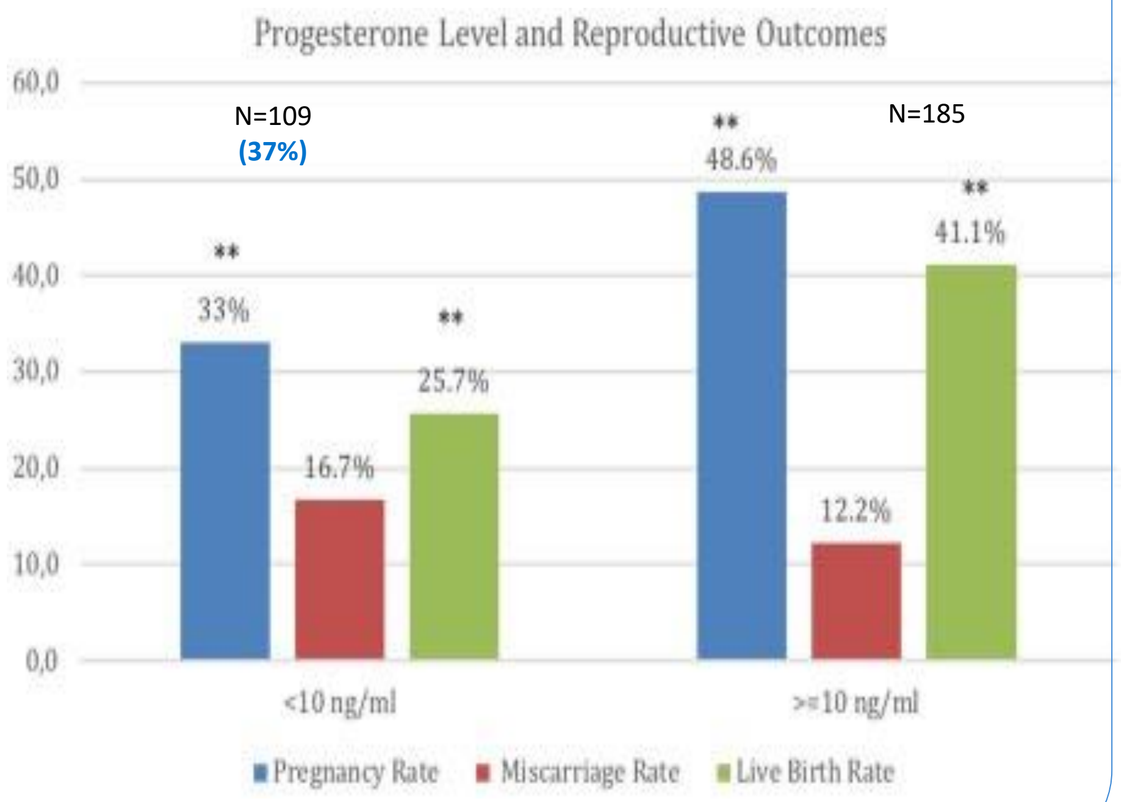
Labarta et al. Hum Reprod 2017

Labarta et al. Hum Reprod 2021

What do the data tell us? Natural cycle

Without LPS : More than 1 out of 3 patients were below 10ng/mL

Retrospective study - FET pure NC



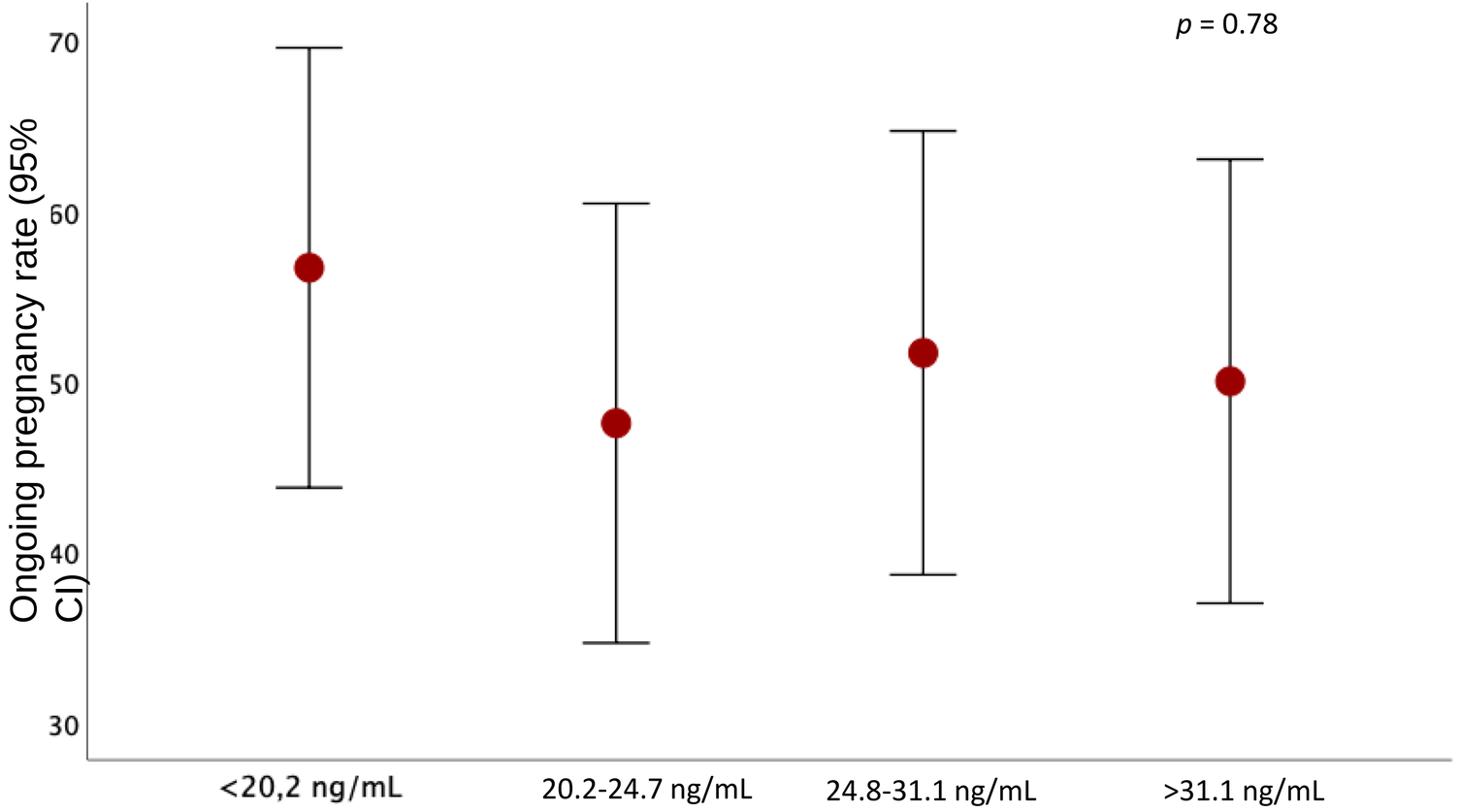
Gaggiotti-Marre et al., 2020

What do the data tell us? Natural cycle

- Prospective study
- 241 patients, FET
- Modified natural cycle
- LPS: 200mg/12h MVP

E2 day of ET	154.1 ± 96.1
P4 day of ET	26.2 ± 9.0

Only 2 patients showed serum P levels below 10 ng/mL (0.8%)



Labarta et al. ESRHE meeting (poster), 2022

Artificial Cycle & Pure natural cycle FET

% of patients with low P levels when receiving vaginal P

Low P levels Good P levels

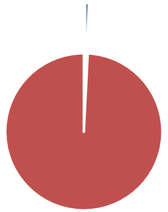
Measure serum P

Individualize LPS

- Adding other ways of P administration
- Increase dose of P
- Change type of P

Modified natural cycle FET

% of patients with low P levels when receiving vaginal P



Low P levels Good P levels

Measure serum P?

- It seems not to be needed
- LPS offers adequate serum P levels
- No impact of serum P on the outcome

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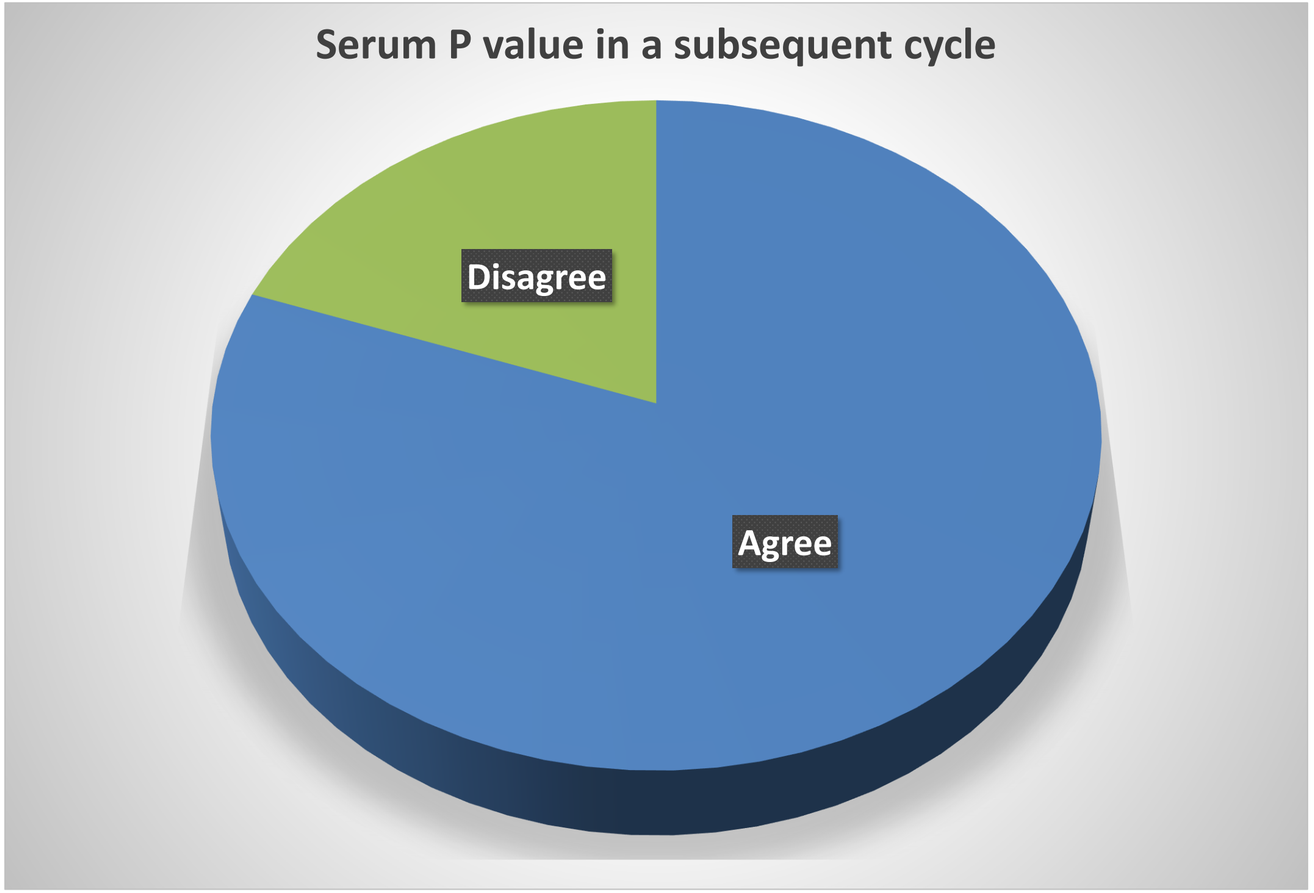
Is low Progesterone recurrent?

Inter-cycle Consistency



N= 149

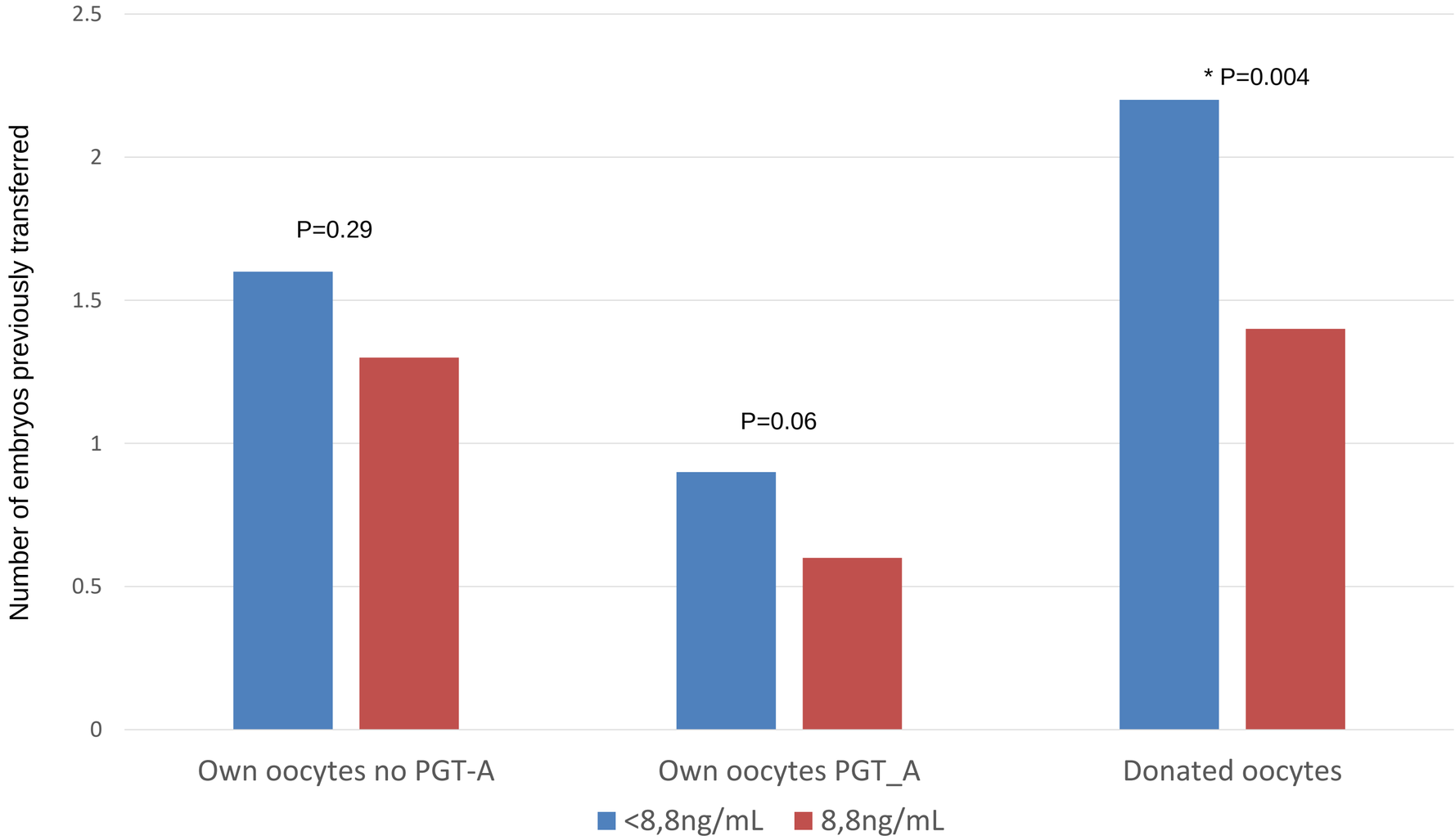
In **80.5%** of the cases the measurement in another cycle was in agreement (Below or Above optimal level).

Receiving same doses of Vaginal P

** 9.2ng/ml:*
Cut-off point taken from:
Labarta et al., Hum Reprod 2017

Labarta. Unpublished data. IVIRMA Valencia

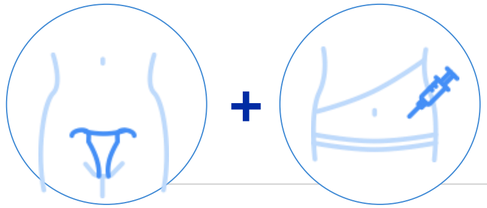
Number of embryos transferred is higher in patients with recurrent low P



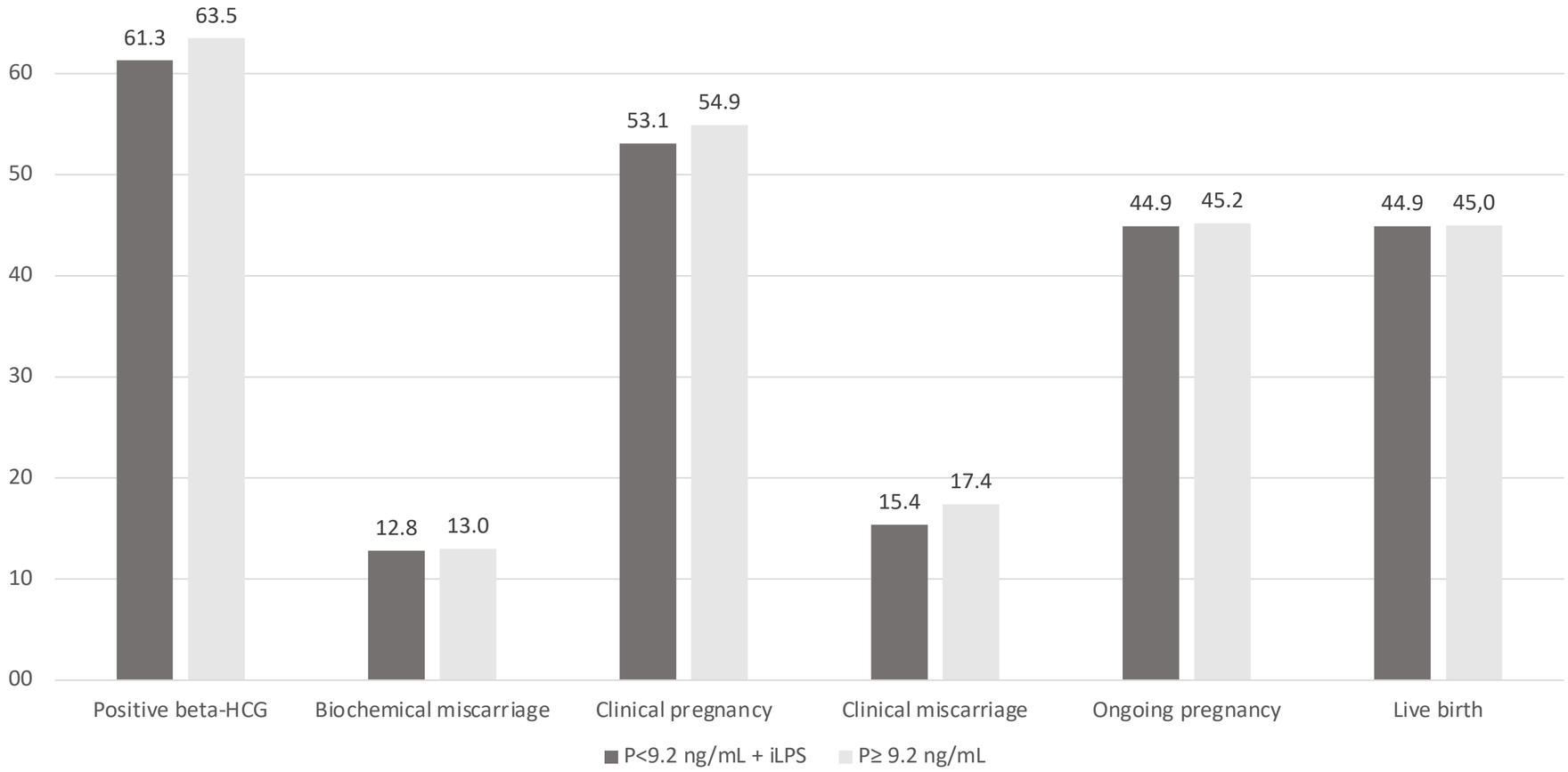
Labarta et al. Hum Reprod 2021

Management of luteal phase support to prevent RIF

Effectiveness of individual luteal phase support (iLPS)

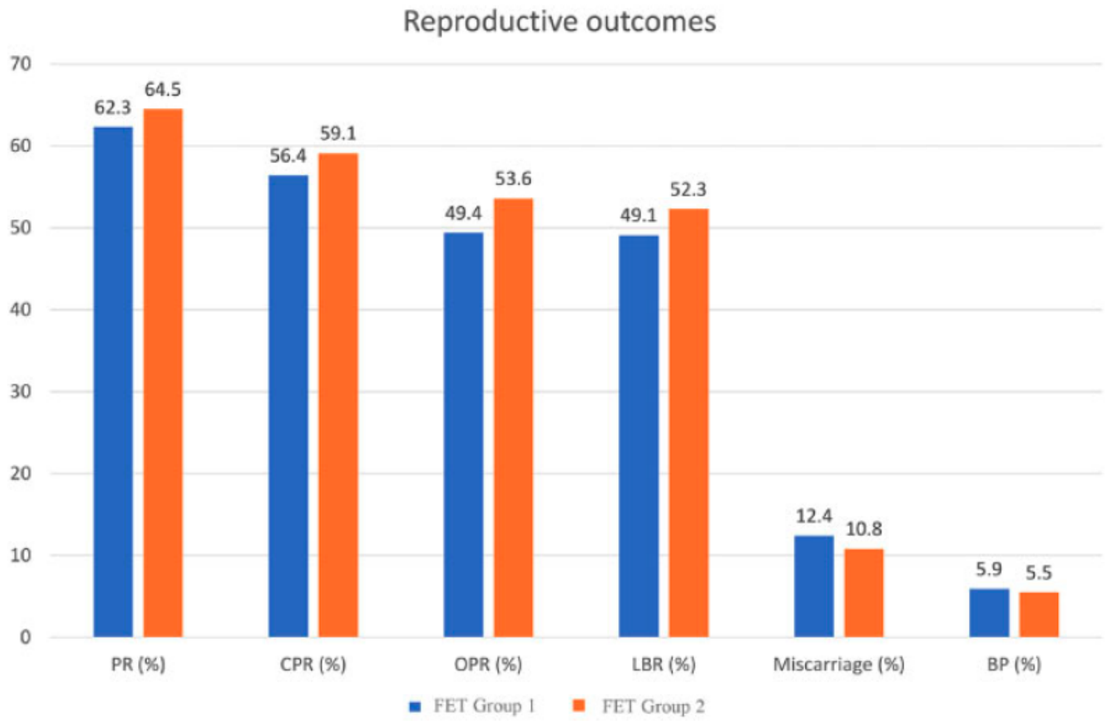


P < 9.2ng/mL + iLPS (n=550)	P ≥ 9.2ng/mL (n=1299)



Labarta et al. Fertil Steril 2021

Other groups observed similar results

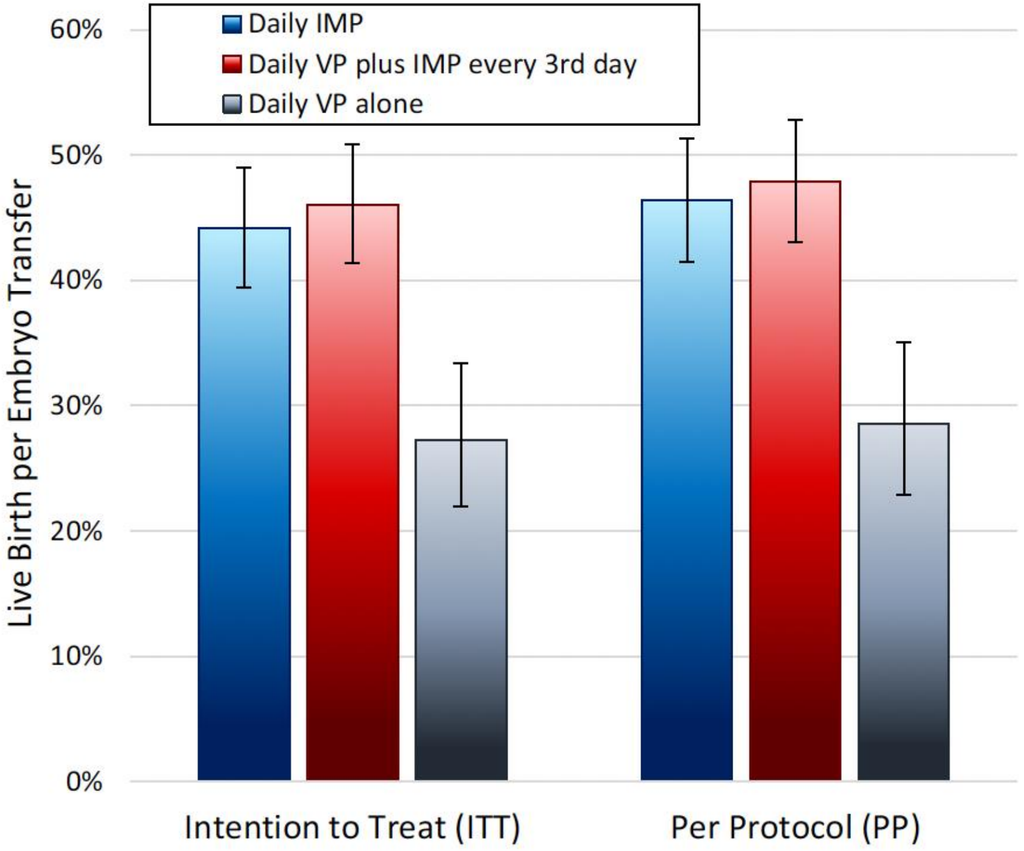


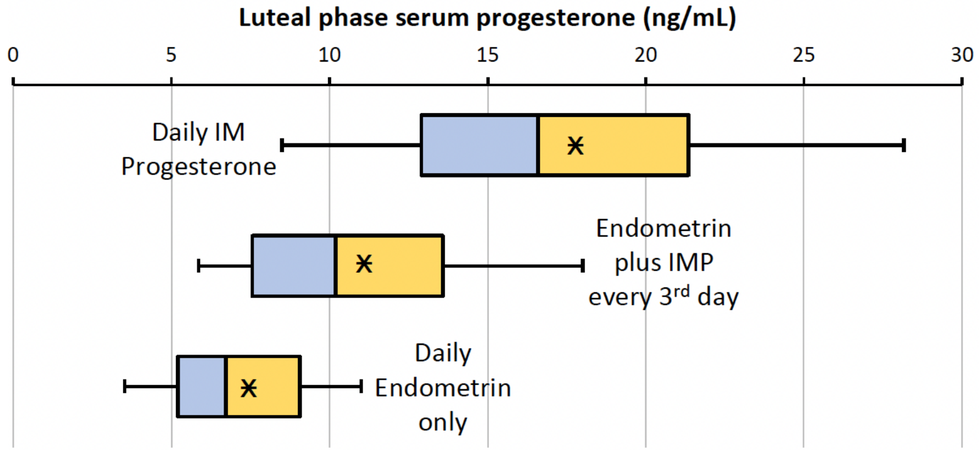
Alvarez et al. Hum Reprod 2021

Characteristic	Rescue group (n = 40)	Control group (n = 120)	P-value
Serum progesterone concentration on the day before embryo transfer, ng/ml	7.84 ± 0.92	15.32 ± 5.02	<0.001
Serum progesterone concentration on the day of embryo transfer, ng/ml	33.43 ± 10.83	–	
Positive HCG	24 (60.0)	80 (66.7)	0.356
Implantation rate, %	45.0 ± 45.0	52.0 ± 48.0	0.399
Biochemical pregnancy loss	2/24 (8.3)	12/80 (15.0)	0.613
Clinical pregnancy rate	22 (55.0)	68 (56.7)	0.856
Miscarriage rate	2/22 (9.1)	10/68 (14.7)	0.500
Ongoing pregnancy	20 (50.0)	58 (48.3)	0.858
Multiple pregnancy rate	1/22 (4.5)	4/68 (5.9)	1.000

Yarali et al. RBM Online 2021

Intramuscular P optimizes live birth from programmed FET: a RCT





Devine et al. Fertil Steril 2021

SUMMARY PROGESTERONE IN RIF

If low Progesterone leads to lower implantation rate

And low Progesterone tends to be recurrent

Low Progesterone can be a cause of recurrent implantation failure

THANK YOU

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