Effect of Prematurely Elevated Late Follicular Progesterone on Pregnancy Outcomes Following Ovarian Stimulation-Intrauterine Insemination (OS-IUI) for Unexplained Infertility

Heather Burks, M.D.

University of Oklahoma Health Sciences Center

Disclosures

- Dr. Hansen reports grants from NIH/NICHD, Yale University, during the conduct of the study; grants from Roche Diagnostics, grants from Ferring International Pharma Science Center US, consulting fees from Ablacare outside the submitted work.

- Dr. Peck reports other from Ferring Pharmaceuticals outside the submitted work.

- Dr. Diamond reports grants from NIH/NICHD, Yale University during the conduct of the study; other from Advanced Reproductive Care, other from AbbVie, Bayer, ObsEva, outside the submitted work.

Background

- Ovarian stimulation with IUI (OS-IUI) is a first line treatment for unexplained infertility (ASRM Practice Committee, *Fertil Steril*, 2020)

- Goal of multi-follicular development in ovary

Background

- Follicular rupture occurs approximately 34-46 hours after subcutaneous hCG injection (Anderson AG et al, 1995)

- ASRM recommends single IUI be performed between 0-36 hours following hCG injection (ASRM Practice Committee, *Fertil Steril*, 2020)

Background

Speroff's Clinical Gynecology Endocrinology and Infertility, 9th ed
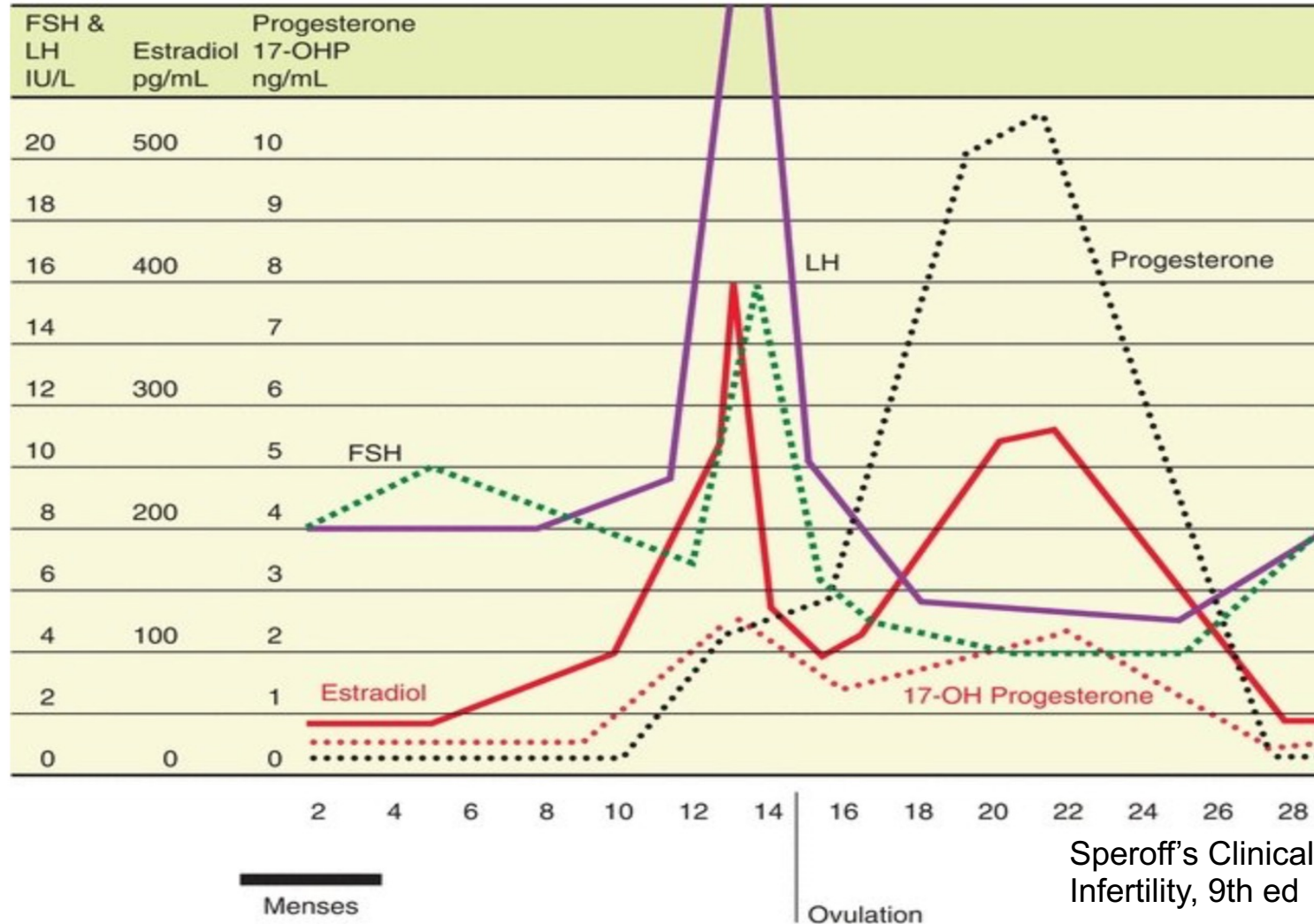
Background

- IVF studies suggest a negative association between elevated progesterone on day of trigger and pregnancy outcomes:

  - Suggested with progesterone ≥ 1.5 or ≥ 2.0 ng/mL, perhaps even as low as progesterone ≥ 0.8 ng/mL

  (Xu et al, *Fert Stert,* 2012; Ochsenkühn et al, *Fert Stert,* 2012; Venetis et al, *Hum Repro Update,* 2013)

Background

- Retrospective cohort study including 2,458 cycles
- Ongoing pregnancy rate was ~ 14% if progesterone < 1.11 ng/ml and ~6% if progesterone ≥ 1.11 ng/ml

Ongoing pregnancy rates in intrauterine insemination are affected by late follicular-phase progesterone levels

Antonio Requena, M.D.,[a] María Cruz, Ph.D.,[a] Alberto Pacheco, Ph.D.,[a] and Juan Antonio García-Velasco, M.D.[a,b]

[a] Department of Reproductive Medicine, Instituto Valenciano de Infertilidad Madrid; and [b] Departments of Nursing, Gynecology and Obstetrics, Pediatrics, and Psychiatry, Faculty of Health Sciences, Rey Juan Carlos University, Madrid, Spain

Background

- Prospective study including 460 couples

- 22% of cycles had progesterone >1 ng/mL

- Live birth rate:
  - progesterone < 1.0 ng/ml: 22.6%   progesterone ≥ 1.0 ng/mL: 7.9%
  - progesterone <1.5 ng/mL: 20.8%   progesterone ≥1.5 ng/mL: 6.4%

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

The impact of premature progesterone rise on the outcome of intrauterine insemination cycles with controlled ovarian hyperstimulation in unexplained infertility

Mehmet Firat Mutlu [a,*], Mehmet Erdem [b], Ahmet Erdem [b], Ilknur Mutlu [c], Ismail Guler [b], Erhan Demirdağ [d]

[a] Department of Obstetrics & Gynecology, Yuksek Ihtisas University Faculty of Medicine, Ankara, Turkey
[b] Department of Obstetrics & Gynecology, Gazi University Faculty of Medicine, Ankara, Turkey
[c] IVF Unit, Novaart IVF and Women Health Center, Ankara, Turkey
[d] Department of Obstetrics & Gynecology, Etlik Zubeyde Hanım Women's Health Education and Research Hospital, Ankara, Turkey

Objective

To determine the impact of an elevated progesterone level on the day of hCG trigger on clinical pregnancy and live birth rates in OS-IUI cycles for unexplained infertility.

Hypothesis: Patients with elevated progesterone on day of hCG trigger will have decreased ongoing pregnancy and live birth rates

- Secondary analysis of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) trial from the Reproductive Medicine Network (RMN) (Diamond et al, *NEJM*, 2015)

- Multicenter, prospective trial evaluating rate of multiple gestation and live birth rate among those receiving ovarian stimulation and IUI
  - n=900 couples
  - clomiphene (n=300), letrozole (n=299), gonadotropins (n=301)
  - Up to 4 cycles with IUI

Materials and Methods

- Study population:
  - Between 18 and 40 years old with regular menses, normal uterine cavity, with at least one patent fallopian tube and male partner with at least 5 million total motile sperm in sample

  - Randomized to treatment with clomiphene, letrozole, or gonadotropins

  - Trigger with 10,000 IU of hCG followed by IUI

- 2,121 cycles had serum available from the day of hCG trigger. Samples were obtained and analyzed for serum progesterone levels in duplicate.

  – Those with progesterone >3 ng/mL (62 cycles) were excluded→ **2,059** cycles for analysis in 823 couples

- Risk ratios (RR) and 95% confidence intervals (CI) were calculated for the outcomes of clinical pregnancy and live birth using the generalized estimating equations method to estimate cluster-weighted modified Poisson regression models

- Progesterone level was evaluated by:

Quartiles

- Q1 ≤ 0.520 ng/mL

- Q2 0.521- 0.765 ng/mL

- Q3 0.766-1.140 ng/mL

- Q4 ≥ 1.14 ng/mL

Cutpoints

- ≥ 1.1 vs < 1.1 ng/mL

- ≥ 1.5 vs < 1.5 ng/mL

- ≥ 2.0 vs < 2.0 ng/mL

- Covariates examined included
  - age (continuous)
  - treatment group (clomiphene, letrozole, gonadotropin)
  - race/ethnicity (White, Black, Hispanic, Other)
  - parity (0, ≥1)
  - duration of infertility (continuous)
  - body mass index (normal, overweight and obese)
  - number of follicles greater than 16mm (one, two, three, four or more)
 - serum anti-Müllerian hormone (continuous)

RESULTS

Table I. Baseline characteristics of 823 patients undergoing intrauterine insemination by live birth outcome

	Live Birth (n= 183)	No Live Birth (n= 640)	
	Median (IQR)	Median (IQR)	p[a]
Age (years)	31.0 (6.0)	32.0 (7.0)	0.02	←
Duration of infertility (months)	24.0 (21.0)	24.0 (30.0)	<0.0001	←
BMI	24.9 (8.9)	25.0 (8.0)	0.71
	n (%)	n (%)	p[b]
Race/Ethnicity			0.35
Non-Hispanic White	140 (76.5)	457 (71.4)	
Non-Hispanic Black	9 (4.9)	56 (8.8)	
Hispanic	18 (9.8)	67 (10.5)	
Other	16 (8.7)	60 (9.4)	
History of Pregnancy Loss			0.27
Yes	45 (24.6)	133 (20.8)	
No	138 (75.4)	507 (79.2)	
History of Live Birth			0.68
Yes	38 (20.8)	124 (19.4)	
No	145 (79.2)	516 (80.6)	
Treatment			0.005	←
Clomiphene	55 (30.0)	219 (34.2)	
Letrozole	49 (26.8)	225 (35.2)	
Gonadotropins	79 (43.2)	196 (30.6)	
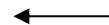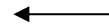
Abbreviations: BMI=body mass index; IQR = interquartile range
[a] Wilcoxon Rank Sum Test, [b]Chi-square test
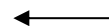
Results

- Mean P4 0.92 ng/mL (SD 0.57 ng/mL)

P4 Quartiles:	Clinical Pregnancy n (%)	RR Adjusted (95% CI)
Q1	101 (19.61)	Ref
Q2	94 (18.18)	**0.79** (0.60, 1.04)
Q3	105 (20.31)	**0.89** (0.68, 1.16)
Q4	111 (21.76)	**1.03** (0.80, 1.34)

Results

- Live birth outcomes

P4 Quartiles:	Live Birth n (%)	Adjusted RR (95% CI)
Q1	47 (9.13)	Ref
Q2	36 (6.96)	**0.68** (0.45, 1.05)
Q3	46 (8.90)	**0.86** (0.58, 1.27)
Q4	54 (10.59)	**1.08** (0.75, 1.56)

Results

Progesterone Cutpoints (ng/mL)	Clinical Pregnancy Adjusted RR (95% CI)[a,b]	Live Birth Adjusted RR (95% CI)[a,b]
P4 ≥1.1	1.09 (0.89, 1.34)	1.15 (0.85, 1.55)
P4 ≥ 1.5	0.89 (0.68, 1.16)	0.92 (0.62, 1.37)
P4 ≥ 2.0	0.72 (0.45, 1.14)	0.92 (0.51, 1.66)

[a] Risk ratio (RR) and 95% confidence intervals (CI) were calculated using generalized estimating equations method to estimate cluster-weighted modified Poisson regression models with robust standard errors

[b] Model adjusted for treatment group

Conclusion

- Elevated progesterone level on day of hCG trigger is not associated with significant decrease in clinical pregnancy or live birth in OS-IUI cycles for unexplained infertility

- **Strengths**
  - Large, multi-centered trial including 2,059 cycles
  - Well characterized patient population

- **Limitations**
  - Inherently low pregnancy and live birth from this type of treatment
  - Study not powered to address this question

Acknowledgements

Reproductive Medicine Network and the NICHD for their support of this secondary analysis.

Co-authors:

- Sarah Z. Gavrizi, M.D.
- Zak Anderson, M.D.
- Jennifer Peck, Ph.D.
- Michael P. Diamond, M.D.
- Karl R. Hansen, M.D., Ph.D.

Questions?

References

1. Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertil Steril 2020;113:305-322.

2. Andersen AG, Als-Nielsen B, Hornnes PJ, Franch Andersen L. Time interval from human chorionic gonadotrophin (HCG) injection to follicular rupture. Human reproduction (Oxford, England). 1995 Dec;10(12):3202-5.

3. Cantineau AE, Janssen MJ, Cohlen BJ, Allersma T. Synchronised approach for intrauterine insemination in subfertile couples. The Cochrane database of systematic reviews. 2014 Dec 21(12):Cd006942.

4. Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J, Zhu G. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. Fertil Steril. 2012 Jun;97(6):1321-7.e1-4.

5. Ochsenkühn R, Arzberger A, von Schönfeldt V, Gallwas J, Rogenhofer N, Crispin A, Thaler CJ, Noss U. Subtle progesterone rise on the day of human chorionic gonadotropin administration is associated with lower live birth rates in women undergoing assisted reproductive technology: a retrospective study with 2,555 fresh embryo transfers. Fertil Steril. 2012 Aug;98(2):347-54.

6. Venetis CA, Kolibianakis EM, Bosdou JK, Tarlatzis BC. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. Hum Reprod Update. 2013 Sep-Oct;19(5):433-57.

7. Cantineau AE, Cohlen BJ. The prevalence and influence of luteinizing hormone surges in stimulated cycles combined with intrauterine insemination during a prospective cohort study. Fertil Steril. 2007 Jul;88(1):107-12.

8. Requena A, Cruz M, Pacheco A, Garcia-Velasco JA. Ongoing pregnancy rates in intrauterine insemination are affected by late follicular-phase progesterone levels. Fertil Steril. 2015 Oct;104(4):879-83.

9. Mutlu MF, Erdem M, Erdem A, Mutlu I, Guler I, Demirdag E. The impact of premature progesterone rise on the outcome of intrauterine insemination cycles with controlled ovarian hyperstimulation in unexplained infertility. Eur J Obstet Gynecol Reprod Biol. 2016 Aug;203:44-8.

10. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. The New England journal of medicine. 2015 Sep 24;373(13):1230-40.