

# Does PCOS Compromise the oocyte and embryo quality or the endometrium?



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# Disclosures

Consultant: Bayer, Ogeda (Euroscreen),  
Kindex, Millendo, Abbvie, Fractyl, NIH

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Settlement Funds PA

Yes PCOS (or our iatrogenic practices) lead to lesser oocyte and endometrial quality in women with PCOS

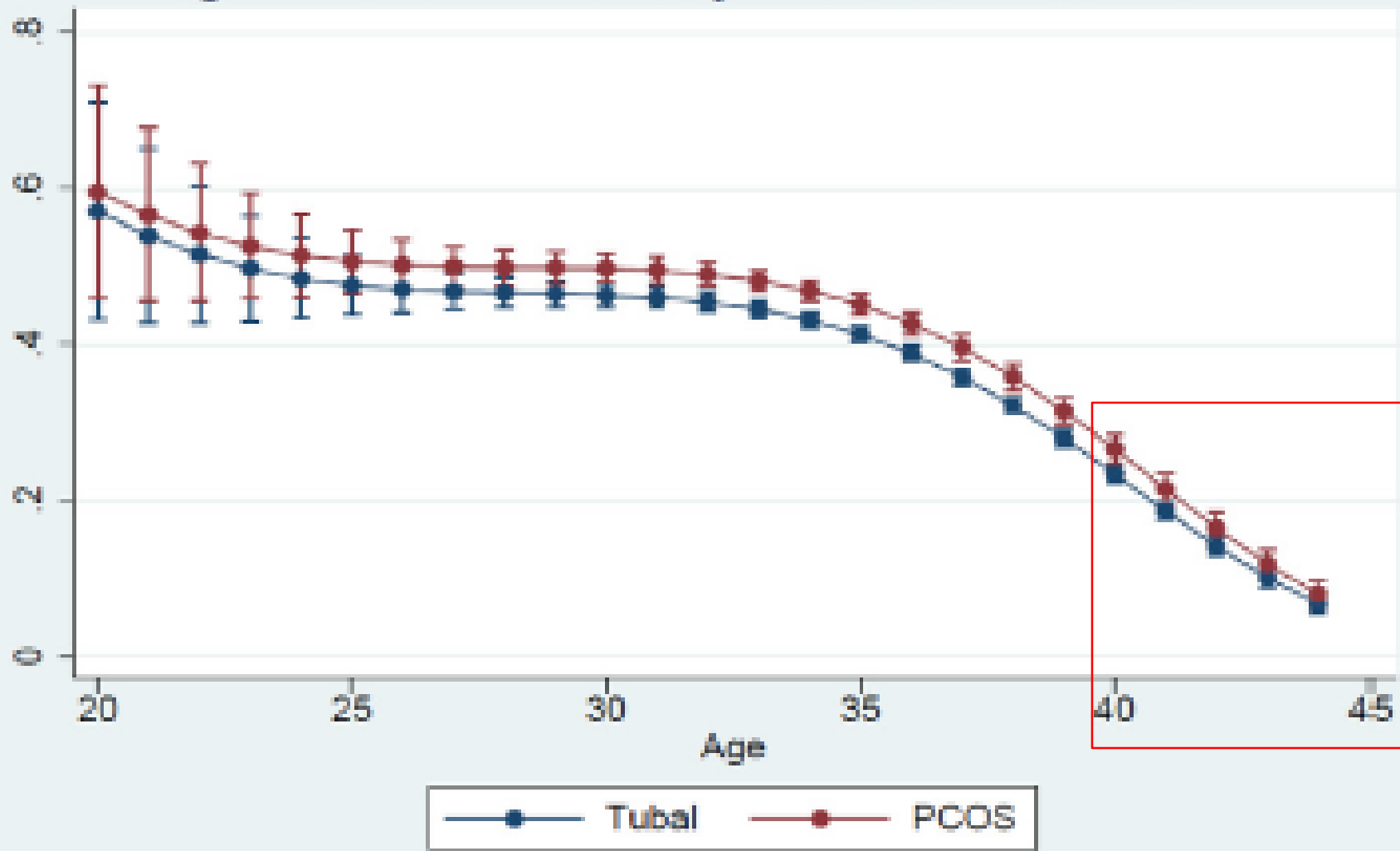
**It may not matter!**

# SART Data: PCOS with Better IVF Outcomes than Tubal Factor

Category	PCOS	Tubal	PCOS vs Tubal OR (95% CI)
Mean # Oocytes	16.4	12.8	1.27, (1.25-1.29)
Clinical Pregnancy Rate	43%	36%	1.32, (1.27-1.38)
Live Birth Rate	35%	29%	1.30, (1.24-1.35)

# Equivalent Live Birth Rates for each year after Age 40 in Women with PCOS vs Tubal Factor

Marginal Predicted Probability of Live Birth with 95% CIs





## Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement<sup>†‡</sup>

The Harbin Consensus Conference Workshop Group  
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ASRM PAGES

All adverse events in mother and fetus should be collected and reported through live birth

The PCOS Society (India) &  
The Androgen Excess & PCOS Society (International)

All Infertility Trials should report on Live Births and this is the preferable primary outcome

## Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement

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Department of Obstetrics and Gynecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China; and Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, Pennsylvania

What iatrogenic practices  
in women with PCOS  
may adversely affect  
pregnancy rates?

**Superovulation during IVF**

# Preventing OHSS in PCOS

Risk Factor	Likelihood in PCOS
Youth	Yes
Thin	No
High Antral Follicle Count/AMH level	Yes
Excess Dose of Gonadotropin	Possible



# Evidence Based Medicine: OHSS/Gonadotropin Therapy in PCOS

**FSH only preparations significantly lower the risk for OHSS compared to hMG preparations: (OR 0.20, 95% CI 0.08- 0.46)**

**The concomitant use of a GnRHa with gonadotropin therapy increases the risk for OHSS (OR 3.15, 95% CI 1.46-6.70)**

- Nugent D et al. Cochrane Database of Systematic Reviews. Issue 4, 2000.

Hypothesis: Elective “Freeze-all”  
Embryos in Women with PCOS  
will lower Iatrogenic OHSS rates  
and improve Live Birth Rates over  
Elective Fresh Embryo Transfer

# Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Chen ZJ et al, NEJM, 2016

1900 Women provided consent

392 Were excluded

1508 Underwent randomization

**1508**

**Randomized**

**About 15%  
Crossover/  
Dropout**

762 Were assigned to undergo fresh-embryo transfer

746 Were assigned to undergo frozen-embryo transfer

82 Discontinued participation or had protocol violation  
14 Did not complete embryo transfer  
8 Received fresh-blastocyst transfer  
57 Received frozen-embryo transfer  
34 Received frozen-blastocyst transfer  
23 Received day 3 frozen-embryo transfer  
3 Did not fulfill eligibility criteria

680 Complied with protocol

1 Was lost to follow-up

320 Delivered live-born infants

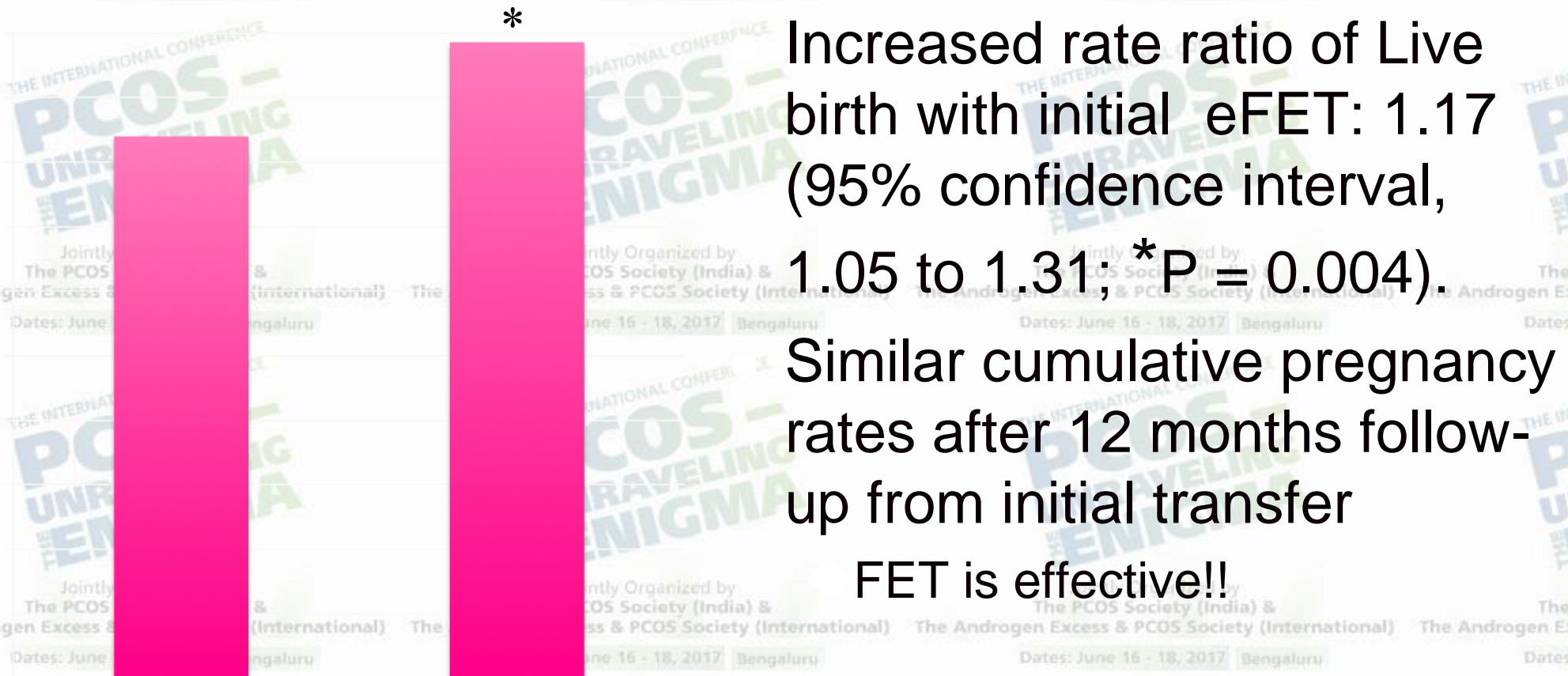
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23 Received frozen-blastocyst transfer  
44 Received fresh-embryo transfer  
4 Received fresh-blastocyst transfer  
40 Received day 3 fresh-embryo transfer  
1 Did not fulfill eligibility criteria

658 Complied with protocol

4 Were lost to follow-up

368 Delivered live-born infants

# Improved Live Birth Rates with elective FET in PCOS



Increased rate ratio of Live birth with initial eFET: 1.17 (95% confidence interval, 1.05 to 1.31; \*P = 0.004).

Similar cumulative pregnancy rates after 12 months follow-up from initial transfer

FET is effective!!

**Elective FET in women with PCOS may improve live birth rates largely through decreased pregnancy loss**

**Mixed risk/benefit ratio**



# Mixed Risk/Benefit of Frozen vs Fresh Embryo Transfer

## FET Risk

Higher rate of preeclampsia (4.4% vs. 1.4%)

Rate ratio of 3.12 (95% CI, 1.26 to 7.73);  $P = 0.009$

All stillbirths ( $N = 2$ ) and neonatal deaths ( $N = 5$ ) were in the FET group

## FET Benefit

Lower rate of pregnancy loss (22.0% vs 32.7%)

Rate ratio of 0.67 (95% CI, 0.54 to 0.83;  $P < 0.001$ )

Marked reduction in OHSS (1.3% vs. 7.1%)

Rate ratio of 0.19 (95% CI, 0.10 to 0.37);  $P < 0.001$

Increased Birth Weight

162 gm increase (95% CI 56 to 267 gms,  $P < .005$ )

# Spectrum of Implantation for an Euploid Embryo

More likely after  
Fresh Transfer

More likely after  
Frozen Transfer

**Failed**

**Poor**

**Successful**

**Excessive**

**No  
Pregnancy**

**Conception  
but pregnancy  
loss**

**Live  
birth**

**Pre-  
eclampsia**

Why is an FET better than a fresh transfer?

Because it avoids superphysiologic hormone exposure during the cycle, and allows for an optimal endometrium

# Why is Letrozole better than Clomiphene for ovulation induction in PCOS?

Aromatase inhibition achieves a more favorable ovulation/conception/implantation environment

Lower estradiol, higher progesterone after ovulation

Endometrium is relatively thinner with letrozole

Probably not an important predictive parameter

Relatively Speaking: Clomiphene superovulates the endometrium and letrozole ovulates it.

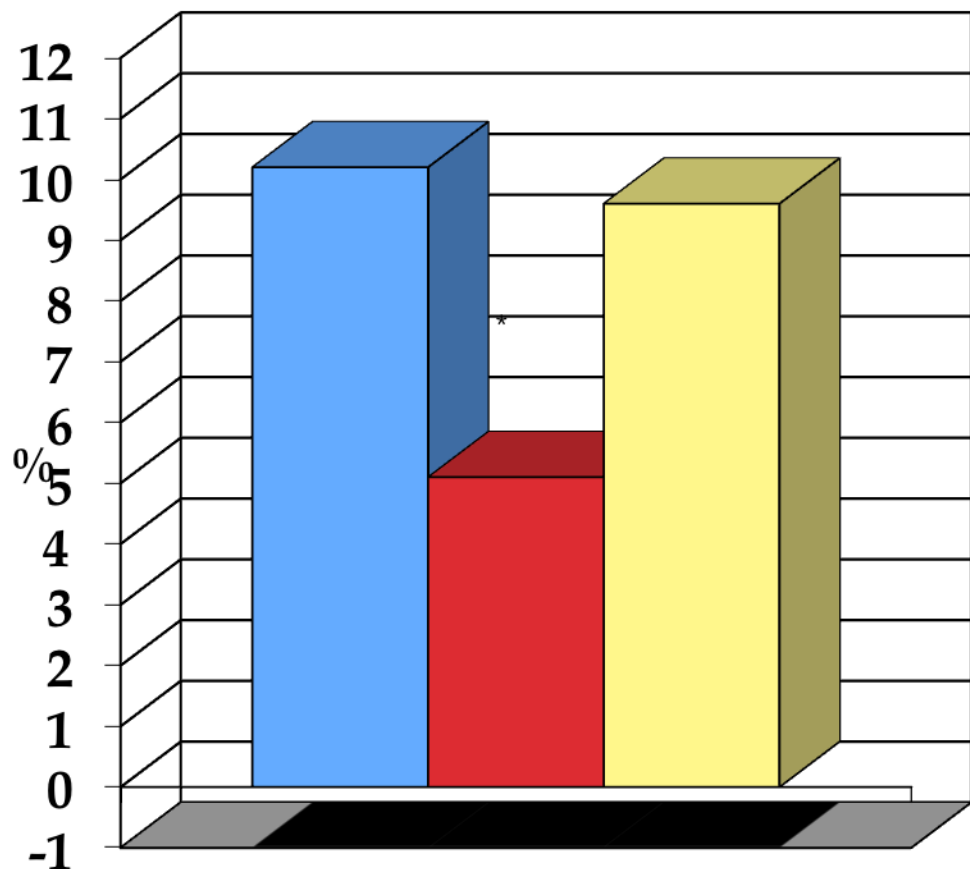
# Significant Change in Key Parameters During Study mean (S.D.) [25%, 75% percentiles]

Category	Change in Measure from Baseline to Last Midluteal Visit	Clomiphene	Letrozole	P Value*
Ultrasound	Antral follicle count (both ovaries)	-3 (23) [-12, 8]	<b>-5 (22)</b> [-16, 5]	0.036
	Endometrial thickness: sagittal plane (mm)	<b>3 (4)</b> [1, 6]	2 (4) [0, 5]	<0.001
Serum	Estradiol (pg/mL)	<b>53 (108)</b> [-2, 92]	9 (60) [-21, 33]	<0.001
	Progesterone (ng/dL)	11 (22) [-0.1, 15]	<b>13 (21)</b> [0.1, 18]	<0.001

Legro et al, NEJM, 2014

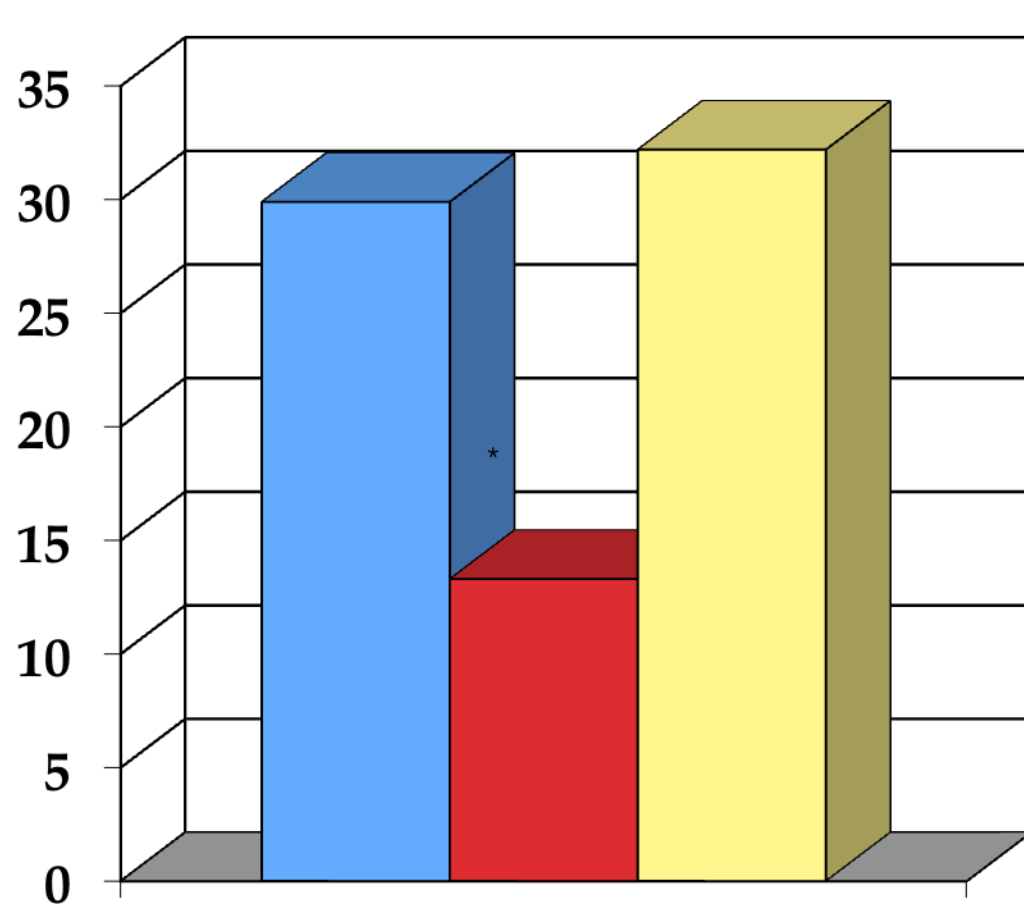


# Fecundity per Ovulation Better with Clomiphene than Metformin



Live Birth/Ovulation

■ CC ■ Met ■ Comb



Live Birth/Ovulated Pt

■ CC ■ Met ■ Comb

\* Significant compared to baseline

Legro et al, NEJM, 2007

# Fecundity per Ovulated Patient with Clomiphene by Pretreatments

Live Data

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

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$P = .04$   
vs OCP



$P = .08$   
vs OCP



**All ovulations are  
not alike!!**

**Ovulation is a surrogate outcome  
for anovulatory infertility**

**Does pretreatment with OCP to start an IVF cycle adversely effect implantation in a fresh embryo transfer?**

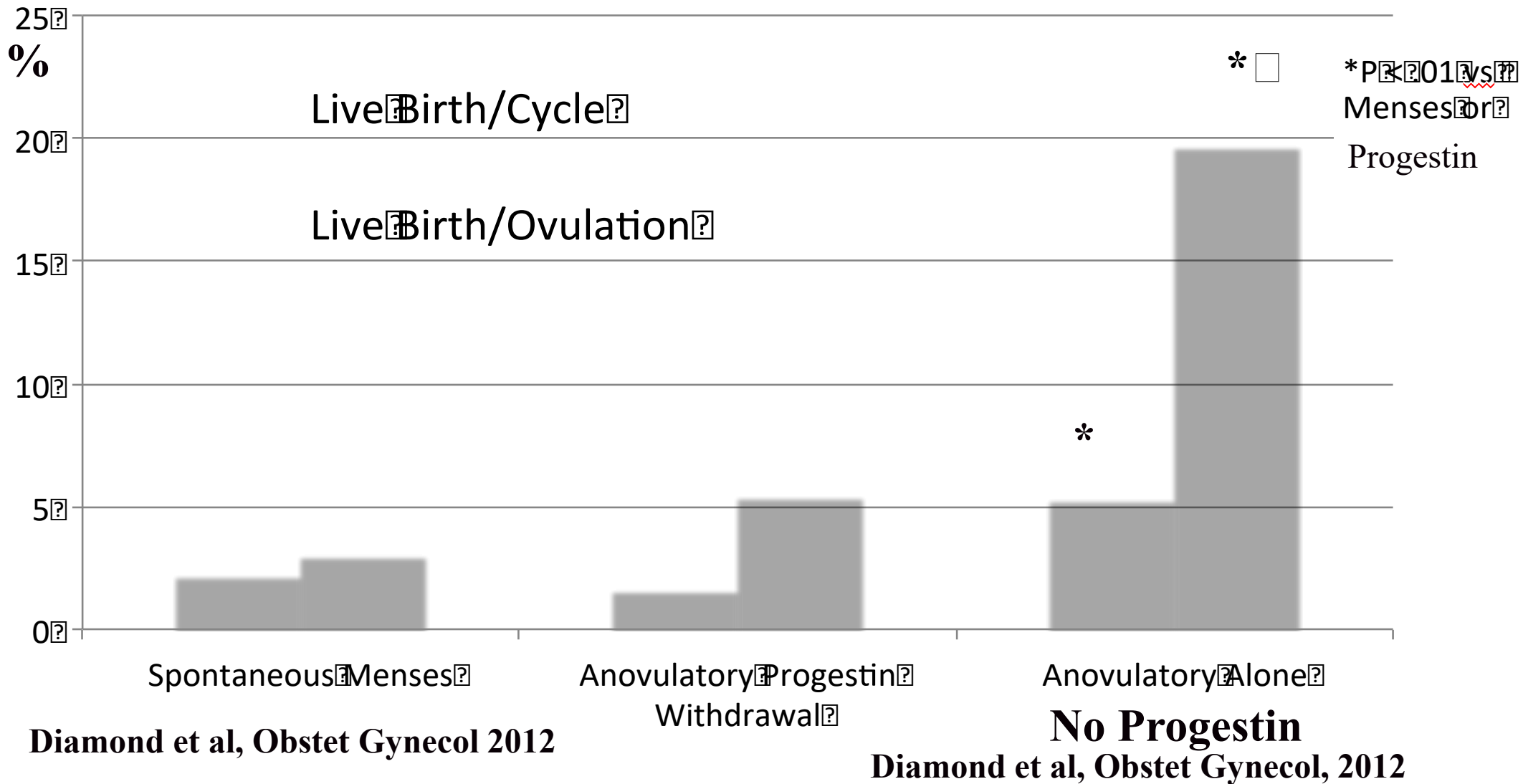
# Effect of Type of IVF Cycle Initiation on Live Birth Rate in PCOS (N =1508)

	Fresh Transfer Live Birth Rate	FET Live Birth Rate	Rate Ratio (95% CI)
Spontaneous Menses	NS	NS	NS
Progestin-Induced	NS	NS	NS
OCP-Induced	36%	49%	0.75 (0.61 to 0.92 )

Wei et al, Hum Reprod, 2017



# Does Iatrogenic Progestin after an Anovulatory Cycle Impair Subsequent Fecundity?



Summary: Pretreatment with OCP prior to ovulation induction likely does not improve outcomes

Routine withdrawal with progestin prior to ovulation induction cycles also likely does not improve outcomes

# Predictive Factors for Live Birth in PCOS

Younger age

Shorter Duration of attempting pregnancy

Lower BMI

Lower Free Androgen Index/Higher SHBG

No Smoking

**Note: No LH, LH/FSH, or AMH levels, No Endometrial Thickness or Morphology**



# *Steering Committee of the PPCOS II Trial*





OWL-PCOS: OCP vs Weight Loss for  
Pregnancy in Polycystic Ovary  
Syndrome (R01HD056510)





# Meeting of the FREFRO Steering Committee

多囊卵巢综合征治疗RCT培训



2013/12/15



# Funding/Collaborators

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National Cooperative  
Medicine

Andrea Dunair, MD

The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

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**Final and deepest thanks to all who  
volunteered for the studies!!**

