Luteal phase rescue after GnRHa triggering – Progesterone and Estradiol

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The Center for Advanced Reproductive Services

Disclaimer

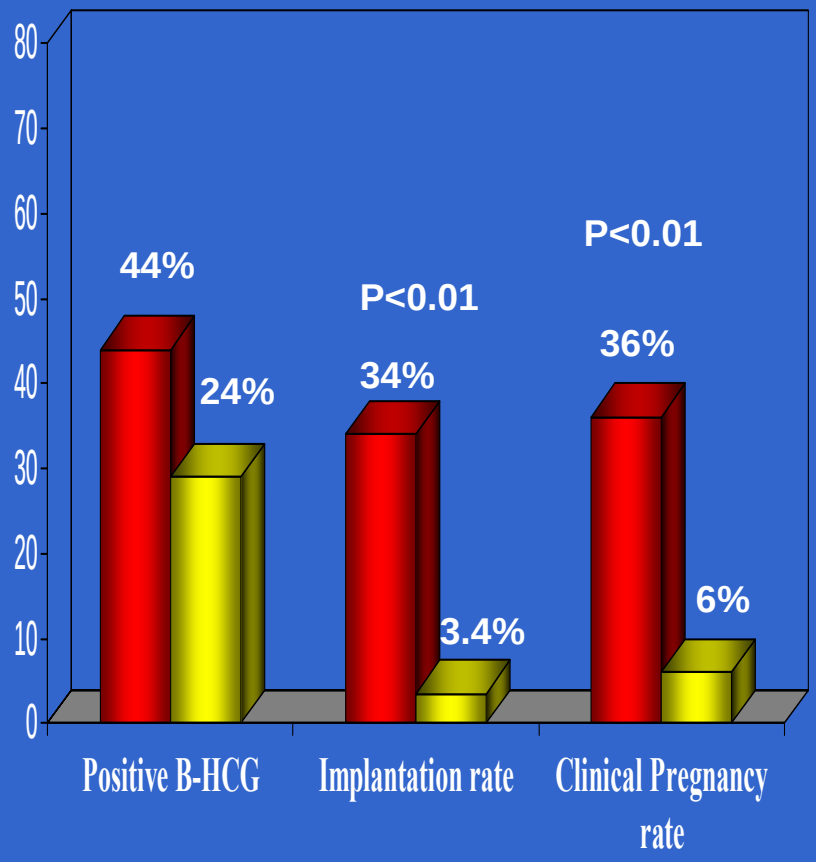
- **Fertility Speaker Bureau**
  - Merck Pharmaceuticals

Introduction

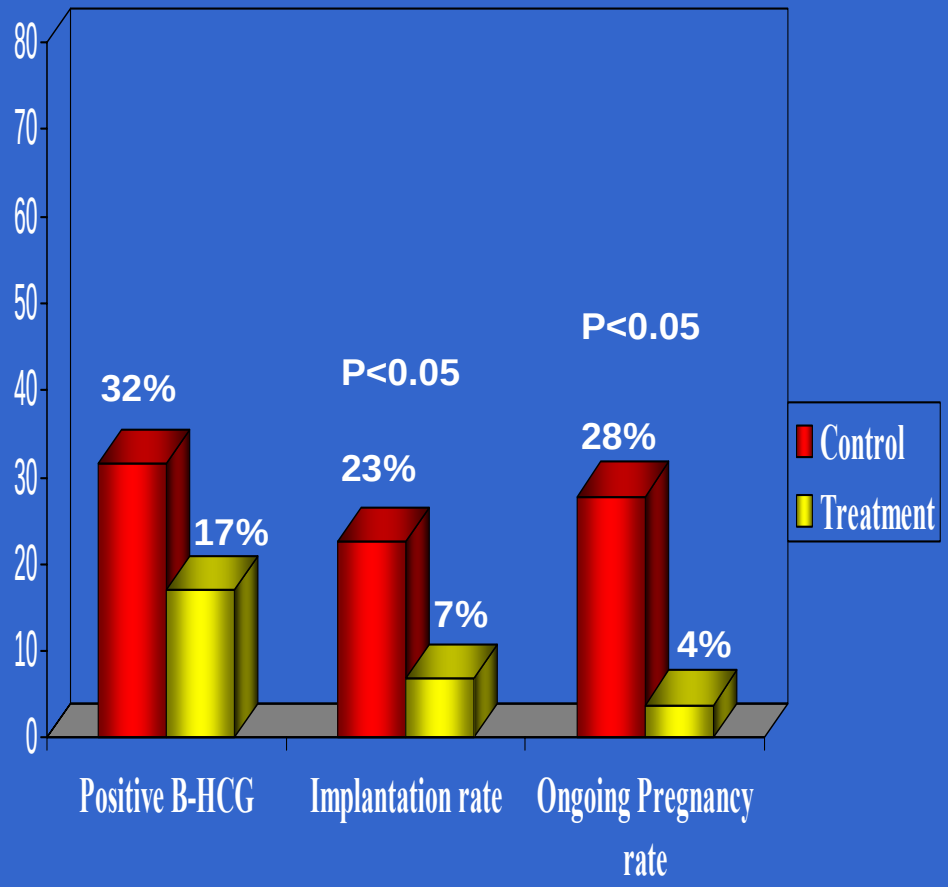
- GnRH agonist is effective in the prevention of OHSS
- Administration of a single dose of GnRH agonist
  - endogenous LH surge with short half-life
  - defective corpus luteum development
- Potential detrimental effect on endometrial receptivity

Consequence of CL dysfunction – Low OPR

Humaidan et al, 2005



Kolibianakis et al, 2005



Potential reasons for poor outcome after GnRH agonist trigger - Limitations

- Differences in study design & study population
- Differences in type and dose of GnRH agonist used
- Type and dose of luteal phase supplementation
- Duration of luteal phase supplementation

Type and dose of GnRH agonist

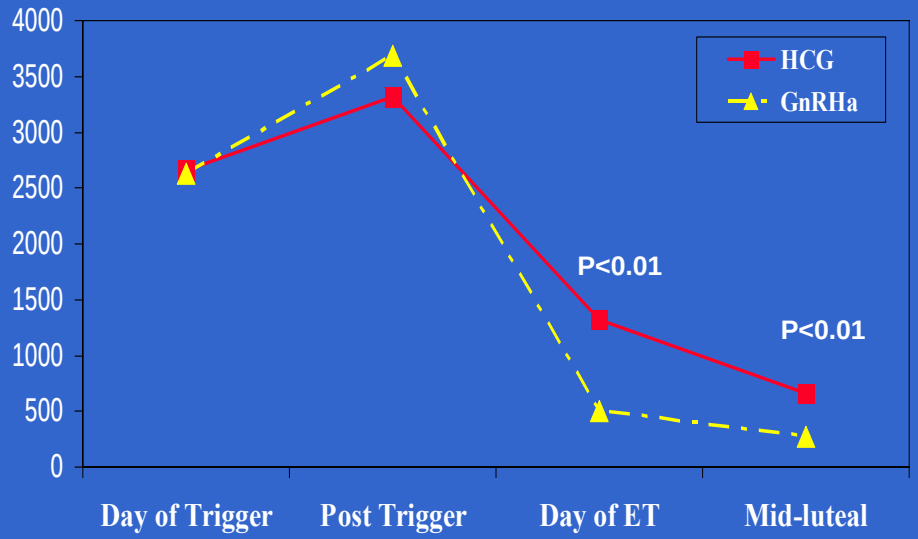
GnRH agonist	Authors	Study design	Dose	Study population
Leuprolide	Engmann et al	Retrospective	1mg	High risk
	Engmann et al	RCT	1mg	High risk
	Shapiro et al	Retrospective	4mg	High Risk
	Castillo et al	Retrospective	1.5mg	High risk
	Fauser et al	RCT	0.5mg	Low risk
Triptorelin	Itskovitz et al	Rétrospective	0.2mg	High risk
	Fauser et al	RCT	0.2mg	Low risk
	Beckers et al	RCT	0.2mg	Low Risk
	Babayof et al	RCT	0.2mg	High Risk
	Kolibianakis et al	RCT	0.2mg	Low risk
Buserelin	Humaidan et al	RCT	0.5mg	Low risk

Potential reasons for low conception rates

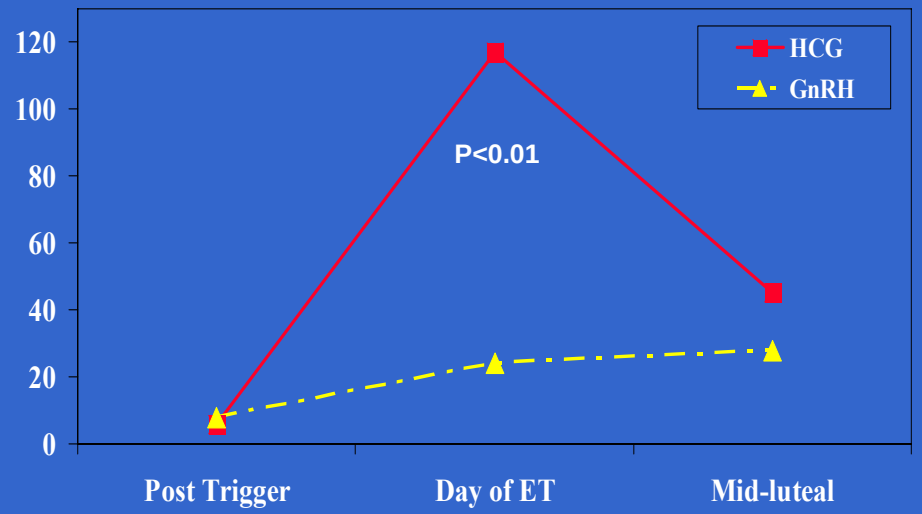
- Adverse effect on oocyte or embryo quality
- Defective corpus luteum formation
- Early corpus luteum demise
- Direct effect on endometrial receptivity

Evidence supporting corpus luteum dysfunction

Low luteal phase serum E_2/P Profile



Serum E_2



Serum P

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Engmann et al, RBM online, 2006

Evidence supporting corpus luteum dysfunction

- Beckers et al (2003) evaluated the non-supplemented luteal phase of 40 patients who underwent GnRH antagonist cycles with trigger of ovulation using GnRHa, recombinant hCG, recombinant LH
- Worst luteal phase characteristics was noted for patients triggered with GnRH agonist
- Median area under the curve for P was lower in the GnRHa group compared with the hCG groups
- Median duration of the luteal phase was 4days shorter in the GnRHa group compared with the hCG group (9days versus 13 days)

Beckers et al, JCEM, 2003

Evidence supporting luteal phase dysfunction

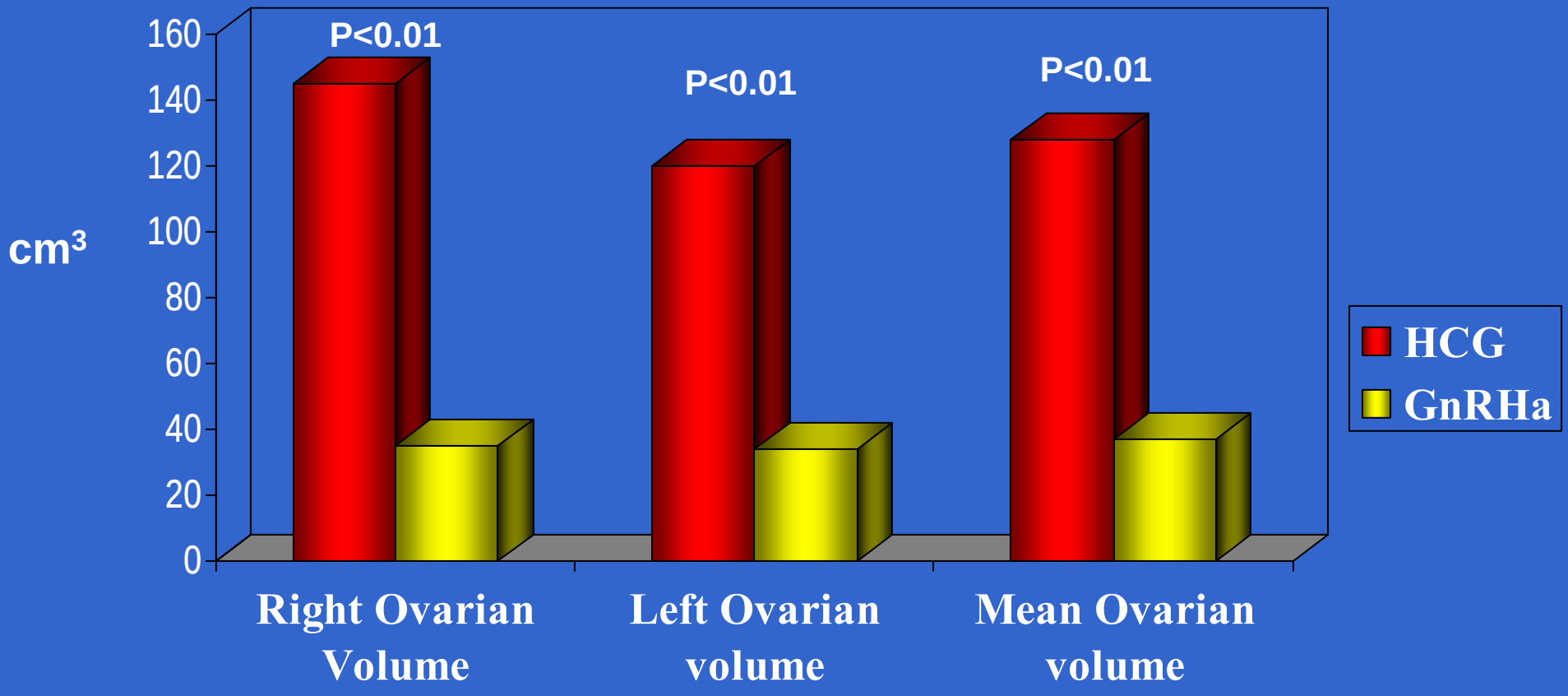
- Triggering final oocyte maturation with GnRHa (triptorelin 0.2 mg) dramatically decreases luteal levels of inhibin A and pro-αC .

- This decrease reflects significant inhibition of CL function.

Nevo et al, Fertil Steril 2003

Evidence supporting corpus luteum dysfunction

Smaller mid-luteal ovarian volume



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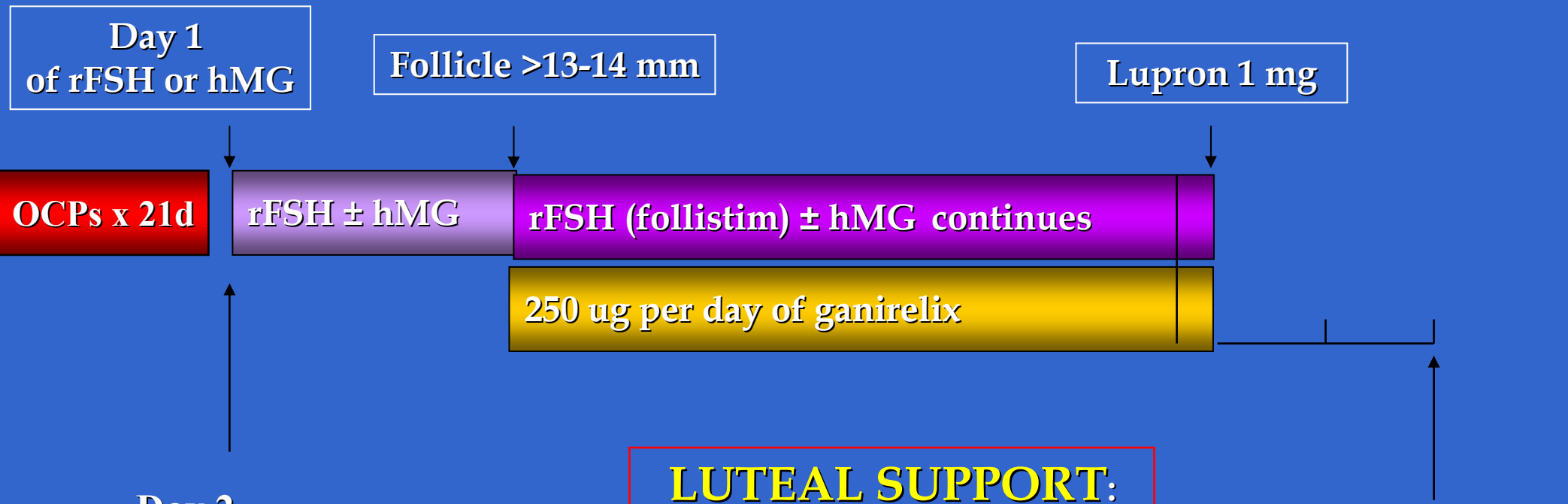
Engmann et al, Fertil Steril 2008

Estradiol & Progesterone supplementation

Reference	n	Ongoing Pregnancy rate	Luteal Phase Support
Humaidan, 2005	55	6%	90mg vaginal P and 4mg oral E2/day, *until the day of the pregnancy test*.
Kolibianakis , 2005	50	4%	Center 1: 600 mg micronized vaginal P and 4mg oral E2/day until 7 weeks Center 2: vaginal + IM P until 7 weeks
Fauser , 2002	17 15	18% (triptoreline) 20% (leuprolide)	IM P 50 mg for at least 2 weeks
Babayof , 2006	15	6.6%	IM P 50 mg , oral E2 4 mg only if E2 levels < 200 pmol/l
Engmann , 2008	30	53.3%	IM P 50 mg and 0.3 mg E2 patches every other day until 10 wks and dose adjusted according to serum P and E2 levels

Lupron trigger protocol



LUTEAL SUPPORT:

E2 patches 0.1 mg X 3, qod
P4 in oil, 50 mg/day;
Continue until 10 weeks
MONITOR E2+P4 LEVELS!

Why the differences in outcome between studies?

- Choice of luteal phase estradiol supplementation
  - Patches versus oral
- Choice of luteal phase progesterone supplementation
  - IM versus vaginal
- Duration of luteal phase/early pregnancy steroid supplementation
- Strict monitoring and adjustment of steroid dose
  - Ideal levels – E2 > 200pg/mL, P4 > 20 ng/mL

GnRH agonist trigger: case presentation

Treatment Strategy: G4P2 Ht:63 Wt:152/BMI:26.92 Bld type:O Pos Allergies:NKDA Med Hx:none Surgical Hx: C/S X2; BTL

Cycle

Cycle #: 1 | Cycle Type: IVF | Status: Pregnant Ongoing | Plan: AH, Cryo, Transfer 2 MC, ICSI/NO, ICSI/Optional | IVF Undec:

Age: 31.8 | Stim Type: Antagonist | Prim Diag: Tubal Occlusion/Bilat Lig | Diags | Fin Stat: Uncleared

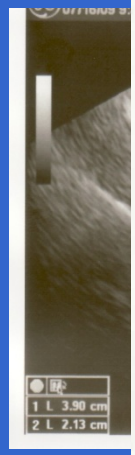
TOH: 11:45 PM | Don Sp: None | Sec Diag: | Start Dos: FSH 150 | Allergy | Cp | Prim

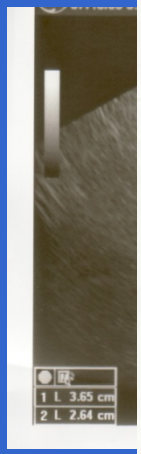
Comments: 2009-622 Possible Lupron trigger *Spainish class; Thrombocytopenia (under evaluation).CAB *Precision Rx

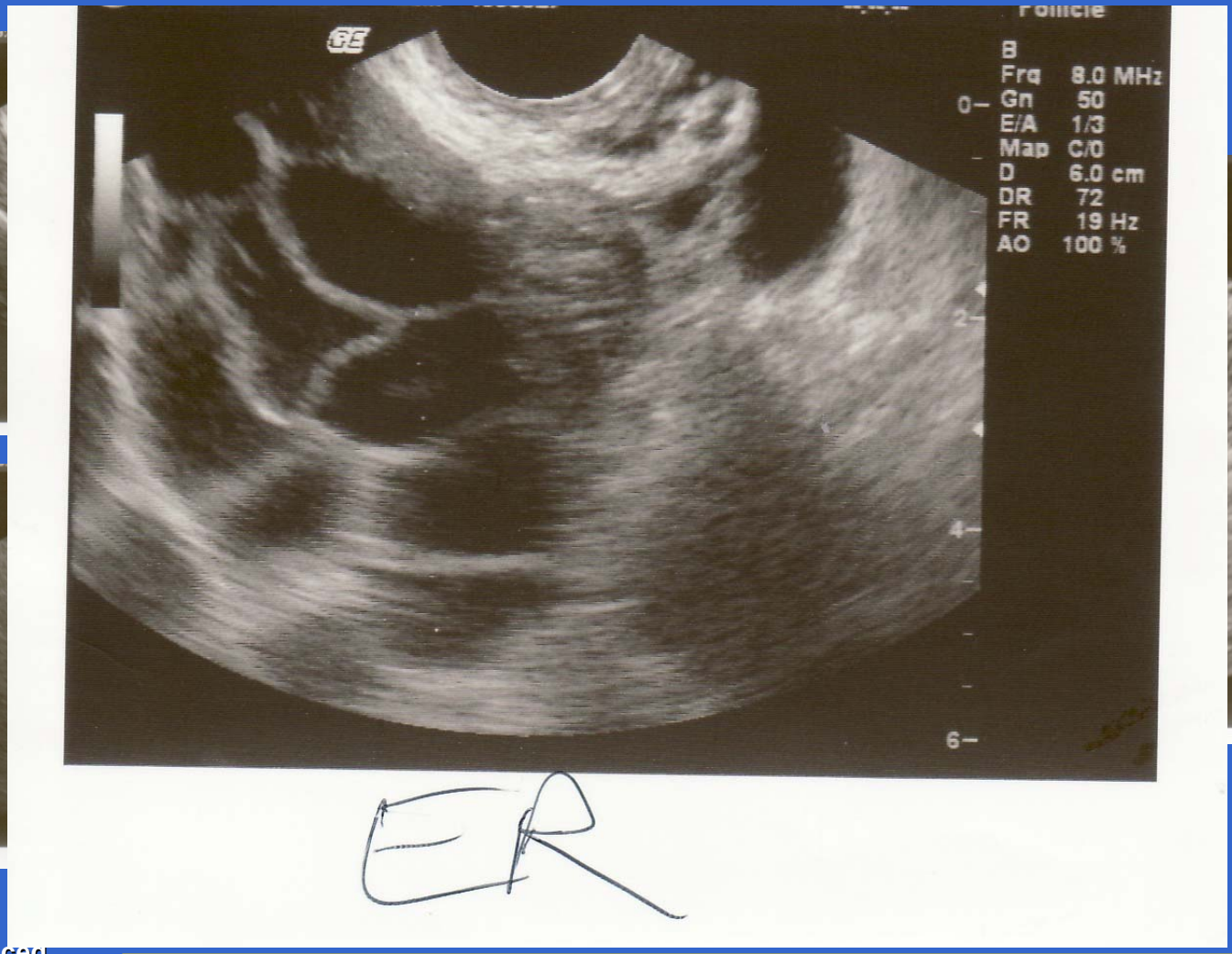
Complete: Signed off by LB on 5/24/2009

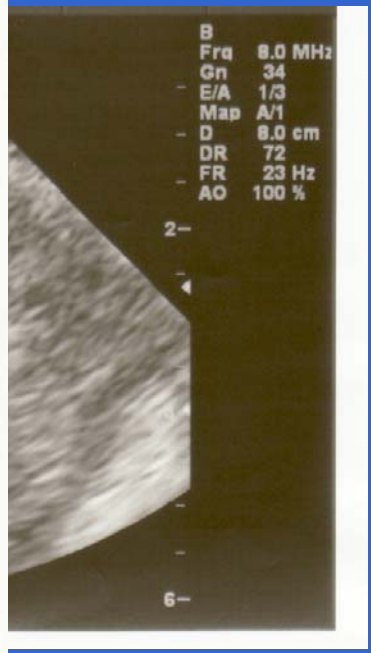
Day Info		Planned				Status				Pen G AM	Pen G PM	Lupro	Ganir	Methy	Doxy	Vivelle	Prog		Blood Work				
Day	Date	Event	Lab	Proc.	Cp	PROV	Cl By	Cl	Comments	Amt.	Amt.	Amt.	Amt.	Amt.	Amt.	Amt.	Amt.	X	E2	P4	bHCG	FSH	LH
0	06/02/09	Mns		Start	✓													1					
1	06/03/09		SU B	Gnd	✓	CB		✓	nc ovaries		150							3	20		<5	4.3	5.1
4	06/06/09		B			CB	PF	✓	Call with d		112							3	343				
7	06/09/09		SU B			CB	DD	✓	Call with d		112		250					1	1315				4.8
8	06/10/09		B			CB	DD	✓	b/w only.		112		250					1	1445				1.1
9	06/11/09		SU B			CB	DD	✓	call with dc		75		250					1	2679				2.9
10	06/12/09	Srg	SU B			CB	JT	✓	call with tri			20						1	4648				1.8
+1	06/13/09		B			CB		✓	nc									1	6051	20.			65.
+2	06/14/09			VOR	✓	LE			42 oocytes					16	100			1					
+3	06/15/09													16	100	3	50	1					
+4	06/16/09													16	100		50	1					
+5	06/17/09	Cryo	B	ET	✓	CB	DD	✓	Call: increa					16	100	3	75	1	638	18.			
+6	06/18/09																75	1					
+7	06/19/09	Cryo							1 blast fro:									1					
+8	06/20/09	Cryo							3 blasts fr									2					
+10	06/22/09		B			CB	DD	✓	pt needed							3	75	7	206	25.			
+17	06/29/09	Preg	B			CB	DR	✓	Reported r							3	75	2	513	34.	355		
+19	07/01/09		B			CB	DR	✓	Is she tole							3	75	7	370	26.	882		
+26	07/08/09		B			CB	cc	✓	5w3d; Sch							3	75	6	718	24.	14878		

Lupron trigger: case presentation









Our experience at UConn

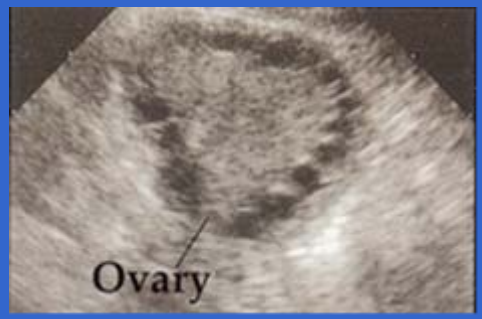
The use of GnRH agonist to induce oocyte maturation after co-treatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled Study

L Engmann, A DiLuigi, D Schmidt, J Nulsen, D Maier, C Benadiva

Engmann et al, Fertil Steril 2008

Study Design

- < 40years, FSH < 10 with
- PCOS or PCO Morphology
- Or Previous High Response



Randomization

Dual suppression OCP's & Lupron

HCG trigger

OCP's + Ganirelix

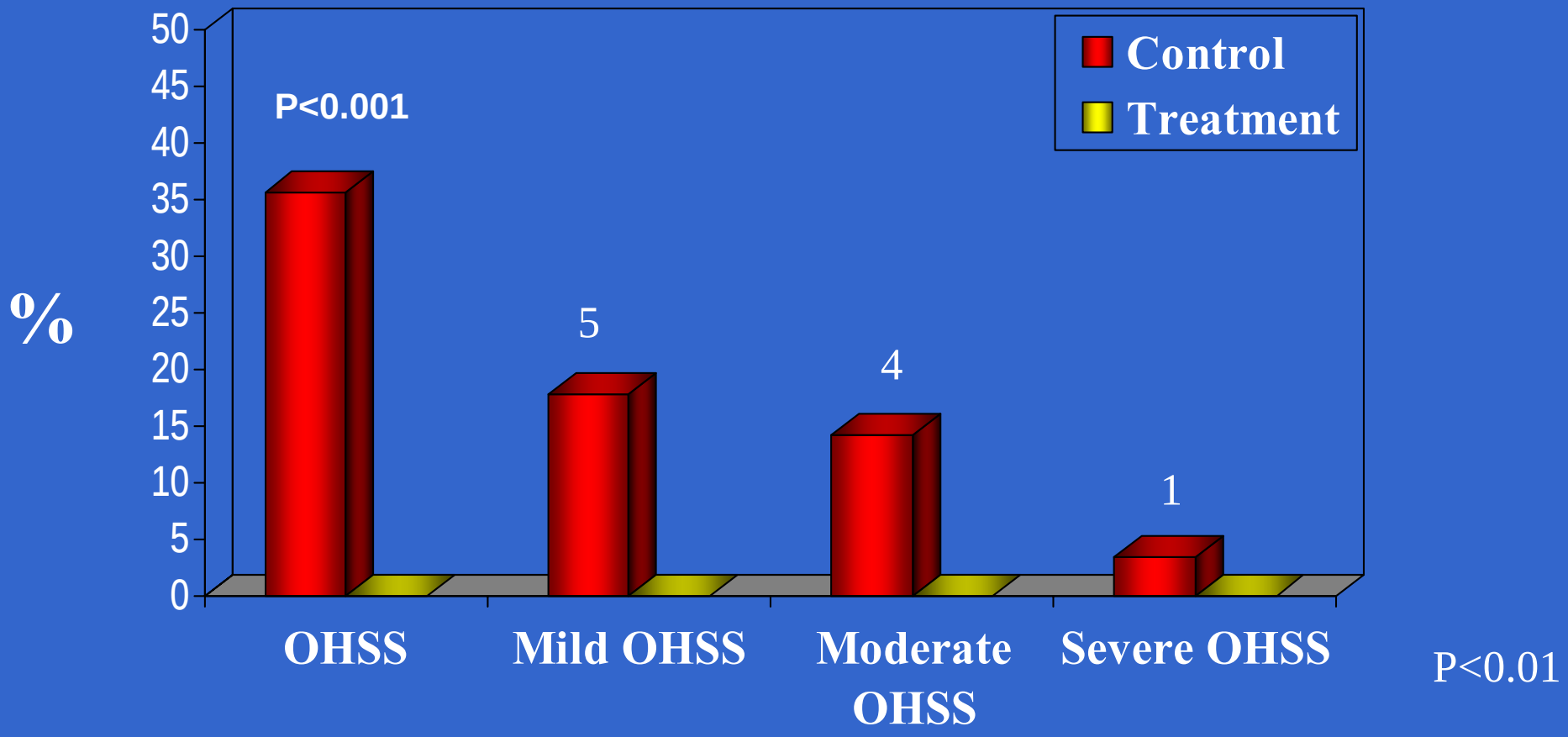
Lupron trigger

Outcomes of Ovarian Stimulation

	Study Group (n=30)	Control Group (n=29)
Days of stimulation	9.9 ± 1.7	9.6 ± 1.7
Dose of gonadotropins (IU)	1589 ± 511	1527 ± 534
# of oocytes	20.2 ± 9.9	18.8 ± 10.4
% Mature Oocytes	81.0 ± 16.3	83.8 ± 13.2
Fertilization rate (%)	71.6 ± 14.1	74.9 ± 17.3
# of embryos transferred	2.0 ± 0.2	2.2 ± 0.6
Good quality embryos (%)	80 ± 14	82 ± 16
# of embryos Frozen	3.9 ± 4.4	4.3 ± 4.7

Engmann et al, Fertil Steril 2008

Incidence of OHSS



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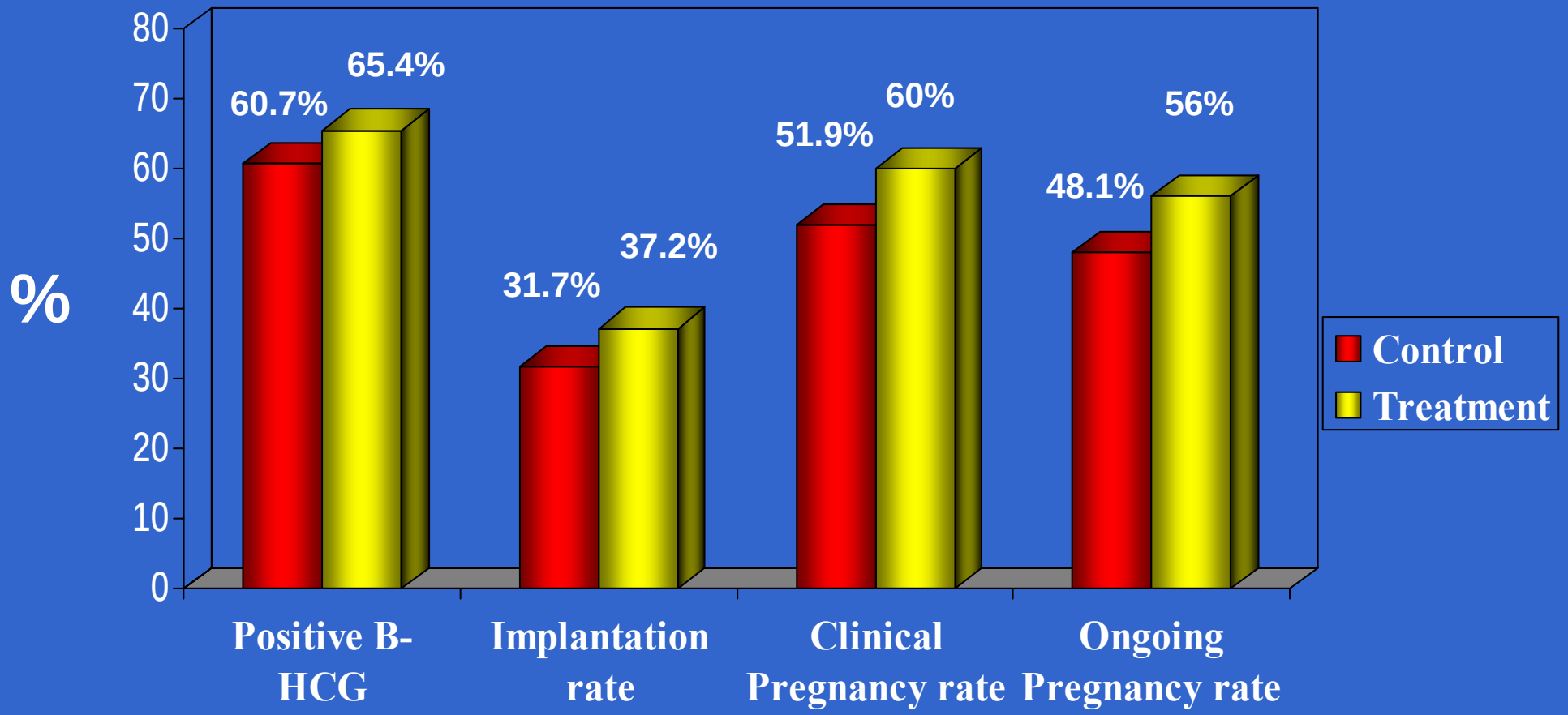
Engmann et al, Fertil Steril 2008

Cycle Outcome



Engmann et al, Fertil Steril 2008

Our Clinical Experience

2004-2009

(n = 316 at high-risk of OHSS, age < 40 years)

Kummer et al, 2010, abstract ASRM

Baseline Patient Characteristics*

	E2 < 4000 (n=247)	E2 > 4000 (n=69)
Age	32.3 ± 3.7	32.6 ± 3.9
BMI (kg/m^2)	30.7 ± 6.4	28.3 ± 7.1
Baseline E_2 (pg/mL)	40.2 ± 18.2	44.1 ± 19.0
Baseline FSH (mIU/mL)	5.6 ± 1.7	6.5 ± 1.5
Baseline LH (mIU/mL)	6.2 ± 4.1	7.1 ± 5.0

* No significant differences between groups

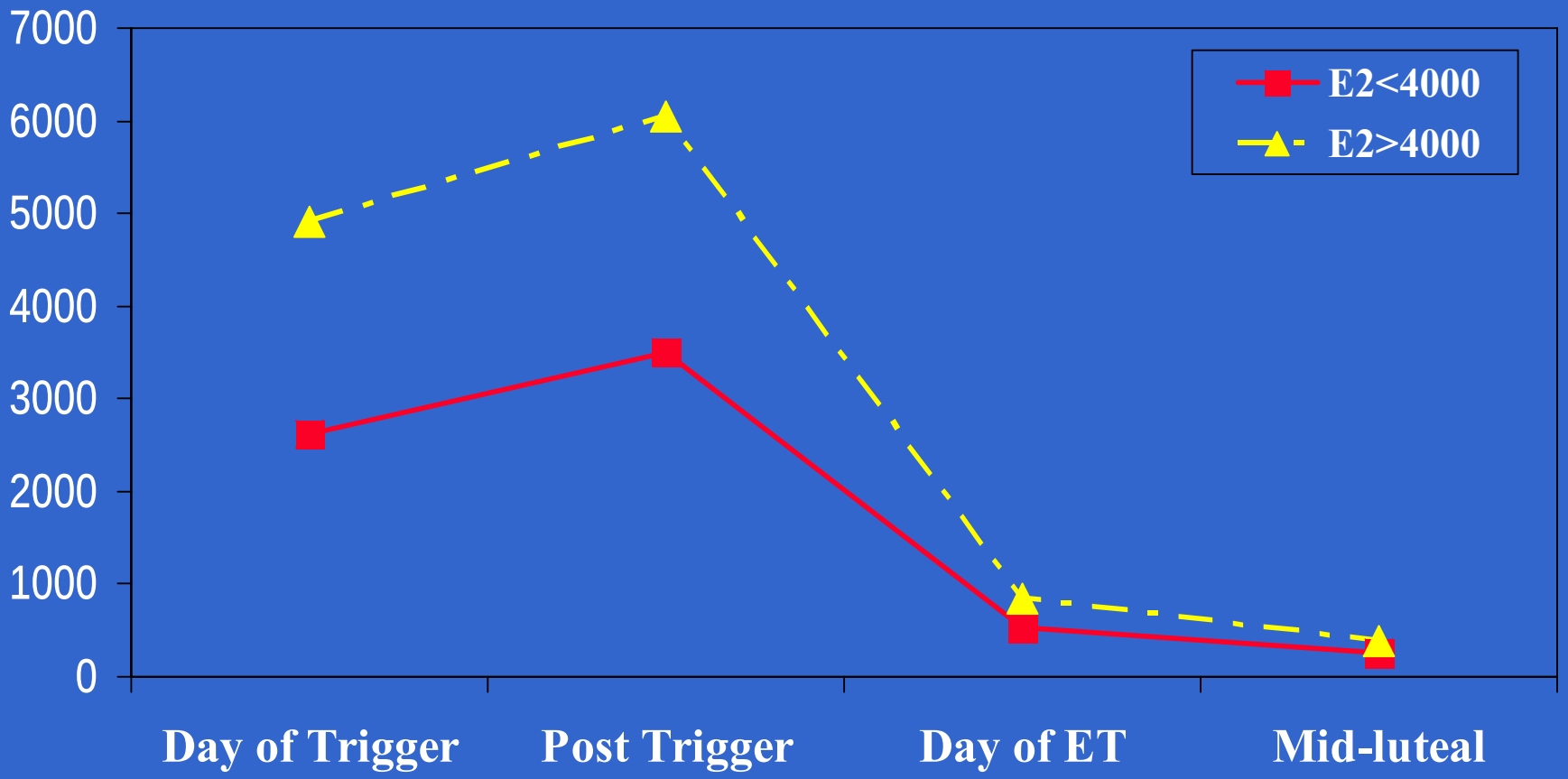
Kummer et al, 2010, abstract ASRM

Outcomes of Ovarian Stimulation

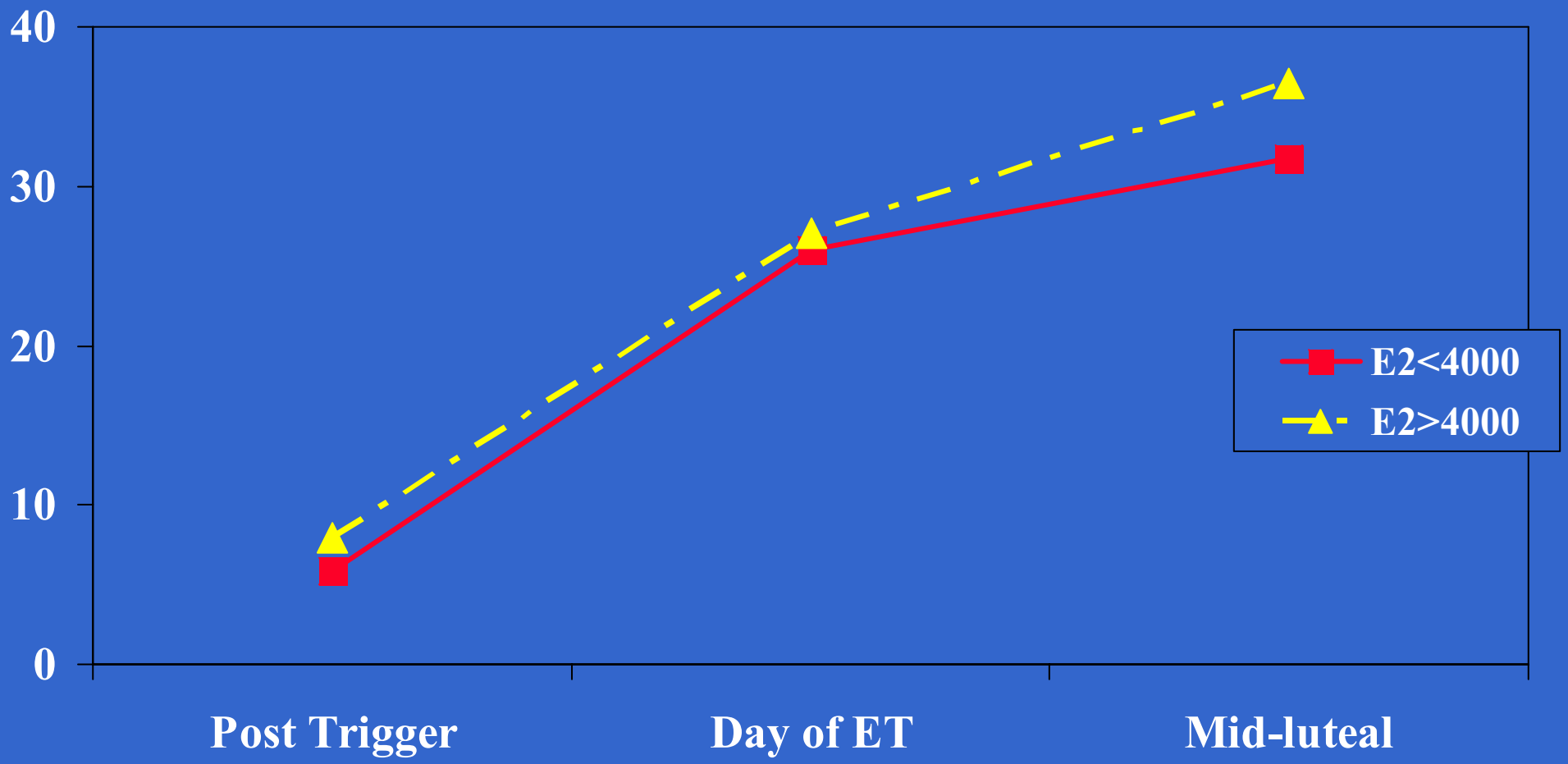
	E_2 < 4000	E_2 > 4000
Days of stimulation	9.8 ± 1.4	9.9 ± 1.2
Dose of gonadotropins (IU)	1816 ± 724	1712 ± 759
# of oocytes	25.3 ± 11.8	28.2 ± 9.3
% Mature Oocytes	74.7 ± 18.8	69.7 ± 20.0
Fertilization rate (%)	73.7 ± 16.0	74.5 ± 15.2
# of embryos transferred	2.0 ± 1.2	2.1 ± 0.5
Good quality embryos (%)	83 ± 29	83 ± 34
# of embryos Frozen	3.1 ± 3.9	4.1 ± 4.5

Kummer et al, 2010, abstract ASRM

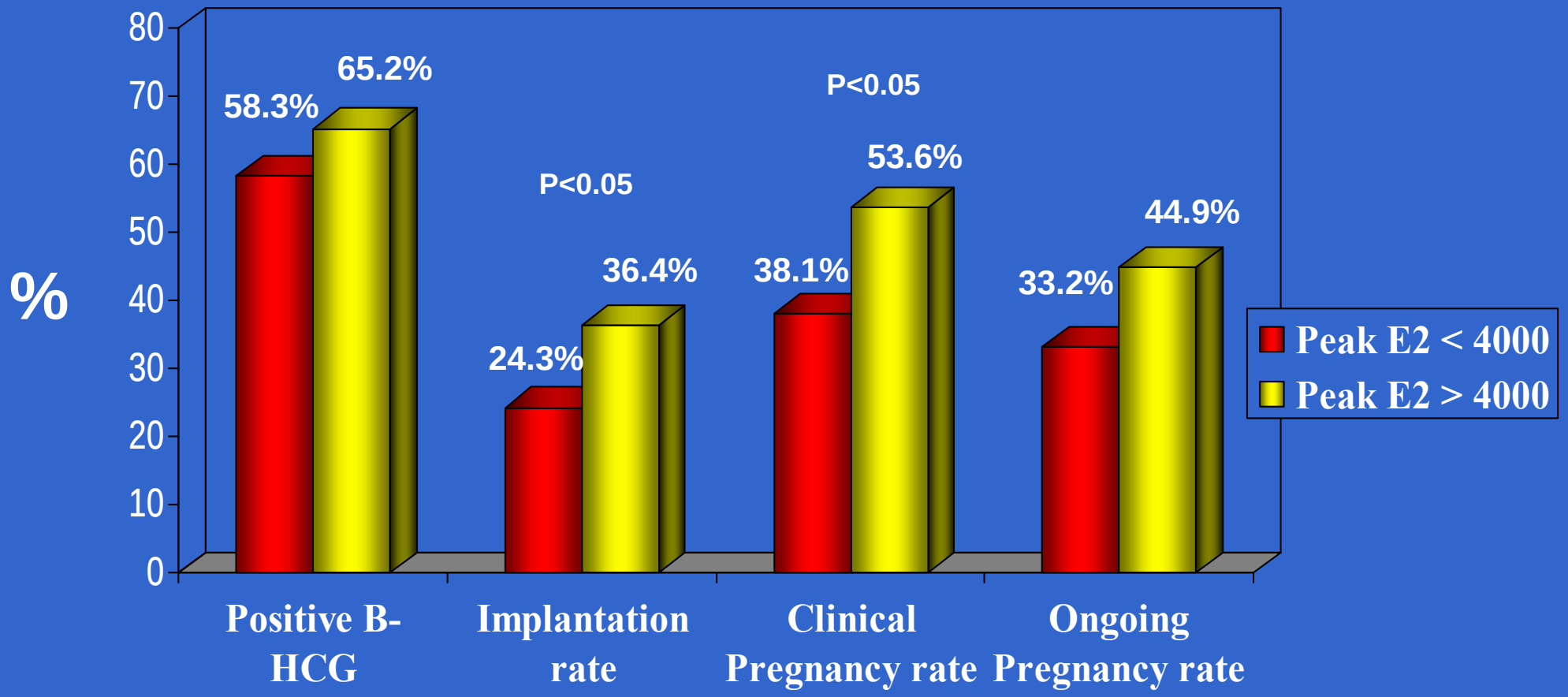
Serum Estradiol Profile (pg/mL)



Serum Progesterone Profile (ng/mL)



Cycle Outcome – according to peak E_2



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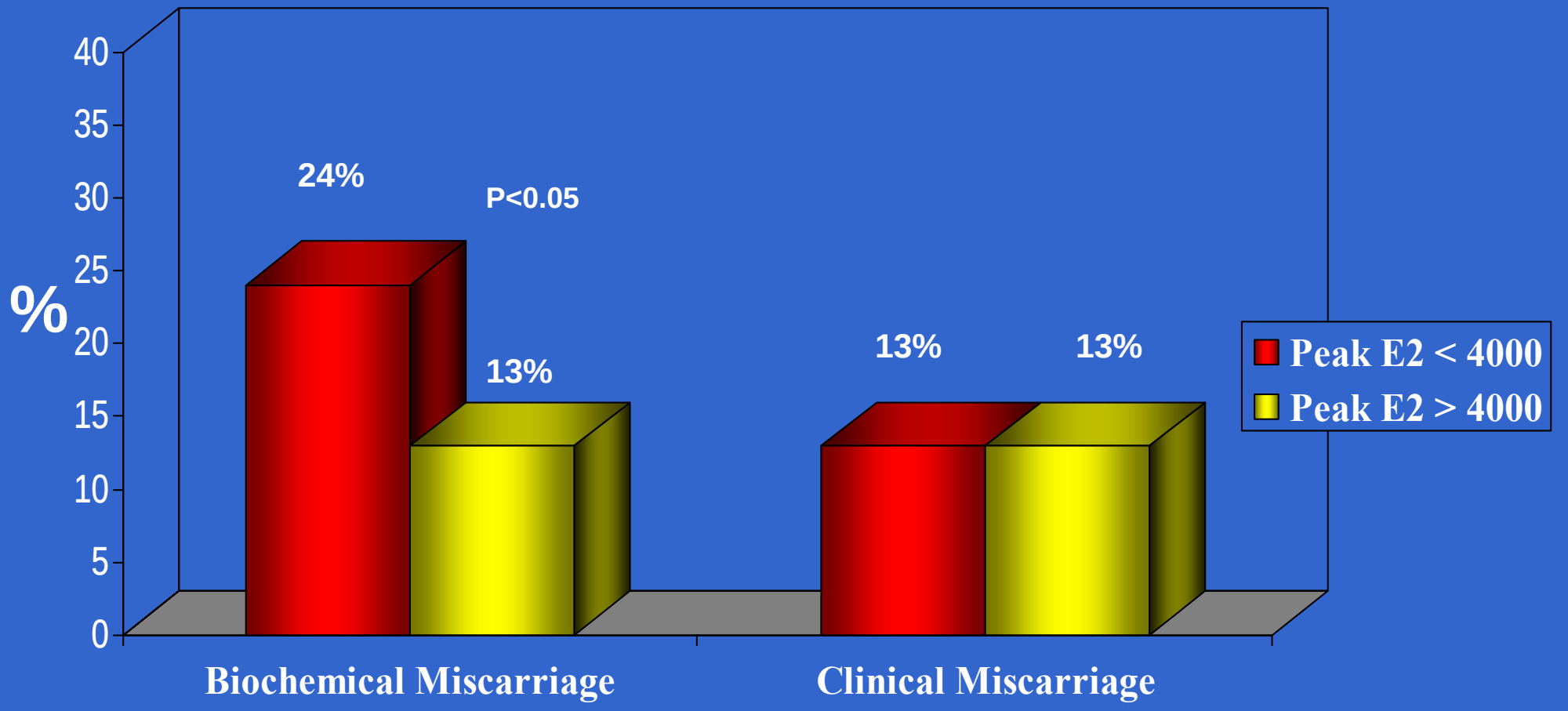
Kummer et al, 2010, abstract ASRM

Biochemical Miscarriage – according to peak E_2



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Kummer et al, 2010, abstract ASRM

Incidence of OHSS

0/316

Kummer et al, 2010, abstract ASRM

GnRHa to induce final oocyte maturation prevents the development of OHSS in high-risk patients and leads to improved clinical outcomes compared with coasting

	LA trigger group (n=61)	Coasting group (n=33)	*P* value
No. oocytes / retrieval	26.9 ± 9.5	17.7 ± 9.3	<0.001
No. normally fertilized oocytes (2PNs)	15.0 ± 7.8	10.3 ± 6.3	0.01
Fertilization rate (%)	72.6 (669/921)	66.2 (186/281)	0.04
Patients with surplus cryopreserved embryos (%)	66.7 (40/60)	9/23 (39.1)	0.02
% of OHSS	0%	0%	NS
Implantation rate (%)	31.4 (44/140)	22.6 (12/53)	NS (0.23)
Clinical pregnancy rate (%)	52.5 (32/61)	27.2 (9/33)	0.02
Ongoing pregnancy rate (%)	49.2 (30/61)	24.2 (8/33)	0.02

DiLuigi et al, Fertil Steril, 2010

Conclusions

- The use of GnRH agonist trigger is probably the only effective method for prevention of OHSS
- However, GnRH agonist trigger leads to lower luteal phase steroidal concentrations
- Adequate estradiol and progesterone supplementation in the luteal phase and early pregnancy is essential to maintain normal pregnancy rates
- Efforts should be made to develop new protocols to improve ongoing pregnancy rates in the subset of patients with lower peak E_2 levels

References

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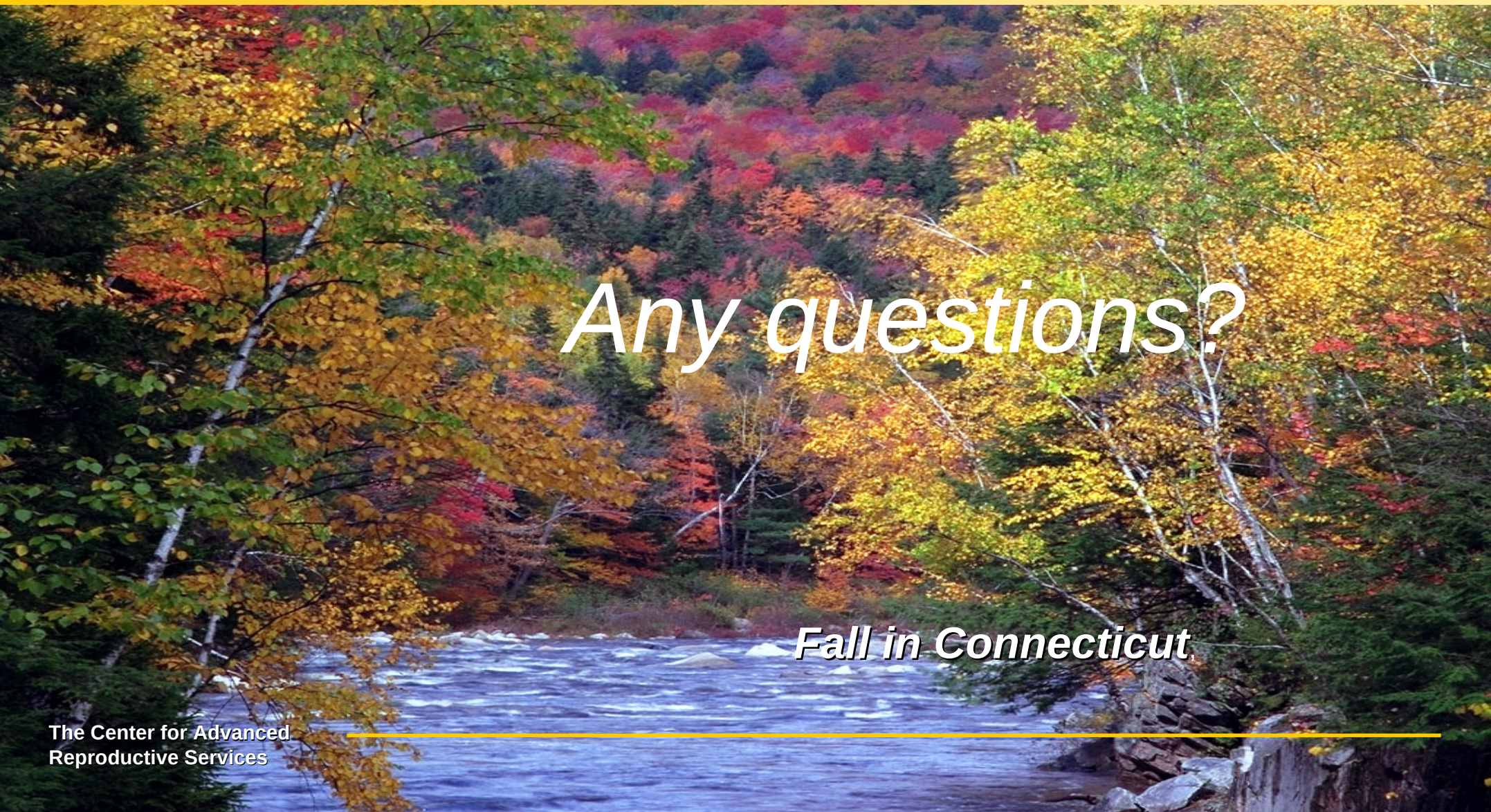
Thank you!



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