Serono Symposia International

Welcome

IV INTERNATIONAL WORKSHOP

ON

OPTIMIZING INFERTILITY TREATMENTS

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Management of Poor Responders

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Aging Follicular Apparatus

- Reduction in the number of follicles (Gougeon)
- Increased oocyte abnormalities
  - meiotic spindle (Battaglia)
  - aneuploidy (Benadiva)
- Reduced hormone production by luteinized GC (Pellicer)
- Decreased GC proliferation (Seifer)
- Increased GC apoptosis (Seifer)

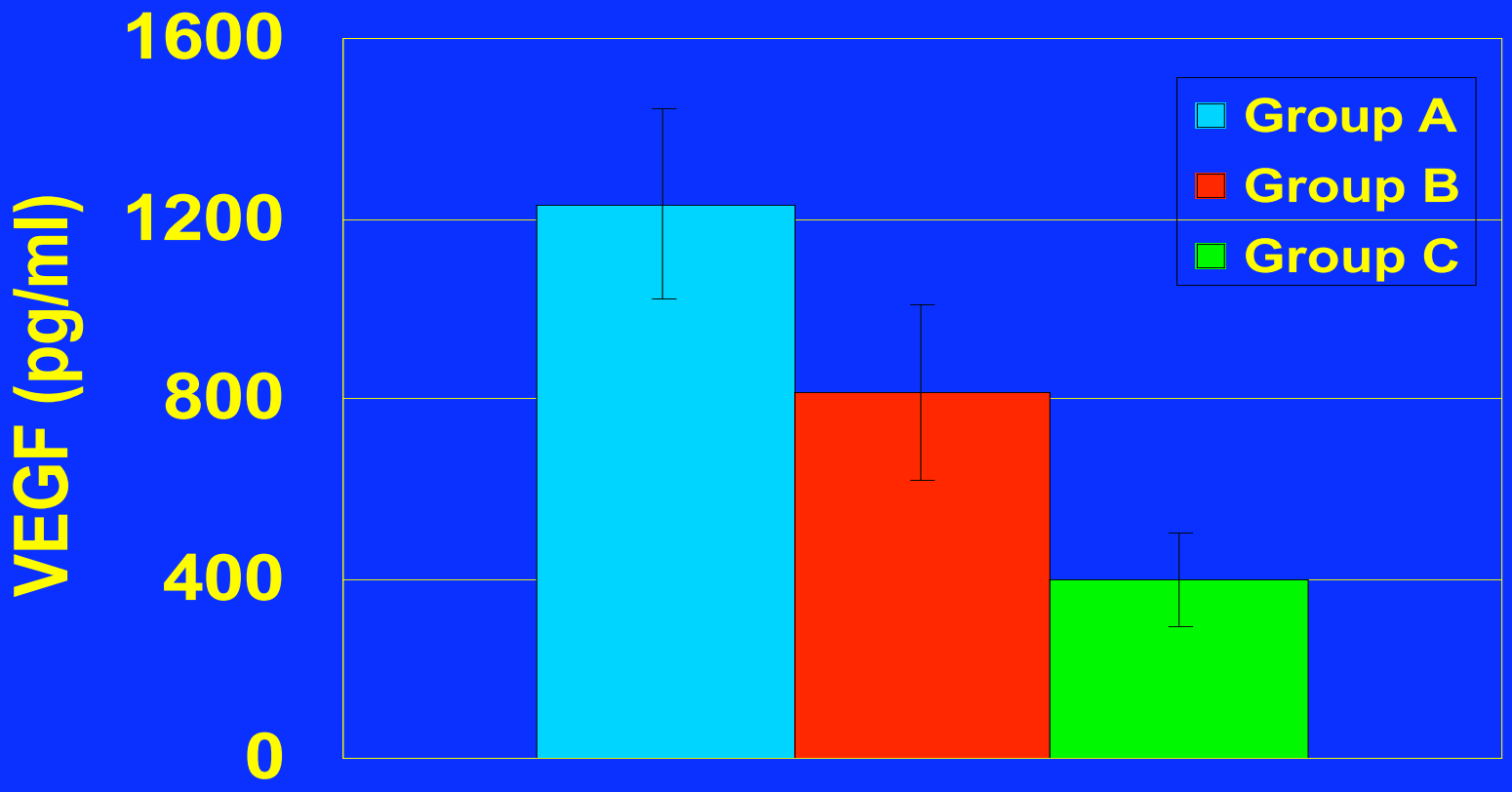
VEGF and Apoptosis in Hyporesponders to COH

"Relationship of ovarian stimulation response with VEGF and granulosa cell apoptosis"

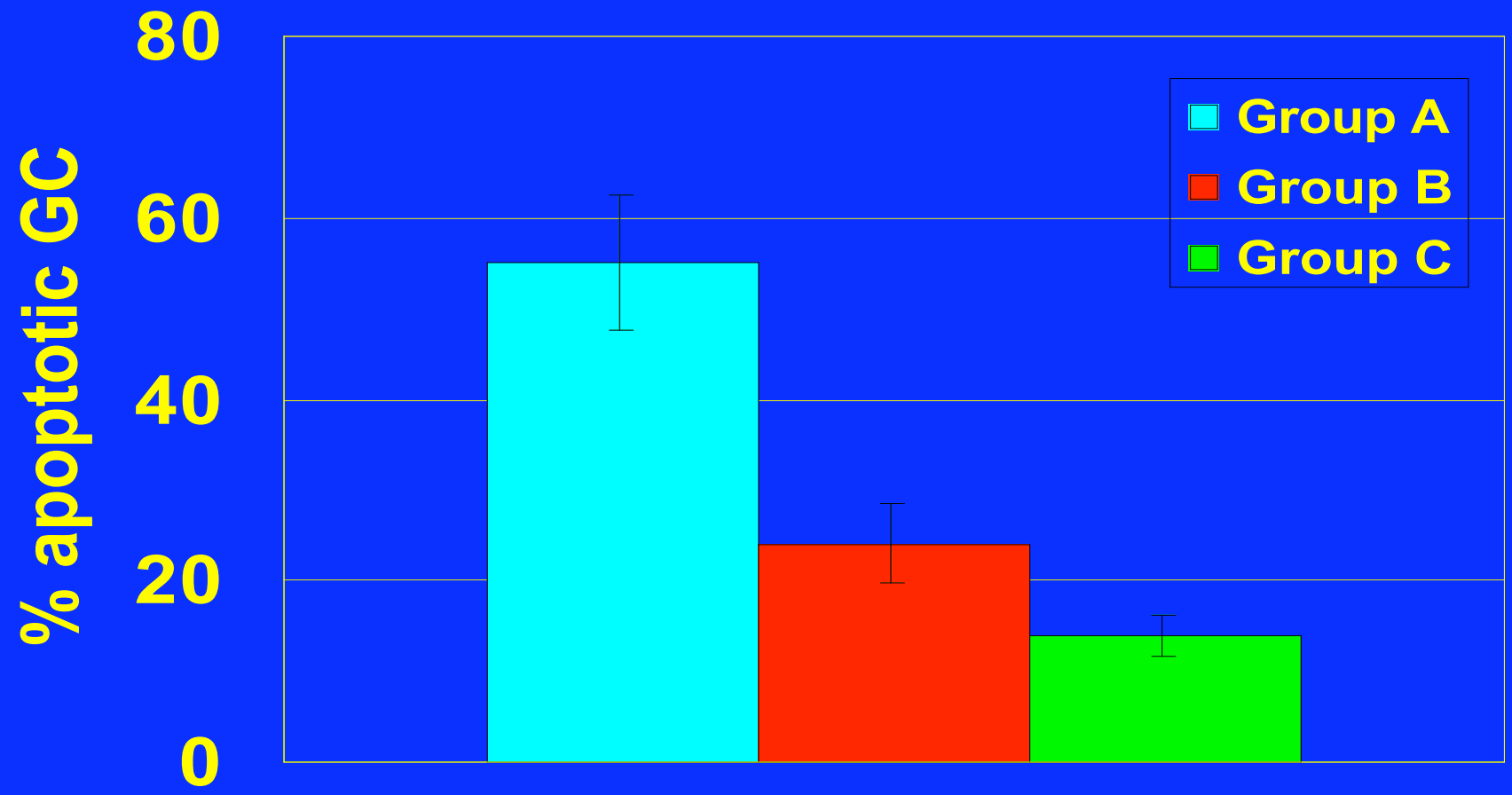
Quintana R,Kopkow L,Sueldo C et al.

Human Reproduction, September 2001

VEGF - Apoptosis in Poor Responders



VEGF –Apoptosis in Poor Responders



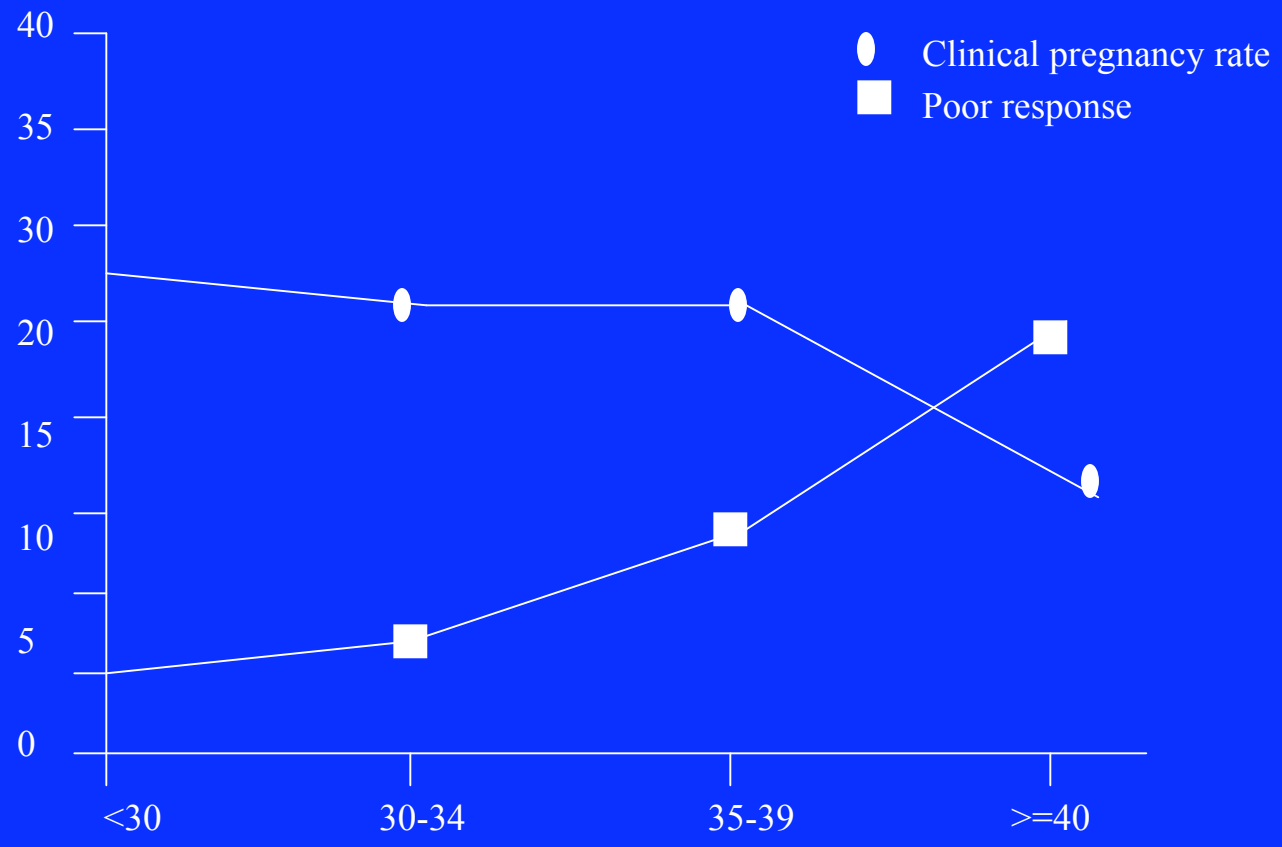
Poor Response to COH

- Incidence between 5-15% of ART patients.
- Their pregnancy rate with ART is low.

Risk Factors

- Advanced chronological age (over 40)
- Unilateral gonadectomy.
- Previous ovarian surgery (cystectomy)
- Large bilateral ovarian endometriomas
- Idiopathic infertility.
- Hx of poor response to COH.

Poor Response:Age and Declining Pregnancy Rates



ART in Older Women when OD is not a Therapeutic Option

- All IVF-ICSI patients (n=208) 1998-2000 where the female was >41 y/o. Only 153 reached ET.

- 41 y/o =74 CPR(18.2) SAB(30) LB(12.7)
- 42 y/o =44 CPR (18.8) SAB(50) LB (9.4)
- 43 y/o=46 CPR(12.1) SAB(25) LB (9.1)
- 44 y/0= 25 CPR (5) SAB (100) LB (0)

Valcarcel et al (IFER, 2001)

Definition of Poor Responders (Lack of Uniformity)

- Hx of poor ovarian response to COH
- Less than 4 follicles (HCG day)
- Less than 4 oocytes retrieved
- Less than 100 pg/ml of serum estradiol after 5 days of gonadotropin stimulation
- Less than 500-1000 pg/ml estradiol on HCG day. (and many other definitions).

Diagnostic work-up

- Day 3 serum FSH (NL:levels below 10-12 mIU/ml)
- Day 3 serum Estradiol (NL:levels below 75 pg/ml)
- Day 3 serum Inhibin B (NL: levels above 45-65 pg/ml)
- Clomiphene challenge test (CCCT).
- Anti-Mullerian Hormone serum levels.

Inhibin B and Ovarian Reserve

- Women with declining ovarian reserve may demostrate a low serum Inhibin B before a rise in day 3 serum FSH. (Seifer 1999)

- Serum Inhibin B basal levels as predictors of ovarian response and pregnancy in ART patients with normal serum FSH testing.

  (De Zuñiga, Young et al. 2002)

Diagnostic work-up by Ultrasound

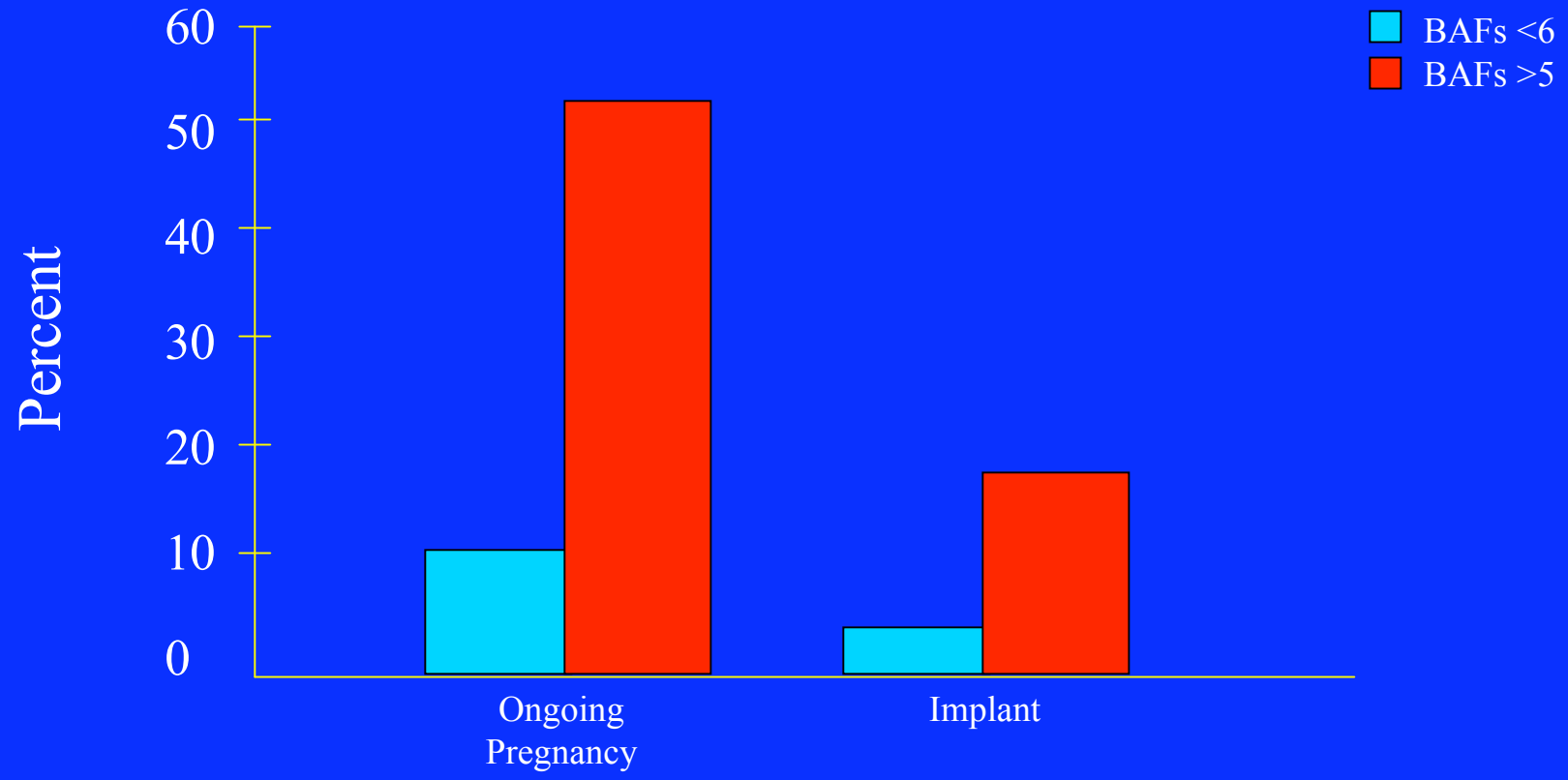
- Baseline antral follicle count under 6 by vaginal ultrasound (Chang 1998)
- Baseline antral follicle count by 3D (Pellicer 1998)
- Color doppler showed increased flow resistance at the uterine and ovarian levels in poor responders (Battaglia et al 2000).

Young Poor Responders with Normal D3 FSH Levels

Variable	Low Response	Controls	*P* Value
No of patients	10	8	
Age (years)	31.1 + .7	29.1 + 1	
Basal FSH (IU/mL)	7.9 + .5	5.9 + .4	0.05
Basal E2 (pg/dL)	51.3 + 4.6	45.6 + 3.0	
Total follicles	4.4 + .5	13.7 + 2.2	0.0001
2-5 mm follicles	1.9 + .4	8.3 + 2.0	0.001
Ovarian volume (mL)	35.1 + 2.9	41.3 + 2.6	

Pellicer A, 1998

Pregnancy Rates in GnRH Antagonist Treated Cycles in Patients with Low and Normal BAFs Counts



Shapiro et al ASRM 2002

Anti-Mullerian Hormone Levels and Ovarian Reserve

- AMH produced by GC of small antral follicles and levels assessed in serum.
- AMH levels correlated positively with number of follicles and oocytes retrieved.
- If FSH and Inhibin B are also tested, improved the prediction of ovarian response.

Van Rooij et al. Human Rep 2002

Predictors of Poor Ovarian Response in IVF:Basal Markers

- Prospective study (n=120 pts)
- Number of antral follicles, day 3 FSH, Estradiol and Inhibin B.
- Antral follicles count was best, adding FSH and Inhibin B improved the prediction, while serum estradiol did not.
- Poor responders had lower pregnancy rates.

Bancsi et al. F&S, Feb 2002

Diagnostic work-up

- Prospective (ART patients at risk for poor response as per reviewed criteria)
- Retrospective (ART patients with history of unexpected poor response to COH)

Poor Responders in ART

BEST

Young patients "normal testing"

Young patients "abnormal testing"

Older patients "normal testing"

WORST

Older patients "abnormal testing"

Is age or FSH Level more significant in ovarian reserve ?

50 pts > 40 y/o and FSH <15mIU
36 pts< 40 y/o and FSH >15 mIU

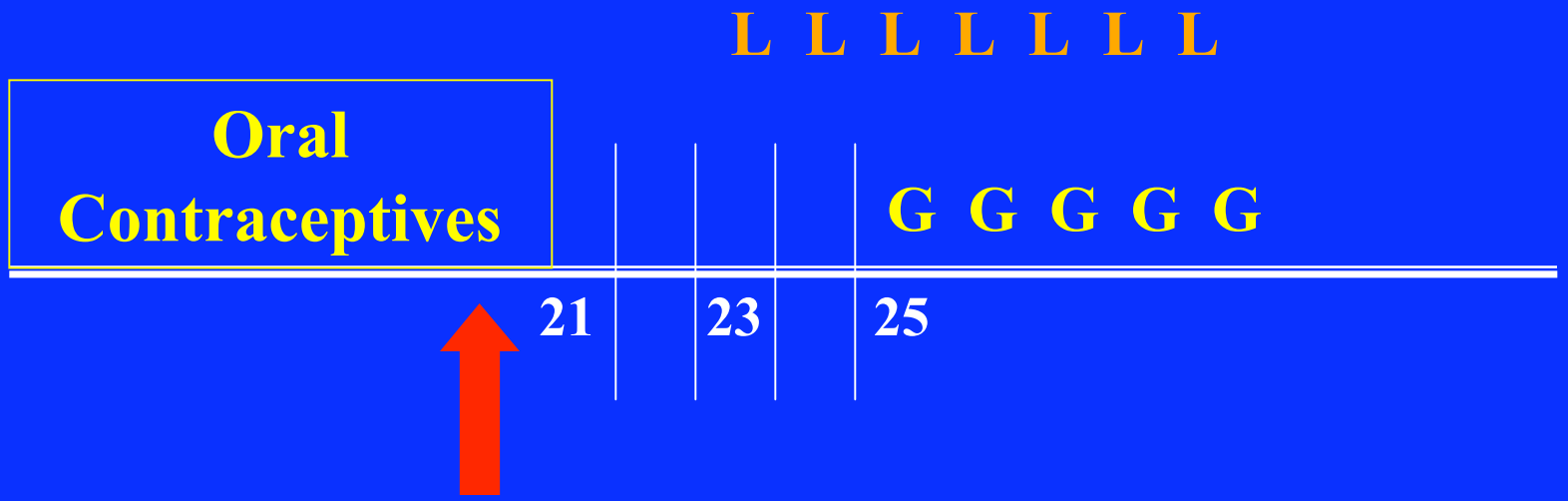
High FSH had more cancellations but better implantation and ongoing PR/ET

Van ROOIJ et al , F&S 2003

Stimulation Protocols for Poor Responders

- Increased dose of gonadotropins
- Clomiphene c.+ gonadotropins
- Adjunctive growth hormone
- Adjunctive aromatase inhibitors ?
- Low dose GnRha luteal phase
- Flare protocol
- Cessation of luteal phase GnRha
- **Microdose GnRha with OCs pre-treatment**
- **GnRh antagonists**

Flare microdose regimen with GnRH-a



L Lupron 20-40 mcg 2 x day

G Gonadotropins 450 IU/daily

Microdose GnRha with OCs Pretreatment

- 14-21 days of combined Ocs
- Leuprolide A. 40 mcg/s.c BID (starting 3 days after Ocs)
- FSH 450 IU s.c (starting 3rd day of Lupron)
- Cancellation rate of 12.5 %.
- Clinical pregnancy rate 61% (381 cycles).
- Implantation rate 22 %.

Schoolcraft et al. 1997

Microdose GnRha with OCs Pretreatment

- 34 poor responder ART patients
- 15 patients less than 40 y/o (Group I)
- 19 patients older than 40 y/o (Group II)
- COH similar to Schoolcraft but -GH.
- Cancellation rate: Gr. I (53%---6%)
  Gr. II (73%--31%)
- Ongoing PR: Gr. I = 33%
  Gr. II = 18% Surrey 1998.

Microdose GnRha with OCs Pretreatment in "good" PR

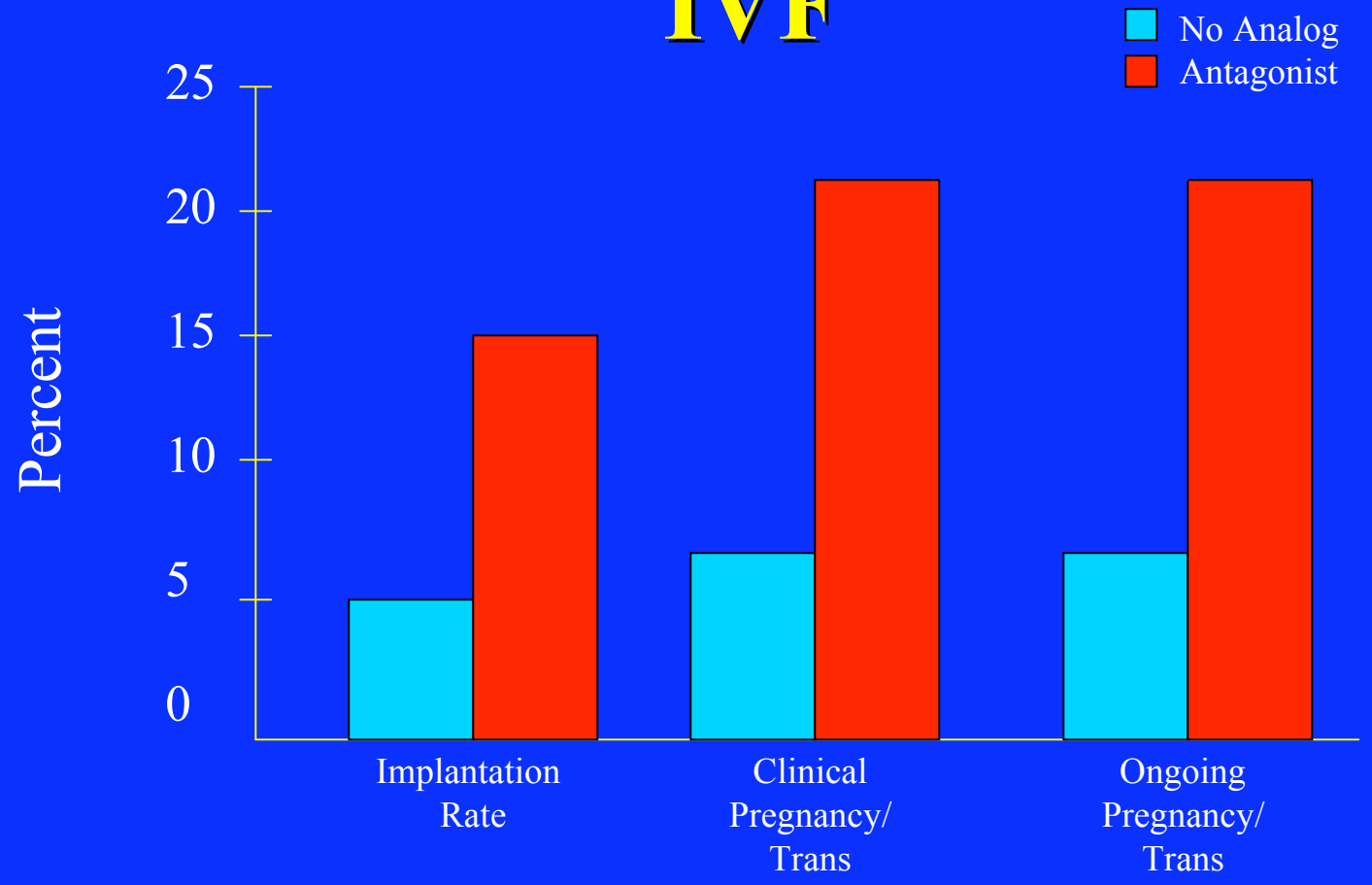
- 35 poor responder patients with normal FSH/E2 and ultrasound evaluation (all less than 40 y/o).
- OCs (Desogen for 14-21 days)
- Lupron 40 mcg/s.c BID 3days after Ocs.
- r-FSH 450 IU s.c /day for 2 days then 300 IU/day for 3 days----serum estradiol and ultrasound.

Microdose GnRha with OCs Pretreatment

- Cancellation rate = 20 % (n=7)
- Clinical pregnancy rate = 32 % (aspiration)
- Miscarriage rate = 22 %
- Ongoing pregnancy rate = 25 % (aspiration)

Sueldo et al. 2001

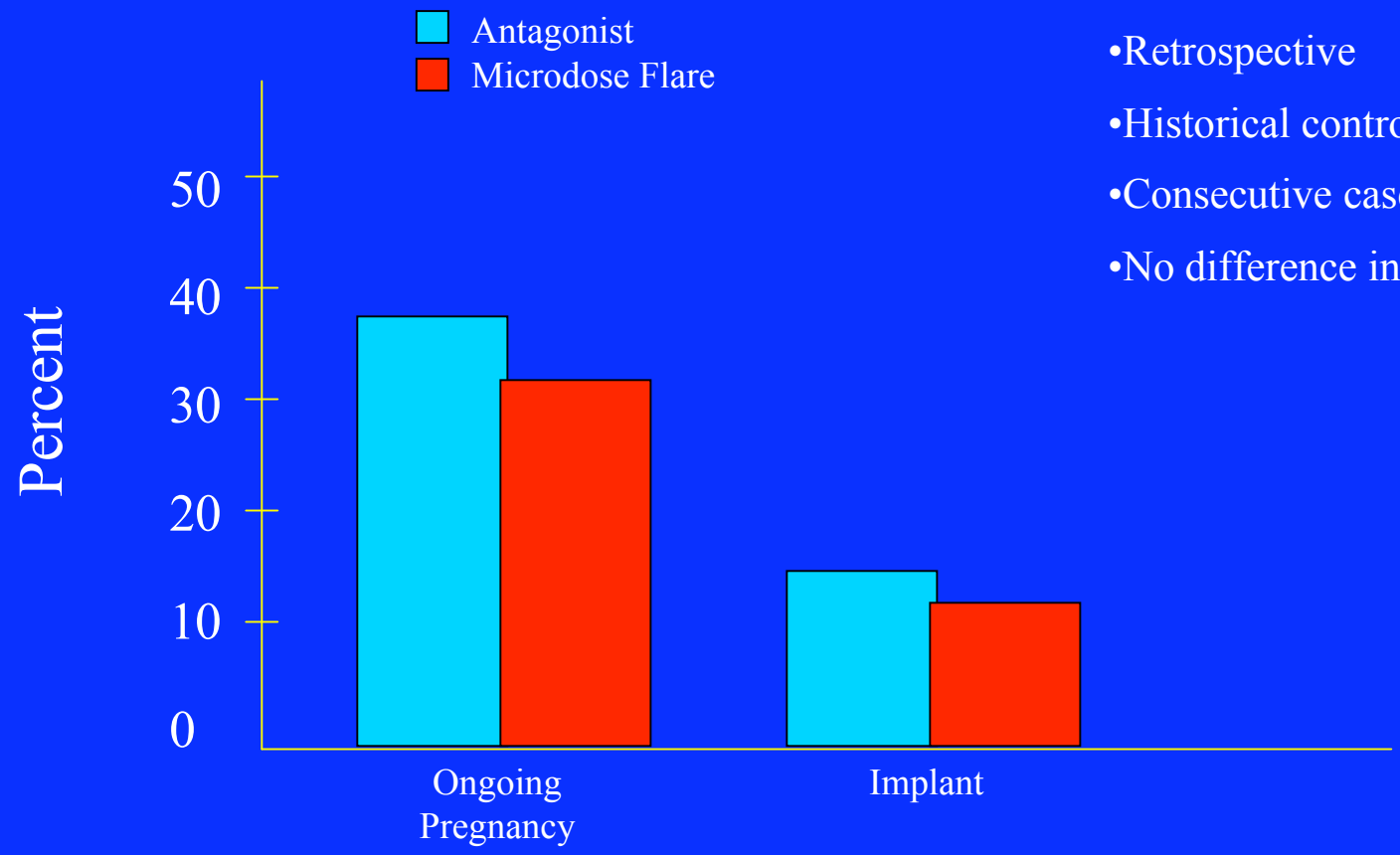
Addition of GnRH Antagonist in Cycles of Poor responders Undergoing IVF



P= NS for all comparisons

Aleman MA, et all. Hum Reprod 2000;15:2145-2147

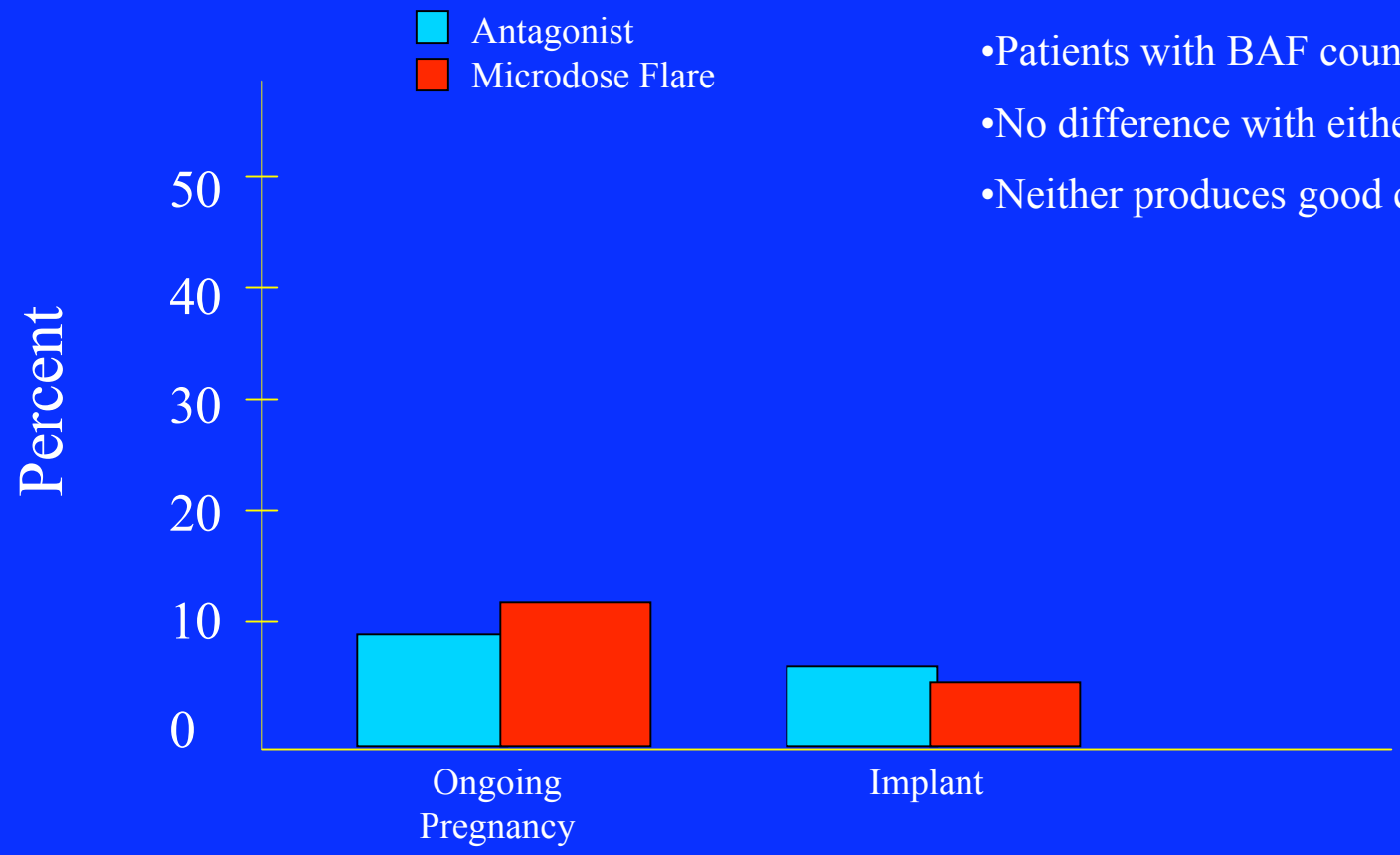
GnRH Antagonists vs Microdose Flare



- Retrospective
- Historical controls
- Consecutive cases
- No difference in outcome

Shapiro et al ASRM 2002

GnRH Antagonists vs Microdose Flare

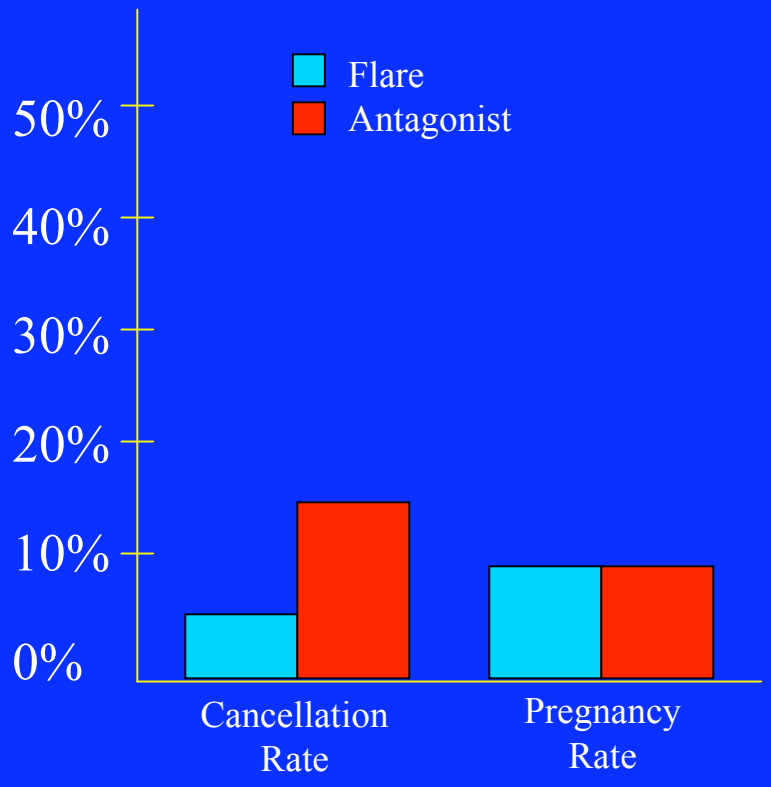


- Patients with BAF counts <6
- No difference with either protocol
- Neither produces good clinical results

Shapiro et al ASRM 2002

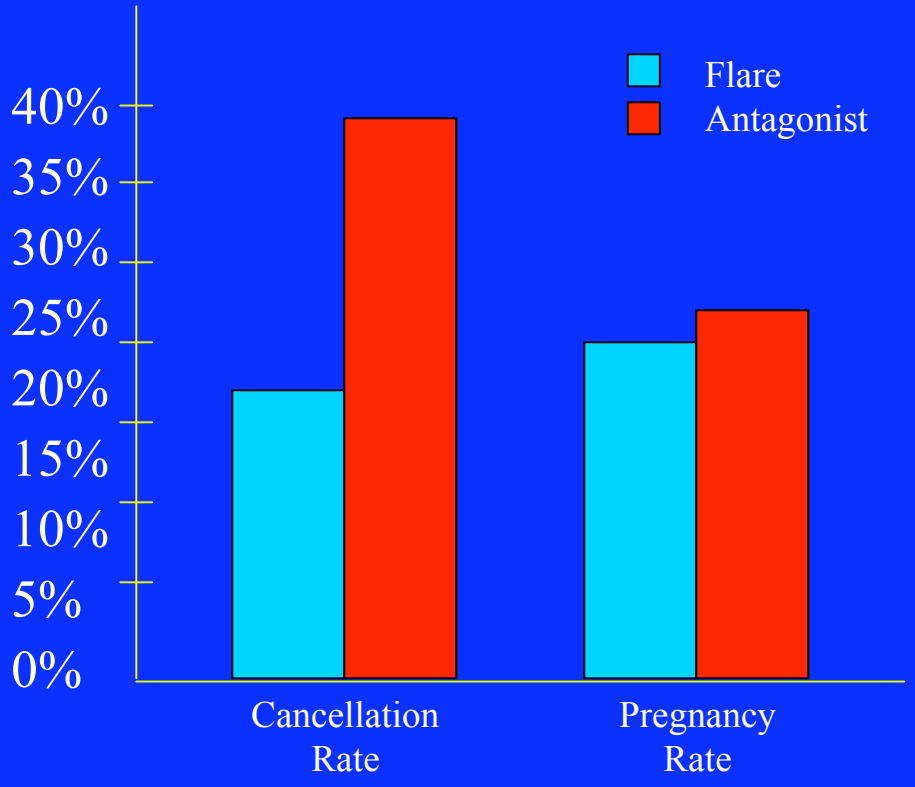
Flare vs Antagonist in Low Responders

•27 low responders
•Cross-over



Chen SH, et al. ASRM abstract 2002

•457 low responders
•Non-random



Noyes N, et al. ASRM abstract 2002

Conclusions I

- Assessment of ovarian reserve is indicated in high risk patients for poor response to COH for ART (as per reviewed criteria).
- Serum FSH/Estradiol D3 (or CCCT) plus basal ultrasound seem to be the most helpful Dx tests. Serum Inhibin B/AMH are still under clinical evaluation and not routinely used.
- Abnormal testing identifies patients with poor ovarian reserve with less than optimun ART outcome.

Conclusions II

- There is a lack of uniformity in the definition of Poor Responders, therefore comparison between studies is somewhat difficult in terms of selecting an appropiate COH protocol.
- Avoid standard down regulation (long prot).
- Increasing gonadotropins dose has a limited impact on ART outcome.
- Both,Microdose flare and GnRH antagonist protocols work well, especially in younger patients with normal ovarian reserve.

Conclusions III

- It is obvious, that if there is nothing there to stimulate nothing is going to work !
- When everything else fails, there is always oocyte donation (if it is an acceptable option to the infertile couple)
- Finally, oocyte donation should be the primary therapeutic approach to the older patient with abnormal ovarian reserve, due to the poor results seen when using their own gametes.