23RD NICHD MFM/NEO/REI YOUNG INVESTIGATORS CONFERENCE AUGUST 2011

Overview of Clinical Trial Topic

A Three-Arm Randomized Controlled IVF Trial In Women With Diminished Ovarian Reserve

IVF – controlled ovarian stimulation

Poor responders

- What is the problem?
- Improve IVF/ART outcome
  - Adequate oocyte numbers to maximize success rate
  - Limit cancellation – financial/emotional costs
  - Optimize outcome for *individual* patients
- Is it important?
  - 9-24% of IVF cycles

"Controlled Ovarian Stimulation" (COS)

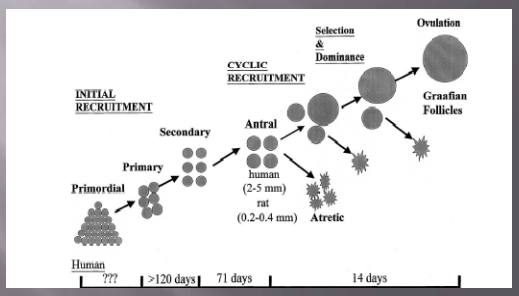
- Why "stimulate" the ovaries
  - 1978 Louise Brown
    - Natural cycle
  - Intrinsic inefficiency of this process
  - Increased eggs ⟶ improved outcome
  - Introduction of superovulation (COH/COS)
    - Australia Clomiphene citrate + human menopausal gonadotropins (hMG) + hCG
    - UK/USA – hMG + hCG

IVF – controlled ovarian stimulation

Poor responders

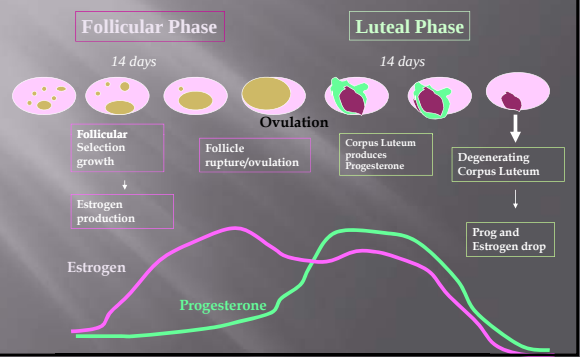
- What stimulations are available?
- How were they developed?
- Do they have biological rationale?
- Do the rationales suggest benefit in poor responder patients?

Follicle Recruitment Natural cycle

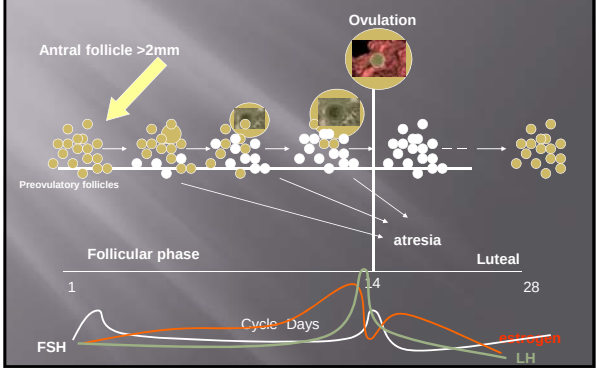


McGee and Hsueh, Endocrine Rev 2000

Stimulation: Endocrinologist's Perspective

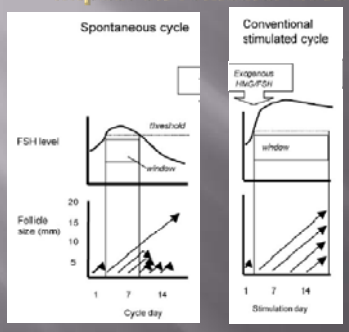


Dominant follicle development



FSH Threshold/Window

Impact on follicular development



Macklon, Stouffer, Giudice, Fauser Endocrine Reviews, 2006

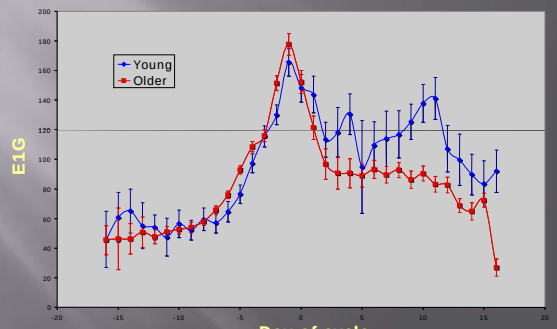
Cycle length and ovarian aging

	25-27 days (N 94)	28-32 days (N 405)	33-35 days (N 26)	P-value
Age	37 5.1	35.7 5.2	35.0 5.8	0.07
AMH (pmol/l)*	19.9 19.1	26.8 22.3	40.3 25.6	0.0001
FSH (mIU/ml) †	7.97 ± 5.39	6.86 ± 2.8	5.75 ± 1.58	0.002
Inhibin B (pg/ml)	48.8 ± 30.9	49.6 ± 27.9	44.8 ± 24.2	0.70
Total AFC*	12.2 ± 8.4	15.4 ± 9.4	21.2 ± 12.3	<0.0001
Follicles 2-4.9 mm ‡	7.2 ± 6.5	9.0 ± 7.6	13.9 ± 11.1	0.0004
Follicles 5-8.9 mm†	4.6 ± 4.3	6.1 ± 4.7	7.2 ± 4.7	0.005
Follicles 9-10 mm	0.45 ± 0.81	0.27 ± 0.70	0.15 ± 0.46	0.05

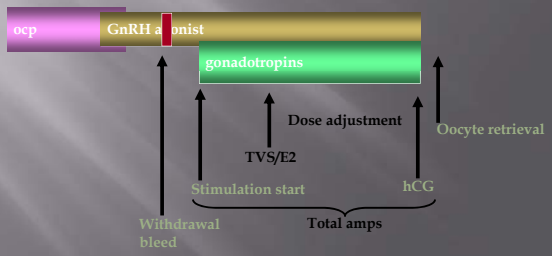
Urinary Metabolites (averaged over cycle phases)

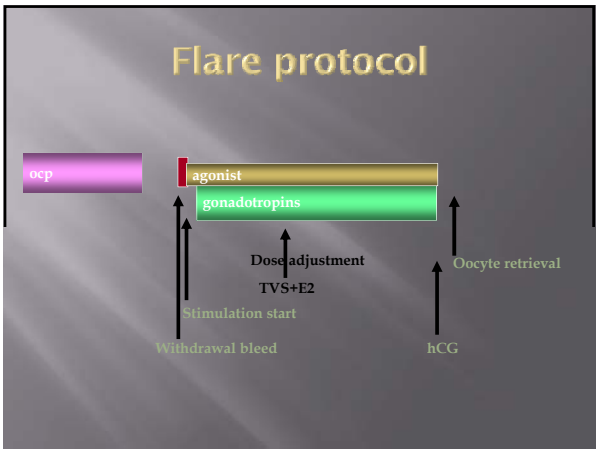
		Younger n=28	Older n=78	p value**
PdG	Total*	11.2 ± 4.5	6.6 ± 3.1	<0.001
	Follicular*	5.6 ± 2.2	2.7 ± 1.3	<0.001
	Luteal*	18.1 ± 8.9	11.0 ± 5.2	<0.001
E1G	Total*	97.2 ± 39.8	89.2 ± 32.7	0.469
	Follicular*	81.7 ± 32.9	88.5 ± 37.3	0.431
	Luteal*	115.4 ± 56.1	90.4 ± 33.6	0.035

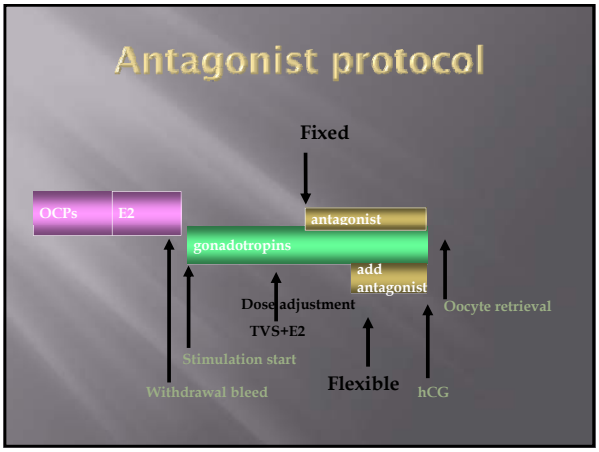
Mean Daily E1G metabolites

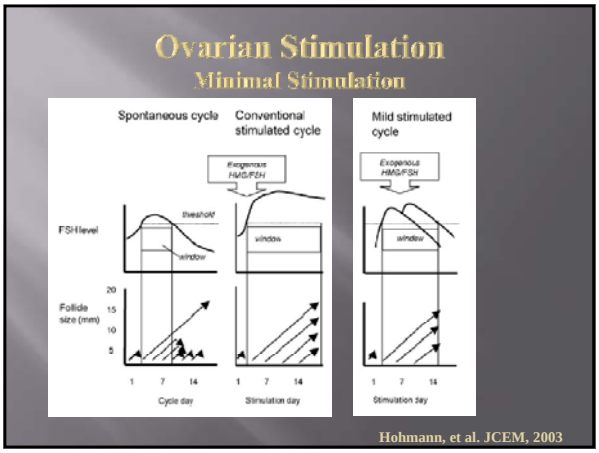


Down-regulated protocol




Flare protocol
ocp
agonist
gonadotropins
Dose adjustment
TVS+E2
Oocyte retrieval
Stimulation start
Withdrawal bleed
hCG


Antagonist protocol
Fixed
OCPs
E2
antagonist
gonadotropins
add antagonist
Dose adjustment
TVS+E2
Oocyte retrieval
Stimulation start
Withdrawal bleed
Flexible
hCG


Ovarian Stimulation
Minimal Stimulation
Spontaneous cycle
Conventional stimulated cycle
Mild stimulated cycle
Exogenous HMG/FSH
FSH level
threshold
window
Follicle size (mm)
Cycle day
Stimulation day
Hohmann, et al. JCEM, 2003

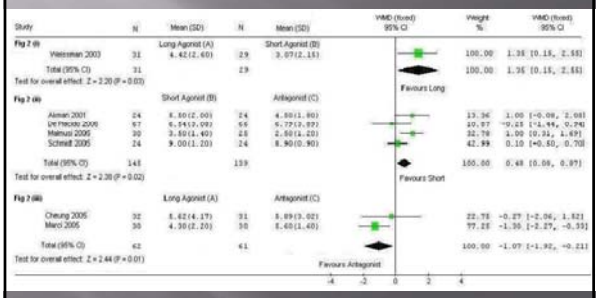
Literature Review

- Importance of literature review
  - Has this question been answered?
  - Has it been answered well in relevant patient populations?
  - If not, what can be learned from the literature?
- What is available in the literature?
  - Other available randomized trials
  - Meta-analyses
  - Cochrane Reviews

Literature Review

- Treatment options
  - Stimulation protocol
    - Long-lupron (suppression)
      - Stop protocols
    - Short lupron (flare) – microdose
    - Antagonist
  - Adjuvants
    - GH/GHRF
    - Androgen – Testosterone, DHEA
    - Letrozole/Clomiphene citrate

Sunkara SK, et al. 2007



Kyrou D, et al. 2009

Odds ratio (OR) of clinical pregnancy rate per patient randomized to be stimulated with GnRH antagonist or a short GnRH agonist protocol.

Review: Poor ovarian Response
Comparison: 02 GnRH antagonist versus short GnRH agonist protocol
Outcome: 01 Clinical pregnancy rate

Study or sub-category	Antagonist n/N	Agonist n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Martinez et al., 2003	5/21	3/23		20.30	2.08 [0.43, 10.07]
Malmusi et al., 2005	3/30	6/30		50.24	0.44 [0.10, 1.97]
Schmidt et al., 2005	5/24	4/24		29.46	1.32 [0.31, 5.65]
Total (95% CI)	75	77		100.00	1.03 [0.45, 2.39]

Total events: 13 (Antagonist), 13 (Agonist)
Test for heterogeneity: $Chi^2 = 2.10$, df = 2 (P = 0.35), $I^2 = 4.6\%$
Test for overall effect: Z = 0.08 (P = 0.94)

0.01 0.1 1 10 100
Favours Agonist Favours Antagonist

Kyrou. Poor responders and pregnancy. Fertil Steril 2009.

Kyrou D, et al. 2009

Odds ratio (OR) of clinical pregnancy rate per patient randomized to be stimulated with a stop or a nonstop long GnRH agonist protocol.

Review: Poor ovarian Response
Comparison: 03 Stop vs. Non–stop long GnRH agonist protocol
Outcome: 01 Clinical pregnancy rate

Study or sub-category	Stop n/N	Non-stop n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Dirnfeld et al., 1999	3/40	3/38		41.57	0.95 [0.18, 5.00]
García-Velasco et al., 2000	6/34	5/36		58.43	1.33 [0.36, 4.84]
Total (95% CI)	74	74		100.00	1.17 [0.42, 3.24]

Total events: 9 (Stop), 8 (Non-stop)
Test for heterogeneity: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$
Test for overall effect: Z = 0.30 (P = 0.76)

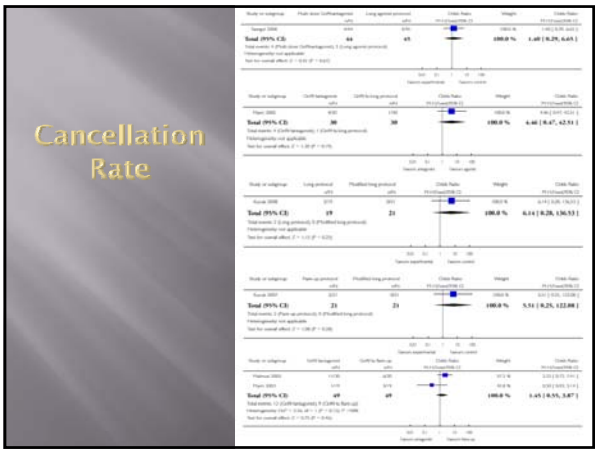
0.1 0.2 0.5 1 2 5 10
Favours Non-stop protocol Favours Stop protocol

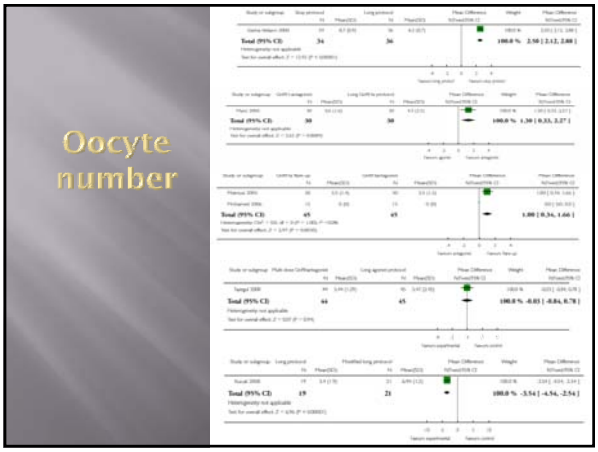
Kyrou. Poor responders and pregnancy. Fertil Steril 2009.

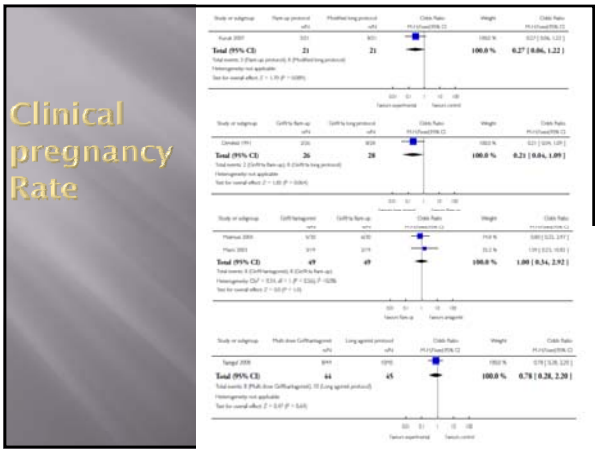
Padian Z, et. al. Cochrane Review 2010

Comparison 4. GnRH antagonist versus GnRHa flare-up protocol

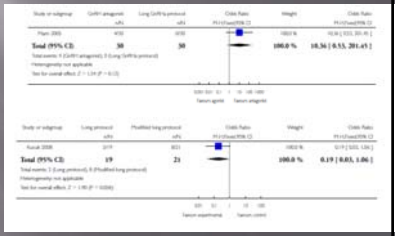
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy rate per woman	2	98	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.34, 2.92]
2 Miscarriage rate	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 7.99]
3 Etopic pregnancy	1	11	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Cancellation rate	2	98	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.55, 3.87]
5 Number of oocytes retrieved	2	90	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.34, 1.66]
6 Dose of gonadotrophins in IU	1	60	Mean Difference (IV, Fixed, 95% CI)	1575.0 [852.87, 2297.13]
7 Dose of gonadotrophins in ampoules	3	100	Mean Difference (IV, Random, 95% CI)	11.21 [-6.88, 29.31]
8 Sensitivity analysis, Dose of gonadotrophins in ampoules excluding Malmusi 2005	2	40	Mean Difference (IV, Fixed, 95% CI)	2.5 [-1.57, 6.57]


Cancellation Rate


Oocyte number


Clinical pregnancy Rate

Clinical Prenancy Rate



Literature Review

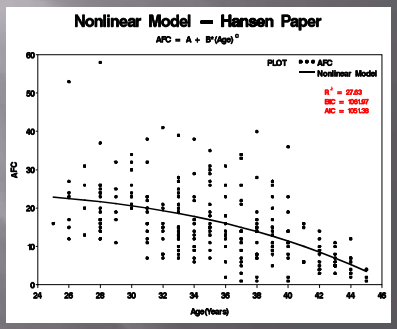
- Problems with the available literature
  - Heterogeneity
    - Definition of "poor response"
    - Outcome of interest
    - Interventions
  - Poor study design
  - Absence of relevant clinical outcome

Poor ovarian response (POR)

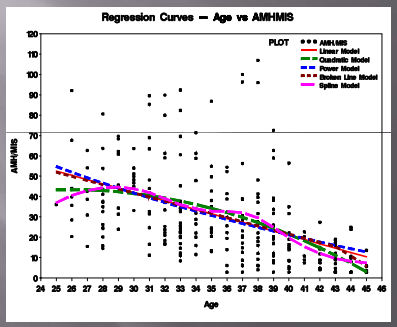
- ESHRE consensus conference 2010
- At least two of the following three:
  - Age ≥ 40 years or any other risk factor for POR (e.g. exposure to alkylating agents, genetic abnormality)
  - A previous POR (≤3 oocytes with a conventional stimulation)
  - An abnormal ovarian reserve test (e.g. AFC < 5-7; AMH < 0.5-1.1ng/mL)

Ferraretti AP, et al. Hum Reprod 2011

AFC and Age



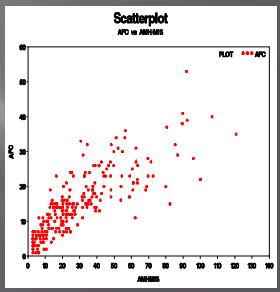
AMH and Age



AFC and AMH

- AFC and AMH both predict ovarian response with high sensitivity and specificity

Ng 2000; Frattarelli 2000; Huang 2001; Bancsi 2002; Hsieh 2001; Broekmans, 2006; Broer, 2009, LaMarca 2010



Assessing "Ovarian Reserve"

- Quantity → number of oocytes retrieved
  - Selection of stimulation protocol
  - Allows for selection for embryo transfer
  - Allows for freezing
  - Affect on pregnancy rate/retrieval
- Quality
  - Pregnancy rate
  - Surrogate marker: Implantation rate per embryo transferred

Quantity = Quality

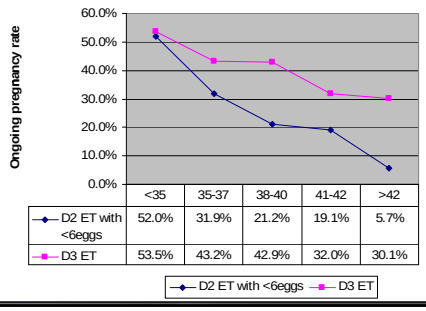
Dogma

N	<35	35-37	38-40	41-42	>42
Day2 ET (DOR)	25	47	85	68	35
Day3 ET	675	377	343	125	36
Average egg# retrieved					
Day2 ET (DOR)	3.9	3.9	3.8	3.8	3.5
Day3 ET	17.1	15.3	14.8	16.4	16.8
#Embryos transferred					
Day2 ET (DOR)	2	1.9	2.1	2.4	2.1
Day3 ET	2.2	2.8	3.5	5.2	6.6
Implantation					
Day2 ET (DOR)	34.0%	25.5%	17.3%	10.3%	3.0%
Day3 ET	38.0%	26.0%	23.0%	12.1%	5.2%
Ongoing Pregnancy Rates					
[redacted]					

Loss of Ooctye Quality
Why do we care?

- Abnormal fertilization, arrest of early development
- Failure to implant
- Post implantation problems
  - Recognized loss
  - Developmentally delayed child (Down syndrome)

What is diminished ovarian reserve (DOR) – reduced quantity vs. reduced quality?



	<35	35-37	38-40	41-42	>42
D2 ET with <6eggs	52.0%	31.9%	21.2%	19.1%	5.7%
D3 ET	53.5%	43.2%	42.9%	32.0%	30.1%

Literature Review

- No identified optimal stimulation can be recommended
- Study flaws identified that can be improved upon
- Data available to generate sample size calculations and assess minimally important difference (MID)

Trial design

- Patient population
- Prior failed cycle vs. prospective identification
  - Age
  - Cycle length
  - AFC
  - AMH

What controls Quality

- Non-modifiable
  - Age
  - (BMI)
  - Endometriosis
- Modifiable
  - Stimulation dosing
  - Hormonal environment

Improving Oocyte Quality

- Optimizing dosing
- Optimizing hormonal environment before and during cycle
  - FSH
  - LH
  - androgens
  - progesterone

Key decision points to designing a study