Options for women with diminished ovarian reserve:

Gonadotropin stimulation regimens

Nick Macklon

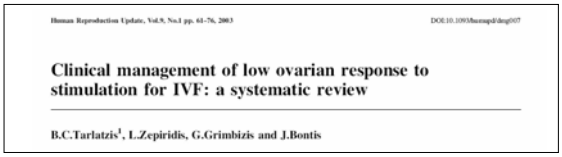
POOR RESPONSE

- **Definition:**

  Less than 4 follicles following ovarian stimulation with conventional long protocol

- **Incidence:**

Observed in 9 -24% of women undergoing IVF


Human Reproduction Update, Vol.9, No.1 pp. 61-76, 2003 DOI:10.1093/humupd/dmg007

Clinical management of low ovarian response to stimulation for IVF: a systematic review

B.C.Tarlatzis[1], L.Zepiridis, G.Grimbizis and J.Bontis

Gonadotropin stimulation in poor responders

What is the evidence?

Pubmed Search:

- Poor response IVF: 286 hits
- RCTs: 32 hits
- RCTs of gonadotropin stimulation regimes: 3

High dose strategies RCT 1

Cedrin-Durnerin Fertil Steril, 2000.

- Fixed high dose (450iu/d) versus step-down dose with micro-flare GnRH
- High dose: lower cancellation rates

  : similar pregnancy rates

  : significantly higher gonadotropin total dose

High dose strategies RCT 2

Van Hooff et al . Hum Reprod 2003

- Intervention: Double dose (450 IU vs 225 IU) from day 5 of stimulation
- High dose: NO DIFFERENCE IN OUTCOMES

High dose strategies RCT3

Klinkert et al, Hum Reprod 2006

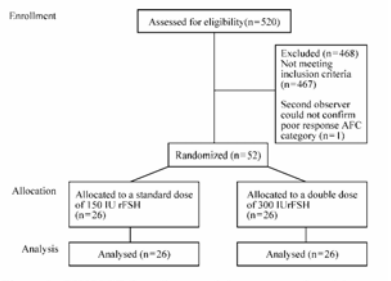


Figure 1. CONSORT flow diagram of the progress of participants through each state of the randomized trial.

RCT 3: No effect of high dose strategy

Table II. Comparison of the ovarian response and outcome of the IVF treatment of patients who received 150 IU rFSH/day after randomization and patients who received 300 IU rFSH/day

Characteristic	Group I 150 IU Gonal-F ($n = 26$)	Group II 300 IU Gonal-F ($n = 26$)	P
Cancels (low response)	5 (19)	6 (23)	0.73[b]
Dose adjustment	9 (35)	NA	NA
Day of hCG	14.0 (9.4–18.2)	13.0 (11.0–17.0)	0.34[a]
Maximum estradiol level (pmol/l)	2706 (200–5889)	2470 (200–6983)	0.48[a]
No. of follicles ≥ 10 mm	4 (1–8)	3 (0–8)	0.18[a]
Total FSH dose (IU)	2100 (1455–4440)	3600 (3000–4800)	NA
No. of oocytes	3 (1–9)	3 (1–6)	0.79[a]
No. of embryos	2 (0–6)	2 (0–6)	0.86[a]
Fertilization rate (%)	63 (3–100)	50 (0–100)	0.78[a]
No. of embryos transferred	1 (1–3)	2 (1–2)	0.45[a]
Low response	17 (65)	16 (62)	0.77[b]
Clinical pregnancies	3 (12)	4 (16)	0.30[b]
Ongoing pregnancies	2 (8)	1 (4)	0.55[b]

High dose strategies: Retrospective studies

- Intervention: Double starting dose 450 IU
- High dose: NO DIFFERENCE IN OUTCOMES

Karande et al . Fertil Steril 2000

- Intervention: Double starting dose 450 IU
- High dose:Increased oocytes, but low pregnancy rates (3.2%)

Land et al, Fertil Steril 1996

IN VITRO FERTILIZATION

Ovarian response and pregnancy outcome in poor-responder women: a randomized controlled trial on the effect of luteinizing hormone supplementation on in vitro fertilization cycles

Gorka Barrenetxea, Ph.D.,[a,b] Jon Ander Agirregoikoa, M.D.,[a] María Rosario Jiménez, M.D.,[a] Arantza Lopez de Larruzea, M.D.,[a] Teresa Ganzabal, M.D.,[a] and Koldo Carbonero, M.D.[a]

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- 84 patients
- FSH>10
- >40 years

TABLE 1

Stimulation protocols in group A and group B patients.

Variable	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Group A															
GnRH analogue[a]	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
rFSH[b]	375	375	375	375	375	300	300	300	300	225	225	225	225		
rLH[b]						150	150	150	150	75	75	75	75		
rhCG[c]															1
Group B															
GnRH analogue[a]	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
rFSH[b]	375	375	375	375	375	300	300	300	300	300	300	225	225		
rLH[b]															
rhCG[c]															1

[a] Leuprolide acetate (Procrin; in mL; 0.1 mL = 0.5 mg).
[b] International units (IU).
[c] Ovitrelle 250.

Barrenetxea. LH use in poor responders. Fertil Steril 2008.

RESULT AND CONCLUSION

TABLE 3

Primary outcome measures in both arms of the trial.

Parameter	Group A	Group B	*t*	χ^2	*P*
Pregnancy rate (%)[a]	23.81	21.43		0.892	.441
Pregnancy rate (%)[b]	26.32	23.68		0.899	.412
Pregnancy wastage (%)	30.00	22.22		0.041	.830
Implantation rate (%)[c]	8.12 ± 2.80	6.86 ± 2.24	0.645		.498

[a] Per started cycle.
[b] Per oocyte retrieval.
[c] Results expressed as mean ± SD.

Barrenetxea. LH use in poor responders. Fertil Steril 2008.

Patient characteristics, rather than the stimulation protocol, appear to determine individual ovarian response. A reduced ovarian response cannot be overcome by changes in the stimulation protocol or by altering the timing and duration of stimulation (1).

Why do alterations in gonadotropin protocols not improve birth rates in poor responders?

1.Poor response represents first sign of ovarian ageing

Regular cycling, ovulatory women, 29-40 years

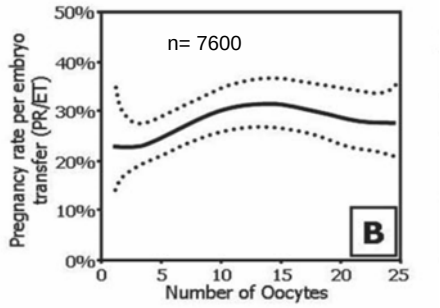
Previous poor response to ovarian stimulation

Studied in spontaneous cycle, versus controls

- Significant fewer antral follicles
- Elevated baseline FSH in less than 50%
- Normal inhibin B levels in 80%

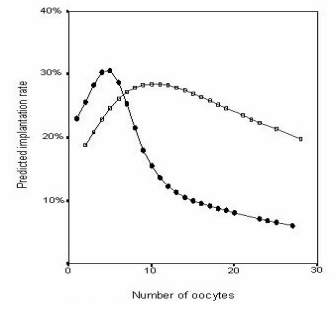
Beckers et al Fertil Steril 2002

2.More oocytes does not mean better outcomes



Van der Gaast et RBM Online 2006

3. 'Poor response' after mild stimulation: GOOD outcomes

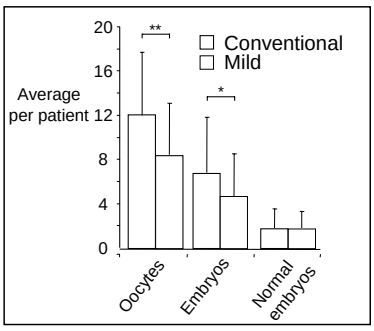


Conventional (n=160)

Mild (n=124)

Verberg, HRU 2008, In Press

4. Harder stimulation does not produce more euploid embryos



Baart et al, Hum Reprod 2007

Summary of Evidence

SO WHY DO WE PERSIST WITH HIGH DOSES?

- 'If patient reaches oocyte pick-up, then feels she has had a chance'.
- 'No other proven beneficial intervention'
- 'Need to do *something*'

Gonadotropin therapy in poor responders

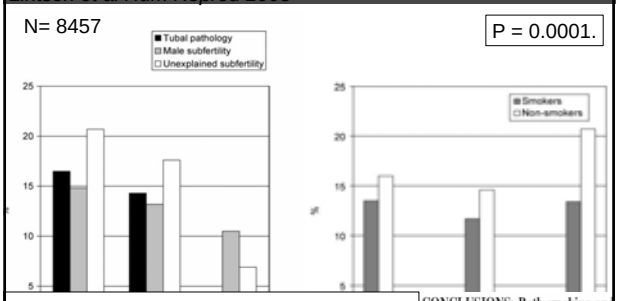
- **What can the doctor do?**
- **What can the *patient* do?**

Effect of ageing versus smoking on birth rate

Lintsen et al Hum Reprod 2005

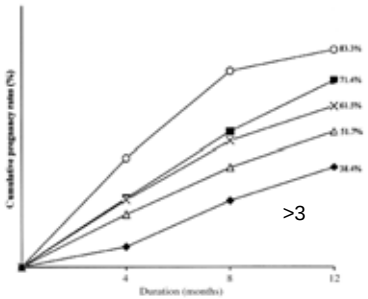
N= 8457

P = 0.0001.



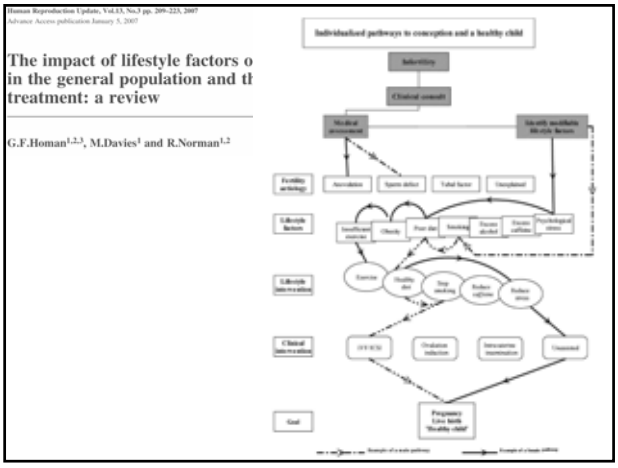
CONCLUSIONS: Both smoking and overweight unfavourably affect the live birth rate after IVF. The devastating impact of smoking on the live birth rate in IVF treatment is comparable with an increase in female age of >10 years from age 20 to 30 years. Subfertile couples may improve the outcome of IVF treatment by lifestyle changes.

Effect of increasing negative lifestyle variables



Nil
1
2
3
4

Hassan et al, 2004



Integrating Preconception Care

The 'PROCONCEPTION' Clinic

- **Preconceptional appointment 4 months before IVF**
- **Screening by website and nurse**
- **Personalised preconception plan**
- **Interventions**
- **Follow up**
- **RCTs**

Conclusions 1

- **Poor response usually represents ovarian ageing**
- **High dose strategies for poor responders:**
  - **Do NOT increase pregnancy rates**
  - **Result in more unnecessary interventions**
  - **Cost more money**

Conclusions 2

- **New focus required on optimising conditions before IVF**
- **Integrate Preconception care into Infertility work-up**
- ***If we invest a fraction of what we spend on high doses gonadotropins into targeted lifestyle interventions..***

THE ROLE OF EDUCATION CAMPAIGNS

Redrawing the map of IVF care