A new approach to IVF?

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‘Soft’ or ‘mild’ IVF

- Less patient discomfort
- Less complex, shorter stimulation regimes
- Less short term complications
- Less chance of long term health risks
- Less expensive

Fauser et al, 1999

‘Soft’ or ‘mild’ IVF

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- Less complex, shorter stimulation regimes
- Less short term complications
- Less chance of long term health risks
- Less expensive
- Fewer oocytes
- Fewer spare embryos for cryopreservation
- Less programmable IVF cycles

Fauser et al, 1999

Agonist or antagonist?

Historically …….

IVF involved

- Deep intramuscular injection of hMG
- Frequent serum and ultrasound monitoring
- Laparoscopic egg collection under general anaesthesia
- Low success rates
- Long protocol GnRH agonist regimes - *Rutherford et al 1988*

Nothing in life is perfect…..

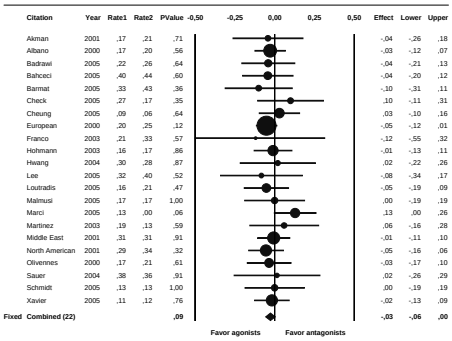
- Duration of treatment
  - Patient perception
  - Staff time (scans, blood tests, discussion etc)
- Menopausal side effects
- Cyst formation
- Failure to downregulate
- OHSS
- Unplanned pregnancies
- Cost

What might be the benefits of using GnRH antagonist?

- Simpler
- More patient friendly
- Safer
- Quicker
- Cheaper
- As effective

What does the literature tell us?

Live birth rate



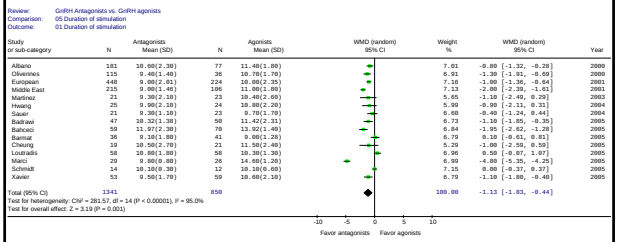
Odds ratio:0.8

p=0.09

Odds ratio 0.86 (95% CI 0.72–1.02)

Kolibianakis *et al. Hum Reprod Update* 2006;12:651–71

Duration of FSH treatment

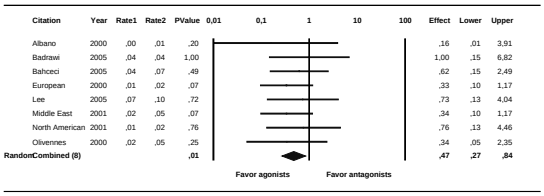


1.1 fewer days of FSH with antagonists

***p*<0.001**

Kolibianakis *et al. Hum Reprod Update* 2006;12:651–71

Hospital admission due to OHSS



Relative risk 0.47

~2 times more risk of hospital admission due to OHSS with GnRH agonists than with antagonists

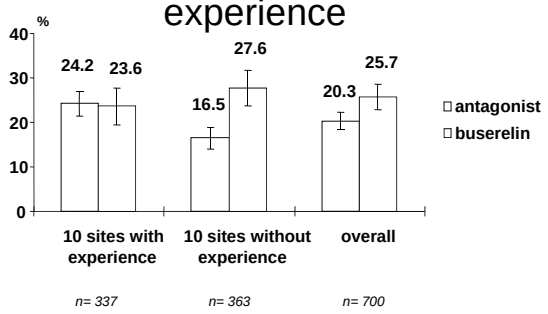
What looked different about antagonist cycles in 2001?

Compared with the 'long protocol', antagonist cycles seemed to:

- Require fewer days of stimulation
- Show lower E2 levels on day of hCG
- Produce one fewer oocyte per 75 IU dose increment

How best to use the antagonists in IVF?

sites
with and without previous experience



Values represent unadjusted means and SE

Exploring the 'learning curve'

GnRH antagonist IVF

Centre for Reproductive Medicine and Fertility
Sheffield
2001 - 2009

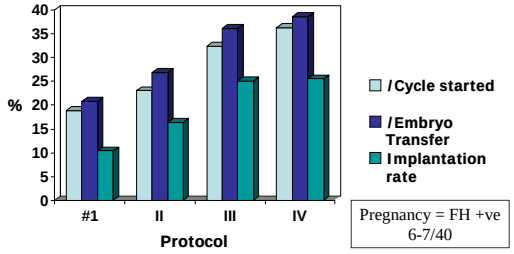
Protocols

I. Orgalutran fixed day 6 start
   Puregon & Orgalutran pm dose
II. Orgalutran day 5 to 9 flexible start
   Puregon & Orgalutran pm dose
III. Orgalutran day 5 to 9 flexible start
   Puregon & Orgalutran am dose
IV. Orgalturan day 5 fixed start
   Puregon & Orgalutran am dose
   First scan on day 7
   hCG when lead follicle > 16mm and at least three follicles at 16mm

Patient Characteristics

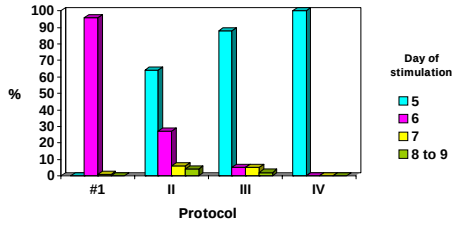
	I	II	III	IV	P value
Mean age (yrs)	33.4	33.1	32.3	32.9	NS
Unexplained (%)	26.4	20.2	23.7	16.5	NS
ICSI (%)	34.5	36.7	42.7	41.7	0.03
No. of oocytes (mean)	8.3	8.1	9.4	8.3	NS
No. of fertilised oocytes	5.2	5.6	6.3	5.2	NS
No. embryos transferred (mean)	1.94	1.9	1.96	1.77	0.2

Ongoing pregnancy & implantation rates

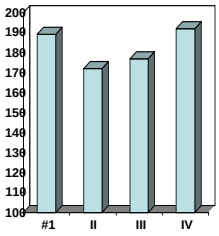


Pregnancy = FH +ve 6-7/40

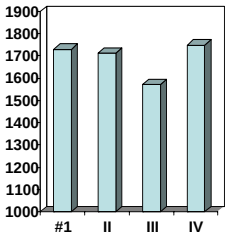
Antagonist Commencement



Stimulation



Starting dose Puregon



Total amount Puregon used

LH Suppression

- Premature LH rise:
  - 13.2% protocol I
  - < 2% protocols II, III, IV
- Mean LH (when antagonist commenced)
  - 4.9 IU/L protocol I vs 2.7 IU/L protocol II, III, IV

Increased pregnancy rates

By preventing LH rises was this preventing

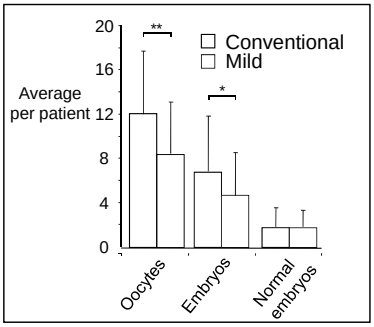
- early rise in progesterone?
- effect on endometrium?
- asynchrony between endometrium and embryo?

And therefore increasing chance of implantation?

Or is this an effect of lower peak E2 on endometrial receptivity or aneuploidy rates??

Or all three?

Mild IVF results in an increased proportion of euploid embryos



Baart et al, 2007

Ovarian hyperstimulation syndrome

- 2-7% of agonist IVF cycles
- Lower incidence with antagonist
- Jessop Wing - maximum of 2 cases hospitalised per year since inception of antagonist protocol
- Three paracenteses in 6 years
- Saves costs and physician time

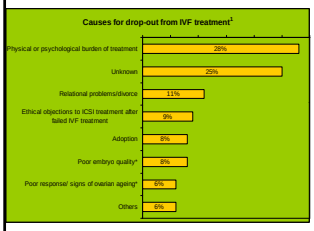
Who should not have GnRH antagonist with recombinant FSH?

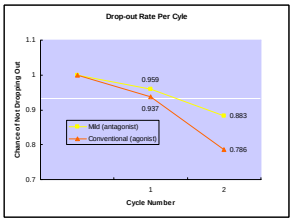
- Severe endometriosis
  - Long/ ultralong agonist protocol
- Previous highly asynchronous cohort development with antagonist
  - Long protocol
- WHO group I patients
  - Need LH

The patient experience

Why it matters

Why do couples drop out of IVF?





Verberg et al, 2008

Single embryo transfer

National IVF live birth rates – Guide to Infertility 2006-07

Fresh		Below 35	35-37	38-39	40-42	Over 42
	Cycles started	**28.2%** (3807/13489)	**23.6%** (1668/7077)	**18.3%** (728/3984)	**10.6%** (314/2965)	**3.2%** (27/836)
	Singleton live births	71.6% (2724/3807)	76.9% (1283/1668)	81.5% (593/728)	87.6% (275/314)	++ (26/27)
	Multiple birth rate	**28.4%** (1083/3807)	**23.1%** (385/1668)	**18.5%** (135/728)	**12.4%** (39/314)	++ (1/27)
	Twin live births	28.0% (1065/3807)	22.6% (377/1668)	18.3% (133/728)	11.5% (36/314)	++ (1/27)
	Triple & higher live births	0.5% (18/3807)	0.5% (8/1668)	0.3% (2/728)	1.0% (3/314)	0

Multiple pregnancy - “the most serious complication of IVF”

- Maternal death
- Severe OHSS
- Pre eclampsia
- Gestational diabetes
- Anaemia
- Antepartum haemorrhage and abnormal placentation
- Postpartum haemorrhage
- Polyhydramnios
- Premature birth
- Caesarean section

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- Premature birth
- Caesarean section
- Nausea/ vomiting
- Fatigue
- Weight gain
- Heartburn
- Sleeplessness
- Haemorrhoids

Multiple pregnancy - “the most serious complication of IVF”

Triplets

- 20x relative risk of delivery before 37 weeks
- Mean birth weight 1735 grams
- Mean gestation 32.5 weeks
- Low birth weight in 90%

Multiple pregnancy - “the most serious complication of IVF”

Twins

- 5.5x relative risk of delivery before 37 weeks
- Mean birth weight 2389 grams
- Mean gestation 35.8 weeks
- Low birth weight in 53% (9x increased risk)

Triplets

- 20x relative risk of delivery before 37 weeks
- Mean birth weight 1735 grams
- Mean gestation 32.5 weeks
- Low birth weight in 90%

Multiple pregnancy - “the most serious complication of IVF”

Increased perinatal morbidities

- Congenital anomaly
- Cerebral palsy
- Intracranial haemorrhage
- Blindness
- RDS
- PDA
- Sepsis

Multiple pregnancy - “the most serious complication of IVF”

Increased perinatal morbidities
- Congenital anomaly
- Cerebral palsy
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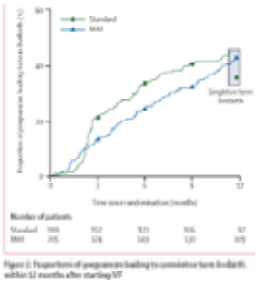
- PDA
- Sepsis

- Cost per mother
  - Singleton
    - $9845
  - Twin
    - $37947
  - Triplet
    - $109765
- Excess hospital cost from ART multiples in 2000 was $640,000,000

Cumulative livebirth rate with mild vs conventional IVF

- RCT of agonist long protocol with DET vs ‘mild’ GnRH antagonist protocol with SET in women under 38 years
- Supernumerary embryos cryopreserved and replaced later
- Further ‘fresh’ IVF cycle undertaken where necessary
- One year of active treatment for all couples



Heijnen et al, 2007

	Mild		Standard	
	singleton	**multiple**	**singleton**	**multiple**
total livebirths	91	3	76	26
liveborn children	91	3	76	51
term livebirth	86	0	69	17
birthweight (kg)	3.34	1.34	3.35	2.34

Heijnen et al, 2007

- ‘Mild’ IVF with SET required more cycles (444 cycles for 205 patients vs 325 cycles for 199 patients) and more embryo transfers
- Equivalent number of livebirths between the two groups (43.4% vs 44.7%)
- **Multiple pregnancy rate 0.5% vs 13.1%**

Heijnen et al, 2007

UK Expert Group on Multiple Births

- Offering elective SET to 50% of patients will result in a twin rate of not more than 10%
- Based on previous experience …. We do not see that professional guidance alone can convince the sector of the need for change
- HFEA - target rate of twins of 10% by 2011

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Pharmacoeconomics of ‘mild’ IVF

What is the true cost of a ‘mild’ IVF cycle?

- Detailed costing of all aspects of IVF cycle
  - Staff costs
  - Consumables
  - Premises
  - Heating/ lighting etc
- Low dose predominantly GnRH antagonist protocol
- Formulary costs of drugs

Ledger et al (2009)

FSH usage and cost per cycle/pregnancy/live birth

	Mean	SD
dose prescribed (IU) per cycle	1,855	(576)
dose dispensed (IU) per cycle	1,891	(588)
cost per cycle (FSH costs)	Euro 646	(219)
cost per cycle (concomitant meds)	Euro 159	(122)
cost per cycle (procedure costs)#	Euro 2,127	(349)
total cost per cycle	**Euro 2,932**	(422)
cost per clinical pregnancy	Euro 8,058	
cost per ongoing pregnancy	Euro 12,017	
cost per live birth (all ages)	Euro 13,326	

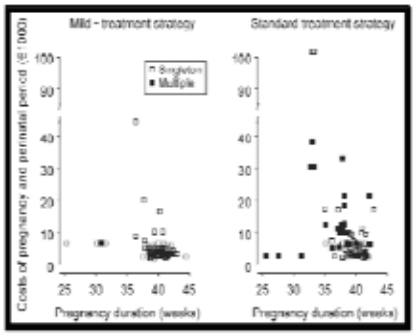
1418 cycles, mean age 35.9 yrs (range 22 - 49)

Cost effectiveness of IVF

- Euro 2950 per cycle at age 30
- Euro 3350 per cycle at 40
  - Higher requirement for gonadotropins
  - More monitoring
  - More cycle cancellations
- Cost per baby at age 30
  - Euro 9033
- Cost per baby at age 40
  - Euro 33500

Ledger et al, 2009

Cost effectiveness of IVF

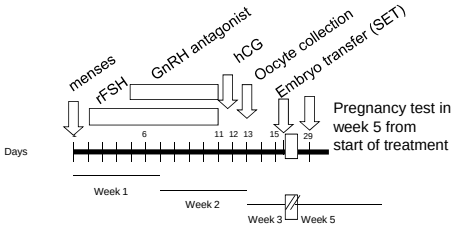


Polinder et al, 2008

The current Sheffield experience

- Puregon/ GnRH antagonist based practice (> 80% of cycles)
  - > 36 yo, 150 IU starting dose
  - > 35 yo, 200 IU
- SET in 25% of patients
- Fixed day 5 start orgalutran
- Embryology laboratory to GMP standard
- Ongoing PR per cycle started - 36%

Jessop antagonist protocol



Practical problems

- Cycle scheduling
  - Less predictable day of cycle commencement
  - Peaks and troughs in workload
  - Week end working
- When to give hCG
  - Ultrasound criteria (which?)
  - E_2?
- Need to monitor LH?

OCP cycle programming before GnRHant controlled superovulation

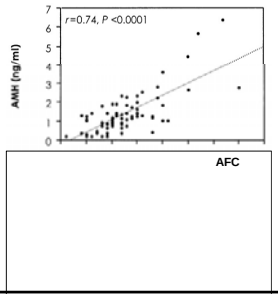
- 64 patients randomised to GnRHant/rec FSH (day 1- 2 start) vs single month OCP pretreatment/rec FSH/GnRHant
- Slower rise in E2 following OCP pretreatment
- Longer duration of recFSH
- Higher number of mature follicles on day of hCG
- Higher number of oocytes
- Hypothesise that this allows development of a larger synchronised cohort of follicles

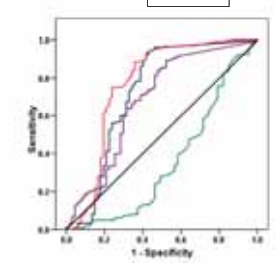
Van Lonen et al, 2001

The next step?

Anti-Müllerian hormone to predict cycle outcome and rationalise programming

AMH, antral follicle count and oocyte yield after superovulation





Fanchin, 2004 & Ledger, unpublished

Use of AMH to dictate stimulation protocol

	AMH < 5 Antagonist + 300 IU	AMH 5-15 Long protocol + 225/ 300 IU	AMH > 15 Antagonist + 150 IU
Number of patients	61	73	34
Mean age	39	37	32
Days of stimulation	10	11	9
Number of oocytes/ embryos	3/2	6/4	10/6
Hospitalisation for OHSS	0	1	0
CPR per cycle started	14.7%	32.9%	61.7%

Nelson et al, 2009

Jessop Wing plan for 2009

ACU medical consult

- Medical history - complete clinical workup
- If ‘normal’ AMH (5 - 15 pmol/l) and patient weight > 60kg
  - Prescribe Puregon 200 iu
  - Orgalutran
  - OCP x 2 packs
- Start OCP with next period
- Give nurse appt for day 21 (+/- 2 days)

ACU nurse consult

- Ultrasound
- Drug training and prescription
- Plan details of cycle
  - Program ‘stop day’ for OCP
  - To start FSH d2 of w/d bleed
  - To start antagonist on d5 of FSH
- Next appointment d7 of FSH

Day 7 visit

- Scan & E2
- Alternate day scan & E2 or plan hCG if 2 follicles 17mm
- hCG 10000 IU
- Single blastocyst transfer if > 3 grade 1 embryos on day 3

AMH >15 or PCOS

- Start OCP as for normal AMH
- 100 IU FSH starting dose
- Scan d5 of stimulation
- Start antagonist if any follicle 14mm or more
- Criteria for cancellation
  - E2 > 20000pmol/L
  - > 10 follicles of 14mm per ovary
- Or freeze all embryos

AMH < 5

- Warn high chance of poor response/ low pregnancy rate
- Start OCP as for normal AMH
- 300 IU FSH
- Antagonist when any follicle >14mm
- D2 transfer

Thank you

What would you do?

- 23 year old nullipara
- Bilateral salpingectomy
- Basal FSH 3.2 IU/L, AMH 4 pg/ml
- Normal semen analysis x 2
  - Protocol?
  - Starting dose of FSH?
  - Number of embryos to transfer?
  - Chance of livebirth?

What would you do?

- 25 year old nullipara
- Anovular PCOS plus severe male factor
- Amenorrhoea for 1 year
- BMI 28
- Basal FSH 3.2 IU/L, AMH 11 pg/ml
- Needs ICSI
  - Protocol?
  - Starting dose of FSH?
  - Number of embryos to transfer?
  - Chance of livebirth?

What would you do?

- 41 year old nullipara
- Unexplained infertility
- New relationship
- Basal FSH 9.2 IU/L, AMH 1.4 pg/ml
- Normal semen analysis x 2
- Normal basal pelvic ultrasound
  - Protocol?
  - Starting dose of FSH?
  - Number of embryos to transfer?
  - Chance of livebirth?