Male and female work-up before IVF and Stimulation Protocols in assisted conception

Raj Mathur
Clinical Lead for Reproductive Medicine and Surgery
Manchester University Foundation Trust
Secretary, British Fertility Society
rmathur@nhs.net T@rajmathur7

This presentation made possible, in part, with the generous non-restricted educational grant support from our sponsor for this workshop:

Aims of male and female work-up

- To decide whether IVF is the right treatment
- To prepare the couple for IVF
- To predict response to stimulation
- To predict chance of success (healthy live birth)
- To identify risks, eg OHSS, child affected by inherited disorder
- To identify modifiable factors that can influence success/risk
- Optimise general health

Male work-up

- History
- Examination if indicated by history or semen analysis
- Semen Analysis
  - Accredited good-quality laboratory
  - WHO Manual 5th edition standards
  - No consensus on indicators for ICSI, but the original indication is in cases of significant semen abnormality

Male tests before IVF

- Severe Oligozoospermia or Azoospermia need further tests to identify nature of problem and prognosis
  - FSH, Testosterone
  - Testicular Ultrasound
  - Karyotype
  - Y-chromosome microdeletions – AZFa very poor prognosis for TeSE
- Sperm DNA Fragmentation – no clear role in routine practice despite much research. Lack of a sufficiently predictive, reproducible test which can modify the management of a couple (Cissen et al 2016)
- Cystic Fibrosis testing if absent vas deferens

Female work-up

- Ovarian Reserve assessment
- Pelvic structural evaluation
  - Ultrasound (Antral Follicle Count, tubal pathology, fibroids, endometrial problems, accessibility of ovaries for egg collection)
  - 3D Ultrasound for congenital anomalies
  - MRI for congenital anomalies, Adenomyosis
  - Hysteroscopy
  - Laparoscopy
- Co-existing medical conditions thyroid, diabetes, hypertnesion, auto-immune

Ovarian Reserve Tests

- **Anti-Mullerian Hormone (AMH)**
  - Produced by granulosa cells of small growing primordial follicles, in the FSH-independent phase
  - Not expressed in FSH-dependent stage
  - Intrafollicular levels decline as follicle grows, with sharp decline in 8 mm follicles
  - Expressed in cumulus cells of pre-ovulatory human follicle
  - Serum AMH is relatively stable throughout menstrual cycle
  - Good marker of quantitative ovarian response to stimulation, hence can be used to tailor stimulation regimes (Nelson et al, Yates et al)
  - AMH ≤5.4 pmol/l predicts poor response and ≥25 pmol/l indicates high response (NICE 2013)
  - Not a good predictor of spontaneous conception (Streuli et al 2014)

Antral Follicle Count

- Known to be a good predictor of ovarian response to stimulation
- AFC does vary depending on phase of cycle, but not so much as to change the prediction of response (Mavrelos et al 2016)
- Allows the opportunity to examine for other pelvic pathology, eg fibroids, cysts, hydrosalpinx
- Probably greater inter-cycle and inter-observer variability than AMH (Disseldorp et al 2010)
- AFC≤4 predicts poor response and ≥17 excessive response (NICE 2013)

AMH and AFC

- AMH reflects primordial and small antral follicle pool, while Antral Follicle Count reflects follicles 2 – 10 mm
- Discrepancy between AMH and AFC may occur:
  - Technical factors
  - Atretic follicles – cannot be distinguished by AFC
  - Large proportion of 1-2 mm follicles in AFC may lead to disproportionately high AMH

Hydrosalpinges

- Clear evidence of 50% reduced live birth rate in the presence of hydrosalpinges. Effect is more marked if bilateral and larger (Strandell 2000)
- Mechanism theories include embryotoxic effect, impaired uterine environment (reduced integrins) and mechanical effect of fluid
- Salpingectomy improves outcomes
- Tubal occlusion appears to be equally effective (Zhang et al 2015)
- Recent meta-analysis did not show any short-term effect of salpingectomy on ovarian reserve (Mohamed et al 2017) but concern remains

Considerations for hydrosalpinges

- Careful patient pre-operative counseling
  - Natural conception will be impossible if both tubes are occluded or removed
  - Not reversible
  - Sometimes best to not do this at the first laparoscopy
- If significant pelvic pain, salpingectomy may be better than occlusion
- If dense adhesions, occlusion may present less risk to ovarian reserve
- Is there a role for reconstructive surgery – mild tubal disease, cannot afford IVF?
- Role of aspiration of hydrosalpinges at the time of egg collection is not clear – fluid can re-accumulate – but could be considered if there is a high surgical risk

Hysteroscopy before IVF?

- Systematic review and meta-analysis –in asymptomatic women (clinical pregnancy and live birth rates).
- 1 RCT and 5 non RCT - 3179 participants
- Significantly higher **clinical pregnancy rate.**
- NNT for hysteroscopy to achieve one additional clinical pregnancy: 10 (95% CI 7-14).
- Further RCT needed.

Pundir et al , Reprod Biomed Online. 2014 Feb;28(2):151-61.

- Multicentre RCT inSIGHT
- Routine hysteroscopy pre-first IVF in patients with normal scans offers no advantage and should not be offered as a routine
- *Lancet. 2016 Jun 25;387:2622-9*

Uterine Fibroids

- Subserous fibriods have no impact, but may make the ovaries difficult to access vaginally
- Submucous fibroids reduce the chance of implantation and live birth

Effect of fibroids on fertility: submucous fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	4	0.363	0.179–0.737	$P=.005$
Implantation rate	2	0.283	0.123–0.649	$P=.003$
Ongoing pregnancy/live birth rate	2	0.318	0.119–0.850	$P<.001$
Spontaneous abortion rate	2	1.678	1.373–2.051	$P=.022$
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

Fibroids without cavity involvement

Effect of fibroids on fertility: intramural fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.696–0.941	$P=.006$
Implantation rate	7	0.684	0.587–0.796	$P<.001$
Ongoing pregnancy/live birth rate	8	0.703	0.583–0.848	$P<.001$
Spontaneous abortion rate	8	1.747	1.226–2.489	$P=.002$
Preterm delivery rate	1	6.000	0.309–116.606	Not significant
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437–1.146	Not significant
Implantation rate	2	0.552	0.391–0.781	$P=.001$
Ongoing pregnancy/live birth rate	2	0.465	0.291–0.744	$P=.019$
Spontaneous abortion rate	2	2.384	1.110–5.122	$P=.002$
Preterm delivery rate	0	—	—	—
C. Studies using hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.845	0.666–1.071	Not significant
Implantation rate	1	0.714	0.547–0.931	$P=0.013$
Ongoing pregnancy/live birth rate	2	0.733	0.383–1.405	Not significant
Spontaneous abortion rate	2	1.215	0.391–3.774	Not significant
Preterm delivery rate	1	6.000	0.309–116.606	Not significant

Pritts. Fibroids and infertility. Fertil Steril 2009.

What about intramural fibroids and IVF success?

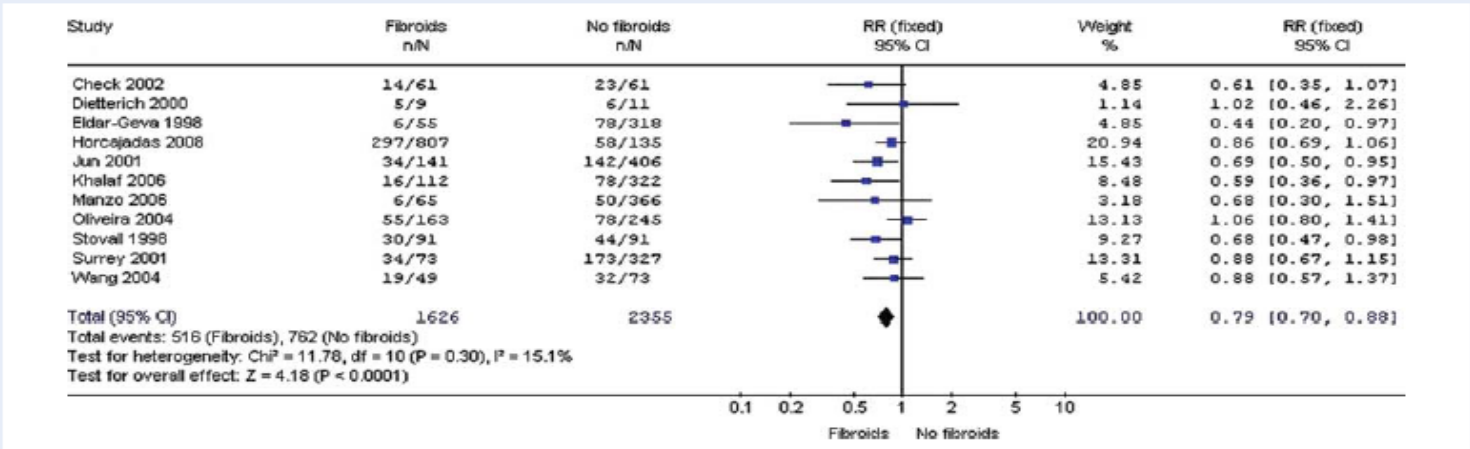


Figure 3 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of live birth rates.

Sunkara et al (2010) Hum Reprod 25; 418-429

Data from 19 observational studies, 6087 IVF cycles

Significant reduction in clinical pregnancy rate and live birth rate (RR 0.79 (070-0.88)) in women with non-cavity-distorting intramural fibroids, compared with women without fibroids

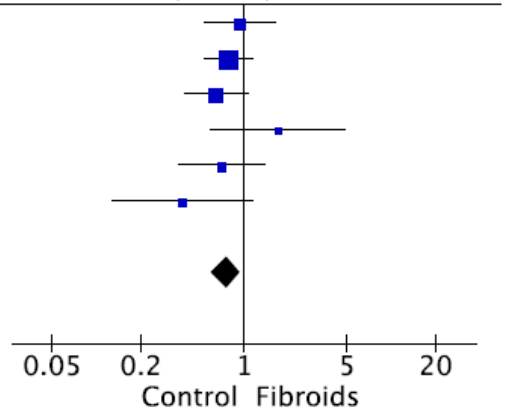
LBR reduced by 21% and CPR by 15%

Non-cavity-distorting intramural fibroids and IVF success

Study or Subgroup	Fibroids Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bozdag et al, 2009	22	61	167	444	15.2%	0.94 [0.54, 1.63]
Horcajadas et al, 2008	431	807	80	135	37.6%	0.79 [0.54, 1.14]
Khalaf et al, 2006	27	112	106	322	24.4%	0.65 [0.40, 1.06]
Ng et al, 2005	11	48	7	47	3.2%	1.70 [0.60, 4.84]
Surrey et al, 2001	27	51	70	114	12.0%	0.71 [0.36, 1.38]
Vimercati et al, 2007	4	31	57	205	7.7%	0.38 [0.13, 1.15]
Total (95% CI)		**1110**		**1267**	**100.0%**	**0.76 [0.61, 0.96]**
Total events	522		487			

Heterogeneity: $Chi^2 = 4.77$, $df = 5$ ($P = 0.44$); $I^2 = 0\%$

Test for overall effect: $Z = 2.29$ ($P = 0.02$)



Metwally et al (2011) RBM Online 23, 2-14

Analysis of studies with low risk of bias confirms a lower IVF Clinical Pregnancy Rate (but no difference in Live Birth Rate with much smaller numbers)

Do intramural fibroids reduce IVF success? Is there room for doubt?

- Some prospective, some retrospective studies
- Variable methods of cavity assessment – some used TV scan only
- Variation in number and size of fibroids
- Different types of assisted conception treatment
- Different cycle numbers – 6 studies on first cycles only

However

Studies scored highly on quality assessment

Likelihood of publication bias was low

Reduction of live birth rate was even more marked when only prospective studies were considered

Two high-quality meta-analyses are in agreement

Does treatment of fibroids improve fertility?

- **For subserous fibroids, no**
- **For submucous fibroids, yes, probably…**

Effect of myomectomy on fertility: submucosal fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. Controls: fibroids in situ (no myomectomy)				
Clinical pregnancy rate	2	2.034	1.081–3.826	*P*=.028
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	2.654	0.920–7.658	Not significant
Spontaneous abortion rate	1	0.771	0.359–1.658	Not significant
Preterm delivery rate	0	—	—	—
B. Controls: infertile women with no fibroids				
Clinical pregnancy rate	2	1.545	0.998–2.391	Not significant
Implantation rate	2	1.116	0.906–1.373	Not significant
Ongoing pregnancy/live birth rate	3	1.128	0.959–1.326	Not significant
Spontaneous abortion rate	2	1.241	0.475–3.242	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

Risks should be discussed with patient

Myomectomy for intramural fibroids and fertility

Effect of myomectomy on fertility: intramural fibroids (fibroids in situ controls).

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	2	3.765	0.470–30.136	Not significant
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	1.671	0.750–3.723	Not significant
Spontaneous abortion rate	1	0.758	0.296–1.943	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

Small numbers

No comparison with control women without fibroids

How do we reconcile this with meta-analyses showing adverse effect of intramural non-cavity-distorting fibroids on natural and IVF fertility?

- Association rather than cause?
- Patient selection?

Cochrane review on fibroid with subfertility

- Insufficient evidence regarding role of myomectomy to improve fertility
- One study – only included single fibroid of 4 cm size
  - no information regarding large or multiple fibroids
  - no sample size
  - study included open and hysteroscopic myomectomies

Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database of Systematic Reviews 2012, Issue 11.

Myomectomy for intramural non-cavity-distorting fibroids

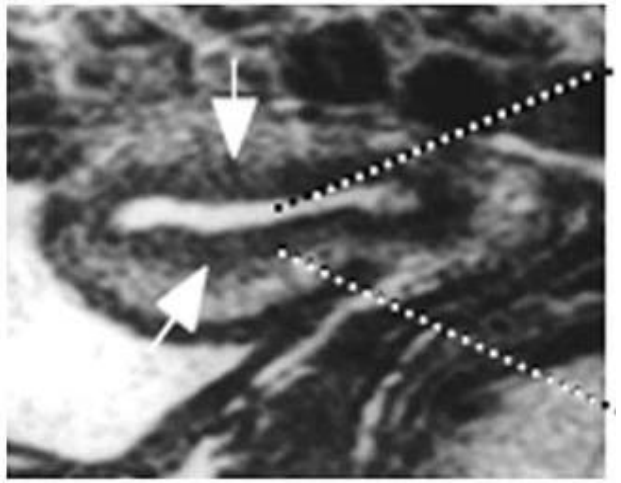
- Adequately powered RCT is clearly needed, but meanwhile the clinical dilemma remains
- Decisions need to be taken with full patient involvement and counselling
- Consider all aspects – age, other fertility factors, egg and embryo quality
- Consider surgical risks
  - Myomectomy is unlikely to be warranted before one cycle of IVF or if the couple have been trying less than 1 year
- Consider size of fibroids?
  - 'Large' fibroids – seems 'logical' to remove these
  - But even intramural non-cavity-distorting fibroids smaller than 5 cm may reduce IVF cumulative pregnancy rate by 40%

Khalaf et al (2006) Hum Reprod 21, 2640-4

How do intramural non-cavity-distorting fibroids reduce fertility?

Altered perfusion
Altered endometrial development
Altered myometrial contractility

} Mostly theoretical



Uterine Junctional Zone

- Inner third of myometrium
- Involved in placentation
- Visible as a low-intensity signal on T2 weighted MR, between higher intensity endometrium and outer myometrium; also visible on TV US
- Origin of myometrial contractions in non-pregnant uterus

Might intramural fibroids arising from, or affecting, the uterine JZ have a worse fertility prognosis?

Increased uterine contractility associated with intramural fibroids?

- JZ contractions: mainly cervico-fundal in periovulatory phase and fundo-cervical in menstrual phase, little or no activity during implantation window.
- Prospective study of 51 women with intramural fibroids and infertility: Cine MR during implantation window found increased contractility
- Lower pregnancy rate in women with higher frequency contractions (>2/3 min) compared to those with less frequent contractions (0/22 vs 10/29; $p<0.005$)

Yoshino et al (2010) Hum Reprod 25; 2475-9

- Higher frequency contractions at ET are associated with a lower implantation rate

Fanchin et al (2009) RBM Online

- ***Could this provide another parameter to consider when selecting patients in whom treatment of intramural fibroids may improve fertility?***

How can we modulate disordered contractility?

- Progesterone
- Reduced oestrogen exposure
- Careful embryo transfer technique

Oxytocin Antagonist

RCT in women with rec implantation failure shows benefit ***Chou et al 2011***

Remove fibroid?

Laparoscopic or Open

Shrink fibroid – Ulipristal? Liver toxicity

Programmed cell death and prolonged effect may create a window during which IVF may be carried out

Ovarian Stimulation regimes

- Should we use ovarian stimulation?
  - Natural cycle
  - Mild stimulation or modified natural
  - Conventional Stimulation

Significantly lower live birth rate, likely lower cumulative birth rate

- Should we use pituitary down-regulation?
  - Without pituitary downregulation
  - GnRH Agonist
  - GnRH Antagonist
- Which gonadotropin preparation to use?
  - Recombinant
  - Urine-derived
  - With LH activity?
- How should we determine dose of stimulation?
- What trigger should be used for final follicular maturation?

GnRH Agonist vs GnRH Antagonist

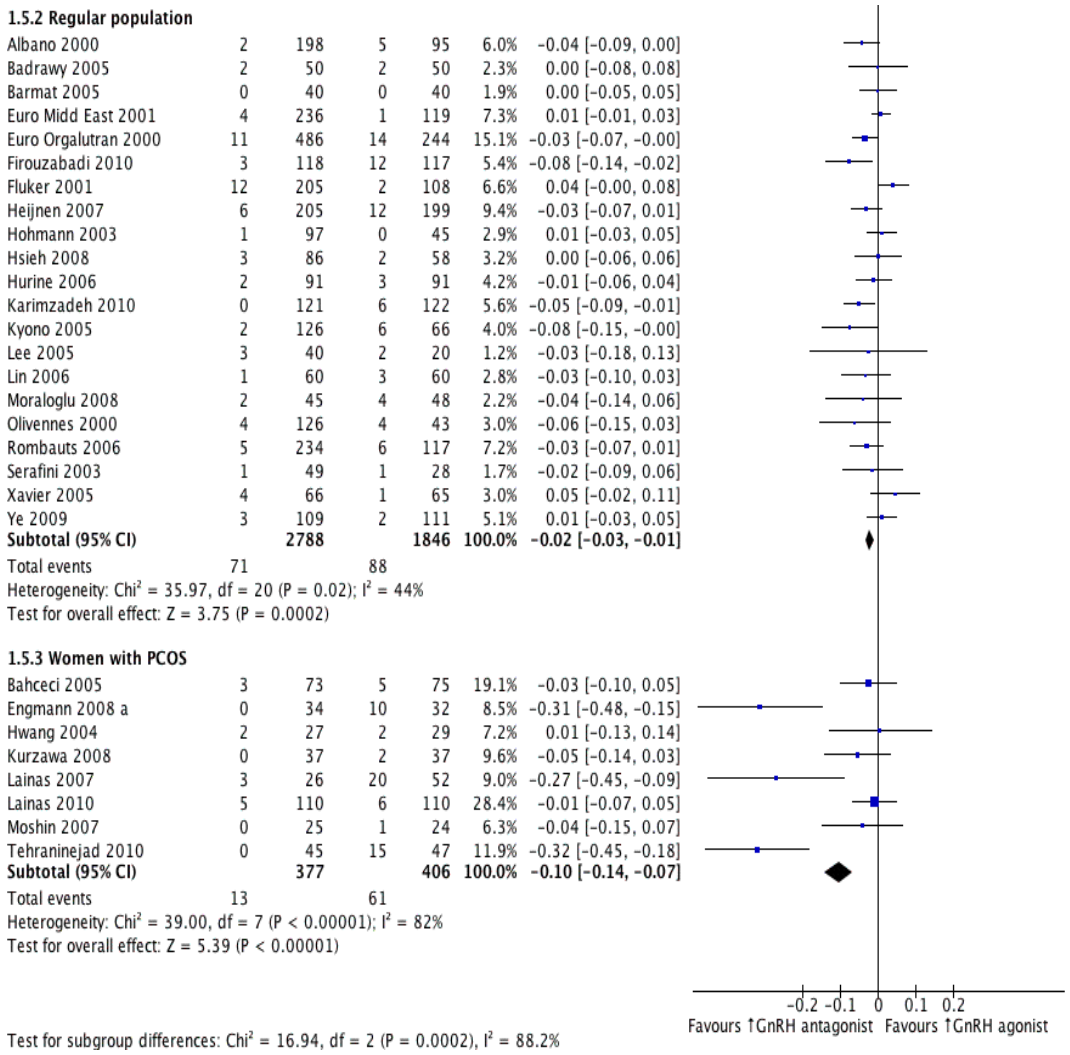
GnRH agonists

- Bind to GnRH receptors
- Initial stimulation, then de-sensitisation
- Inhibitory effect takes ≥7 days
- Flare effect may cause cysts
- Inhibitory effect causes menopausal symptoms
- Typically from middle of luteal phase nasal spray or sc injection
- May benefit women with endometriosis

GnRH antagonists

- Compete with endogenous GnRH for receptor
- Rapid inhibition of LH and FSH release
- Continued action needs high daily doses
- Started during ovarian stimulation
- No 'flare' effect
- No menopausal side-effects
- Lower risk of OHSS

GnRH antagonist



1.5.2 Regular population						
Albano 2000	2	198	5	95	6.0%	-0.04 [-0.09, 0.00]
Badrawy 2005	2	50	2	50	2.3%	0.00 [-0.08, 0.08]
Barmat 2005	0	40	0	40	1.9%	0.00 [-0.05, 0.05]
Euro Midd East 2001	4	236	1	119	7.3%	0.01 [-0.01, 0.03]
Euro Orgalutran 2000	11	486	14	244	15.1%	-0.03 [-0.07, -0.00]
Firouzabadi 2010	3	118	12	117	5.4%	-0.08 [-0.14, -0.02]
Fluker 2001	12	205	2	108	6.6%	0.04 [-0.00, 0.08]
Heijnen 2007	6	205	12	199	9.4%	-0.03 [-0.07, 0.01]
Hohmann 2003	1	97	0	45	2.9%	0.01 [-0.03, 0.05]
Hsieh 2008	3	86	2	58	3.2%	0.00 [-0.06, 0.06]
Hurine 2006	2	91	3	91	4.2%	-0.01 [-0.06, 0.04]
Karimzadeh 2010	0	121	6	122	5.6%	-0.05 [-0.09, -0.01]
Kyono 2005	2	126	6	66	4.0%	-0.08 [-0.15, -0.00]
Lee 2005	3	40	2	20	1.2%	-0.03 [-0.18, 0.13]
Lin 2006	1	60	3	60	2.8%	-0.03 [-0.10, 0.03]
Moraloglu 2008	2	45	4	48	2.2%	-0.04 [-0.14, 0.06]
Olivennes 2000	4	126	4	43	3.0%	-0.06 [-0.15, 0.03]
Rombauts 2006	5	234	6	117	7.2%	-0.03 [-0.07, 0.01]
Serafini 2003	1	49	1	28	1.7%	-0.02 [-0.09, 0.06]
Xavier 2005	4	66	1	65	3.0%	0.05 [-0.02, 0.11]
Ye 2009	3	109	2	111	5.1%	0.01 [-0.03, 0.05]
Subtotal (95% CI)		**2788**		**1846**	**100.0%**	**-0.02 [-0.03, -0.01]**
Total events	71		88			
Heterogeneity: Chi² = 35.97, df = 20 (P = 0.02); I² = 44%						
Test for overall effect: Z = 3.75 (P = 0.0002)						
1.5.3 Women with PCOS						
Bahceci 2005	3	73	5	75	19.1%	-0.03 [-0.10, 0.05]
Engmann 2008 a	0	34	10	32	8.5%	-0.31 [-0.48, -0.15]
Hwang 2004	2	27	2	29	7.2%	0.01 [-0.13, 0.14]
Kurzawa 2008	0	37	2	37	9.6%	-0.05 [-0.14, 0.03]
Lainas 2007	3	26	20	52	9.0%	-0.27 [-0.45, -0.09]
Lainas 2010	5	110	6	110	28.4%	-0.01 [-0.07, 0.05]
Moshin 2007	0	25	1	24	6.3%	-0.04 [-0.15, 0.07]
Tehraninejad 2010	0	45	15	47	11.9%	-0.32 [-0.45, -0.18]
Subtotal (95% CI)		**377**		**406**	**100.0%**	**-0.10 [-0.14, -0.07]**
Total events	13		61			
Heterogeneity: Chi² = 39.00, df = 7 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 5.39 (P < 0.00001)						
Test for subgroup differences: Chi² = 16.94, df = 2 (P = 0.0002), I² = 88.2%						

29 trials, involving 5417 women

Severe OHSS : 2.65% Antagonist

vs

6.61% Agonist

60% lower risk of OHSS in women receiving GnRH antagonist vs GnRH agonist

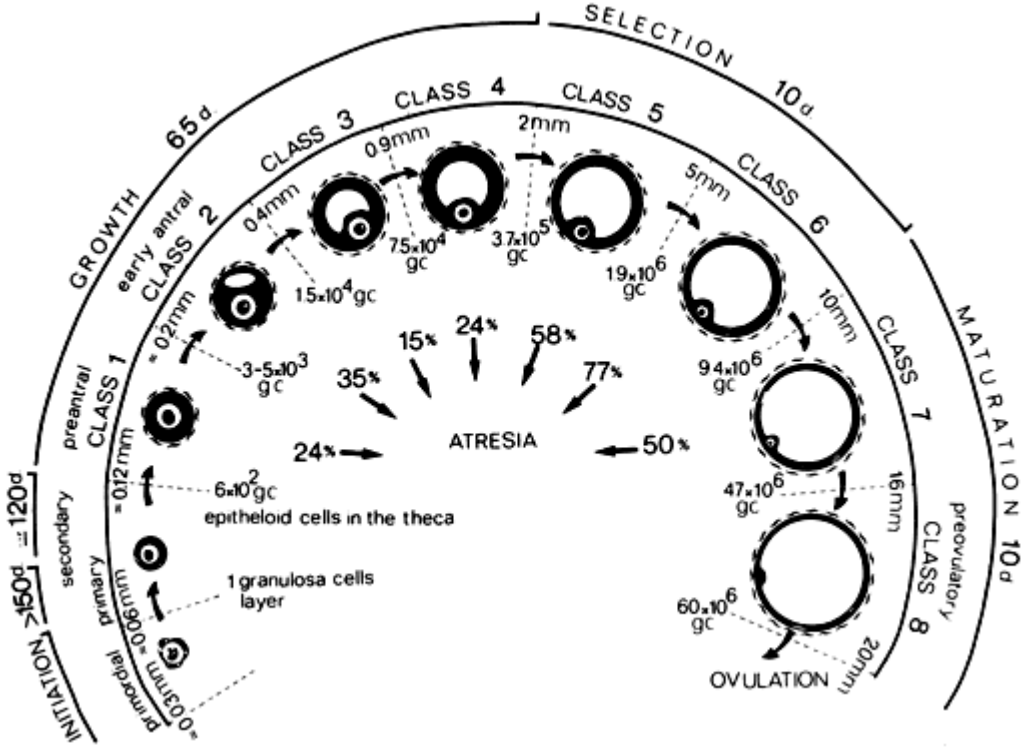
Absolute risk reduction 4% in overall population (95% CI 3 – 5)

Number needed to harm 25

Al Inany et al 2011

Folliculogenesis

- Process of development from primordial follicle to a Graafian follicle with the potential to ovulate
- Takes approximately 1 year
  - Preantral 300 days
  - Antral 50 days
  - Selection and maturation 20 days



Stages of folliculogenesis

- Primordial follicles are triggered to start growing
- Preantral Follicles
  - Primary
  - Secondary
  - Early Tertiary
- Antral Follicle
- Growth of cohort of 2-5 mm antral follicles in luteal phase
- Selection of dominant follicle in mid-follicular phase
- Ovulation
- Atresia

FSH - independent

What is ‘recruitment’

This term may be used for any of the following:

- Triggering of primordial follicles to start developing
- Emergence of a cohort of small 2-5 mm antral follicles, thought to occur in the late luteal phase
- ‘Selection’ of dominant follicle

FSH and follicle recruitment

- FSH rise above threshold leads to recruitment of small antral follicles
- Short duration of rise – fewer follicles
- Longer duration – longer 'window' – more follicles recruited
- Drop in FSH levels leads to follicular dominance, as dominant follicle has greater FSH sensitivity

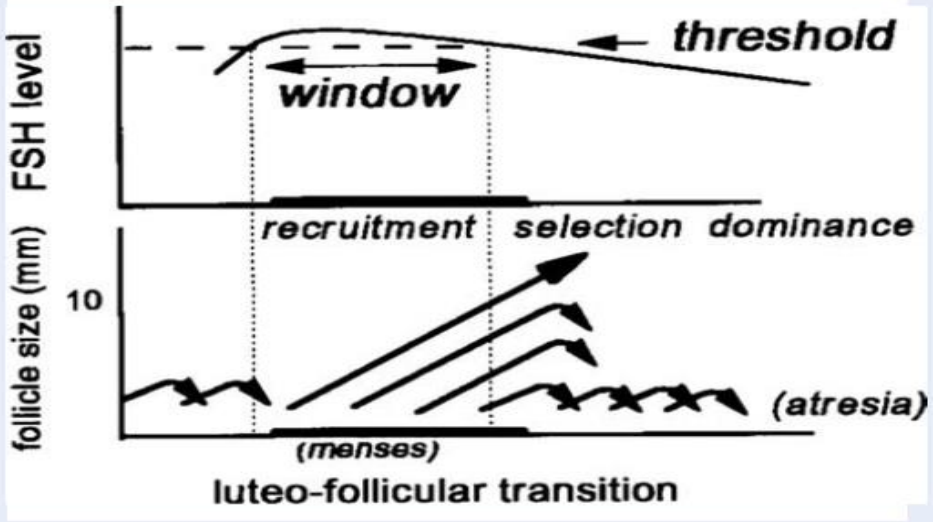


Figure 4 Schematic representation of the FSH threshold (window) concept and follicle growth dynamics (recruitment, selection and dominance) during the follicular phase of the menstrual cycle. [*Reproduced with permission from Elsevier, Fauser and Van Heusden, 1997, Endocrine Reviews, 18(1): 71–105; Originally adapted from Baird et al., 1987, J Steroid Biochem, 71(1): 15–23*].

Patterns of recruitment

- Not just a single episode in late luteal phase
- Multiple waves throughout cycle *Baerwald et al Human Reproduction Update 2012*
- If multiple waves occur, ovarian stimulation could be started at any time in the cycle – 'random start' stimulation protocols
  - Fertility preservation before cancer treatment
  - Poor responders?

Gonadotropins for Ovarian Stimulation

- **Urine-derived**
  - **Human Menopausal Gonadotrophin**: Standard ampoule has 75 iu FSH and 75 iu LH activity.
  - **Urinary FSH**: 75 iu FSH and 0.1 iu LH
  - **Purified urinary FSH**: 75 iu FSH and virtually no LH activity

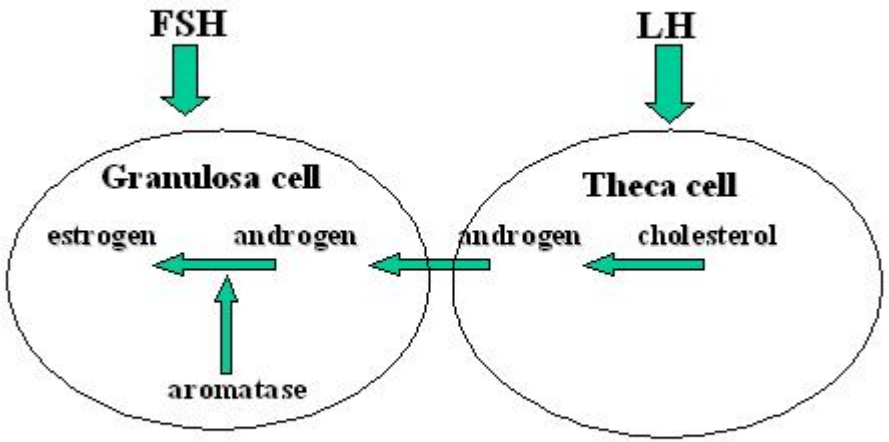
- **Recombinant FSH**: from genetically engineered Chinese Hamster Ovary cells. Offers better purity, bio-availability and batch to batch consistency - but higher costs.
  - Follitropin α (Gonal F, Serono)
  - Follitropin β (Puregon, Organon)
  - Follitropin δ (Rekovelle, Ferring)
  - BIOSIMILARS

- No clear difference between purified urinary FSH and rec FSH in live birth rates or risk of OHSS

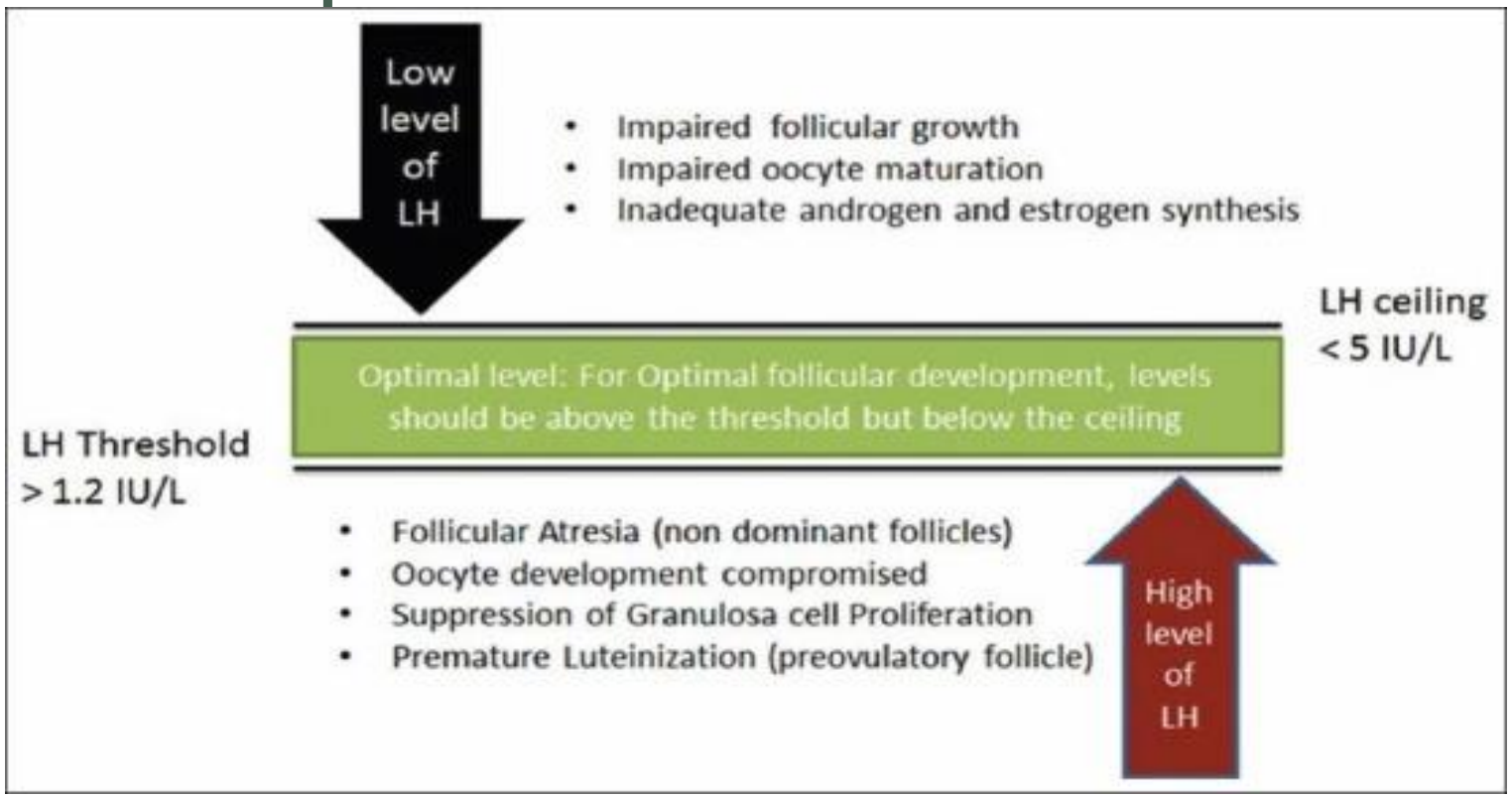
Role of LH in folliculogenesis

- In the normal cycle, ovarian follicle growth and development requires both FSH and LH
- LH drives theca cell androgen production
- Androgens pass to the granulosa where they are converted by Aromatase (under influence of FSH) into oestradiol

Figure 3



Concept of LH threshold



In clinical practice follicular development can be obtained with exogenous FSH alone. However, this does not disprove a role for LH. Endogenous LH levels are not zero in treatment cycles where only FSH is administered.

Choice of gonadotropin

- There is no clear evidence that any single preparation is better than another for efficacy
- In WHO Group I women, with very low LH and FSH levels, LH improves oestradiol secretion, FSH sensitivity and sensitivity to luteinisation by HCG

(ERhLH Study Group 1998, J Clin Endocrin Metabol 83; 1507-14)

- Studies have shown variable results on whether LH supplementation benefits subgroups – eg poor responders and women over 38 years of age
- Meta-analysis did not show any benefit for recombinant LH supplementation in general

(Mochtar et al 2017 Cochrane reviews)

- LH activity from other sources is also present in some highly purified urinary preparations – Menopur (HCG of pituitary orgin) Meriofert (HCG from urine of pregnant women).

Dose of FSH for stimulation

- 'Standard' dose

  or
- Ovarian Reserve Test-based dose

- We would expect ORT-based dosage to produce better results.
- However, of 8 RCTs, only 1 showed a benefit compared to a standard dose of 150 iu daily
- Recent Dutch trial (OPTIMIST van Tilborg et al 2017) showed no difference in livebirth or cancellation rates between AFC-based dose and standard dose. AMH (post hoc) did not make any difference
- Overall risk of OHSS was lower with AFC-based dosage, but severe OHSS incidence was the same

GnRH agonist trigger

- GnRH antagonist does not cause 'down-regulation' of receptors on the pituitary gonadotroph; the pituitary remains responsive to GnRH
- Hence, GnRH **agonist** administration in women who have received GnRH antagonist leads to an initial flare effect, causing release of endogenous LH and FSH
- This LH and FSH 'surge' is sufficient to allow final oocyte maturation. In theory, GnRH agonist could therefore replace HCG as the 'trigger'
  - Buserelin 0.2 -0.5 mg, triptorelin 0.2 mg, leuprorelin 0.5 – 1mg have been used
- Endogenous LH has much shorter half-life than HCG (60 min vs >24 hours) and may cause less sustained stimulation of granulosa cells
- This is associated with a lower risk of OHSS compared with using HCG trigger

Poor responders

- No clear evidence supporting one regime over another (Ubaldi et al 2014)
- Mild stimulation is less effective than conventional
- Antagonist may be preferred because of shorter duration and lower treatment burden than agonist. Also, can assess AFC before starting
- recLH addition may increse egg number (Lehert et al 2014)
- Luteal phase oestradiol priming may improve egg number by synchronising follicular recrutiment (Reynolds et al 2013)
- No evidence that a dose greater than 300 iu makes any difference; some clinics will go up to 450 iu daily

Poor responders – androgens as adjuvants

- **DHEA**
  - Started as a small series and then anecdotal observation in one patient
  - Several retrospective studies
  - 8 Randomised trials of circa 775 patients
  - Meta-analysis shows a benefit overall, but numbers are small, definition of diminished ovarian reserve is variable and data quality is poor
  - Live birth rate was higher with DHEA (n=528, 4 RCTs, 2 cohort studies) RR 1.87, 95 % CI 1.22–2.88, p = 0.004. Control 9.4% DHEA 20.4%

(Zhang et al, J Assist Reprod Genet (2016) 33:981–991

- **Testosterone**
  - Meta analysis of 3 randomised trials shows improved live birth rate in women with diminished ovarian reserve

Gonza´lez-Comadran et al RBM Online (2012) 25, 450– 459

  - Shorter duration of pre-treatment - but no agreed dose or duration (eg 2.5 mg for 5 days or 10 mg for 15-20 days during downregulation)
  - Highly potent androgen, greater risk of side effects and only available on prescription
  - No licensed transdermal preparation of testosterone is available in the UK

Conclusions – ovarian stimulation regimes

- Agonist and antagonist regimes have similar success rates
- GnRH agonist for 3 – 6 months may be preferred in women with endometriosis
- Antagonist is associated with a lower risk of OHSS and is preferred for women with PCOS and for egg donors
- GnRH agonist trigger is associated with a lower risk of OHSS than HCG trigger in Antagonist cycles, but resulting luteal phase is poor
- We don't know the best regime for poor responders; Androgen adjuvant treatment may show some benefit

www.iffs-reproduction.org @IntFertilitySoc Int@FedFertilitySoc