Do aromatase inhibitors have a place in IVF?

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Antalya, September, 2009

Human Follicle Growth

Primordial follicle

1 layer flat granulosa cells (36µm, × 570)

Primary follicle

1 layer cuboidal GCs (46 µm, × 570)

Secondary follicle

2 layers of GCs (77 µm, ×480)

Pre-antral follicle

class 1 (theca cells & arterioles) (120 µm, ×350)

Early antral follicle

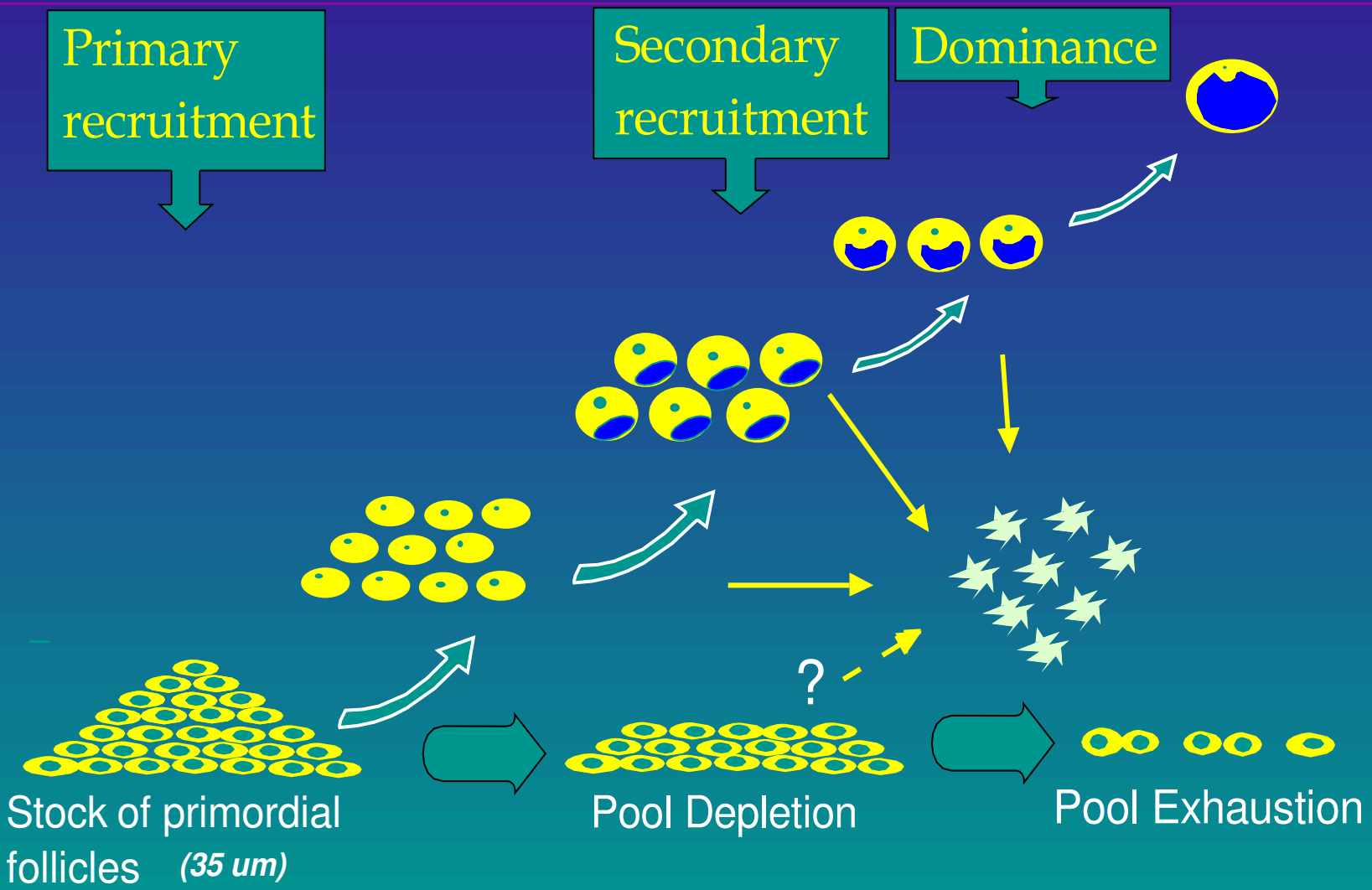
class 2 (180-250 µm, ×170)

Small antral follicle

class 4 (2 mm, ×25)

(Gougeon, Endocr Rev 1996)

Follicle Development



Accelerated follicular development 2-5mm

Primordial

Pre-antral

Early antral

More early antral follicles

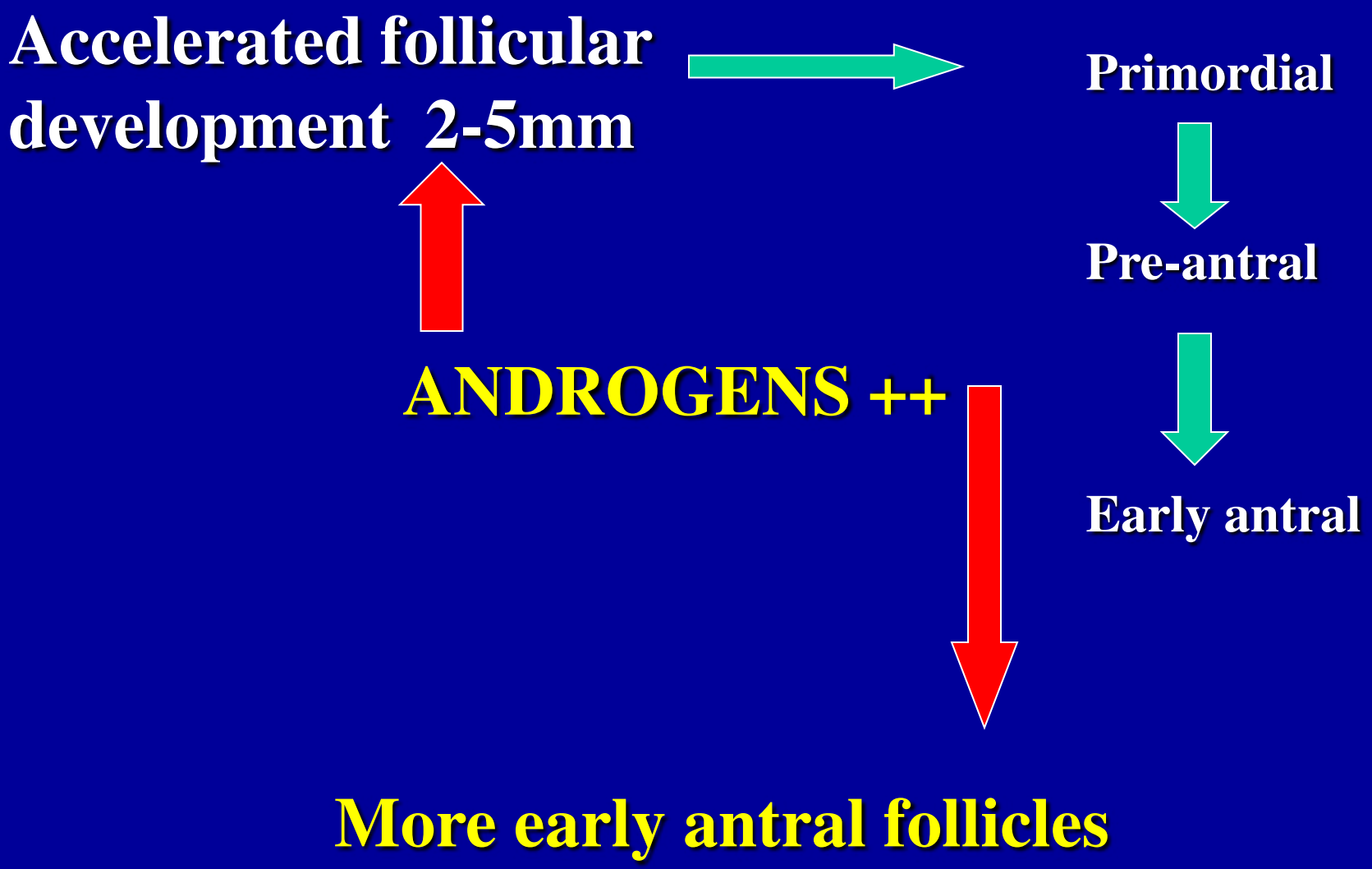
Androgens & follicular development

- Androgens increase the number of pre-antral and small antral follicles

  Hillier et al, 1997

- Androgens stimulate early follicular growth

  Vendola et al, 1999


Accelerated follicular development 2-5mm
Primordial
Pre-antral
Early antral
ANDROGENS ++
More early antral follicles

Androgens & follicular development

- Androgens have a stimulatory role in early follicular growth by augmenting follicular FSH receptor expression and therefore amplifying FSH effects.

Weil et al, 1999

- Androgens enhance FSH receptor expression in granulosa cells.

Hillier & Tetsuka, 1997

Androgens & follicular development

1. Stimulate early follicular growth – before follicle sensitive to gonadotrophins

2. Enhance FSH action

Effect of androgen levels on IVF cycles

Barbieri et al, 2005

- **Testosterone levels decline with increasing age.**
- **LH stimulation of ovarian androgen secretion declines during the ages of 30-40.**
- **Positive correlation between T and number of oocytes retrieved.**

Androgens for poor responders

Addition of androgens in GnRHa cycles for women with diminished ovarian reserve

1. **Supplementation with T or DHEA before gonadotrophins**
2. **Blocking androgen conversion to E with aromatase inhibitors**

Clinical data – testosterone supplementation

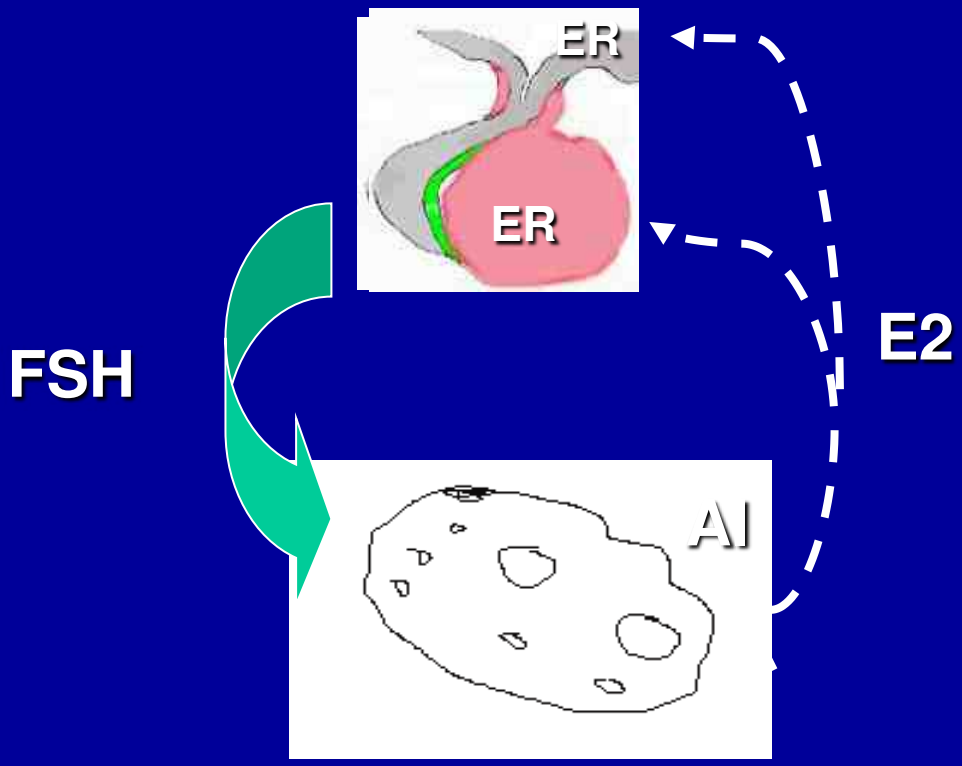
Hugues et al, 2006

- n=49 with previous poor ovarian response and low ovarian reserve
- RCT – Transdermal testosterone (10mg/day) or placebo for 15 days before FSH
- No significant difference in AFC, total and mature oocytes or embryos obtained.

Aromatase Inhibitors (Letrozole, Anastrozole)

- Non-steroidal. Block conversion of androstendione to estrogens.
- Used for treatment of breast Ca in postmenopausal women.
- Dose: Letrozole 2.5 – 5 mg/day,
  Anastrozole ? 1-15 mg/day
- Almost free of side effects.

Aromatase Inhibitor Treatment - day 3-7 of cycle



Casper & Mitwally

Aromatase inhibitors

- Leads to accumulation of androgens
- Will have positive effect in poor responders and in superovulation?

Aromatase inhibitors for poor responders

- n=12 poor responders to FSH.

Lower FSH dose, more mature follicles

Mitwally & Casper, 2002

Aromatase inhibitors for COS

- FSH + letrozole (5mg) (n=60 cycles)
  vs FSH alone (n=145) for IUI

Lower FSH dose, more mature follicles

Healey et al, 2003

Aromatase inhibitors for COS

- FSH + letrozole (n=36)
  vs FSH + CC (n=18)
  vs FSH alone (n=56) for IUI

- Pregnancy rates FSH + letrozole 22.2%
  FSH + CC 11.1%*
  FSH 18.7%

Mitwally & Casper, 2003

Aromatase inhibitors for IVF

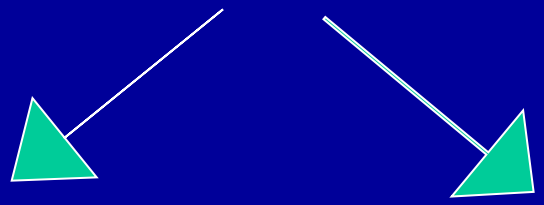
Goswami SK et al, 2004

- Small RCT, poor responders in IVF
  - Letrozole + 150IU FSH
  - vs Long GnRHa + FSH
- Treatment outcomes same
- Letrozole/FSH much cheaper

Aromatase inhibitors for poor responders in IVF

- n=147 with previous canceled cycle

High dose FSH + antagonist



Letrozole 2.5mg/day for 5 days

Controls

Garcia-Velasco et al, 2005

Aromatase inhibitors for poor responders in IVF

Letrozole

- **Increased intra-follicular androgen concentrations**
- **Higher number of oocytes (6.1 vs 4.3)**
- **Higher implantation rate (25% vs 9.4%)**
- **Higher pregnancy rate/cycle (22% vs 15%)**

Garcia-Velasco et al, 2005

Letrozole/antagonist vs Microdose agonist flare for poor responders

	Let/antag		Micro-agonist
Schoolcraft et al, 2008	179	n	355
Yarali et al, 2009	212	n	673

Lower peak E2 in letrozole/ antagonist group

Letrozole/antagonist vs Microdose agonist flare for poor responders

Schoolcraft et al, 2008

- No difference oocytes retrieved, fertilisation rates or embryo score.

Yarali et al, 2009

With letrozole/antagonist:

- Less stimulation and oocytes retrieved
- Higher fertilisation and top quality embryo rates.

Letrozole/antagonist vs microdose agonist flare for poor responders

Ongoing pregnancy rates

	Let/antag	Agonist
Schoolcraft	**37%***	**52%***

"Microdose agonist is preferred"

Yarali **Same**

" Letrozole/antagonist is an effective protocol"

Aromatase inhibitors - questions

- **Timing?**
- **Priming? Before exposure to FSH.**

  de Ziegler, 2003
- **Dose – will a larger dose further extend the window?** **Biljan et al, 2002**

Aromatase inhibitors for IVF poor responders

- Theoretically sound and promising so far but more work needed!