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Infertility Journal Reading

2011-06-07

Letrozole and gonadotropins versus luteal estradiol and gonadotropin-releasing hormone antagonist protocol in women with a prior low response to ovarian stimulation

Fertility and Sterility Vol. 95, No. 7, June 2011

Introduction

- Low **ovarian response**:

➔Lack of uniform definition

➔Difficulty in comparing treatment outcomes

- Tests for **ovarian reserve**:

➔Actual ovarian response to stimulation

➔Reasonable capacity to predict poor response

➔Low ability to predict the occurrence of pregnancy

- Poor responders

➔Generally resistant to a multitude of intervention strategies

➔Sometimes difficult to identify before controlled ovarian hyperstimulation

- Poor response to COH

⇔↓E2 & follicle response to gonadotropins

⇔↓number of retrieved oocytes & available embryos for transfer

Ovarian Stimulation Protocols

- Several are proposed to improve IVF outcomes in patients with low ovarian response
- Some may enhance the ovarian response
- None have demonstrated a significant improvement in pregnancy rates

Antagonist protocols

- Luteal-phase estradiol (E2) and gonadotropin releasing-hormone (GnRH) antagonists before gonadotropin stimulation

→Synchronization of early antral follicle growth in the luteal phase before COH

→Subsequent increase in oocyte

→Improvement in pregnancy rates

- Estrogen

→Prevent luteal FSH ↑

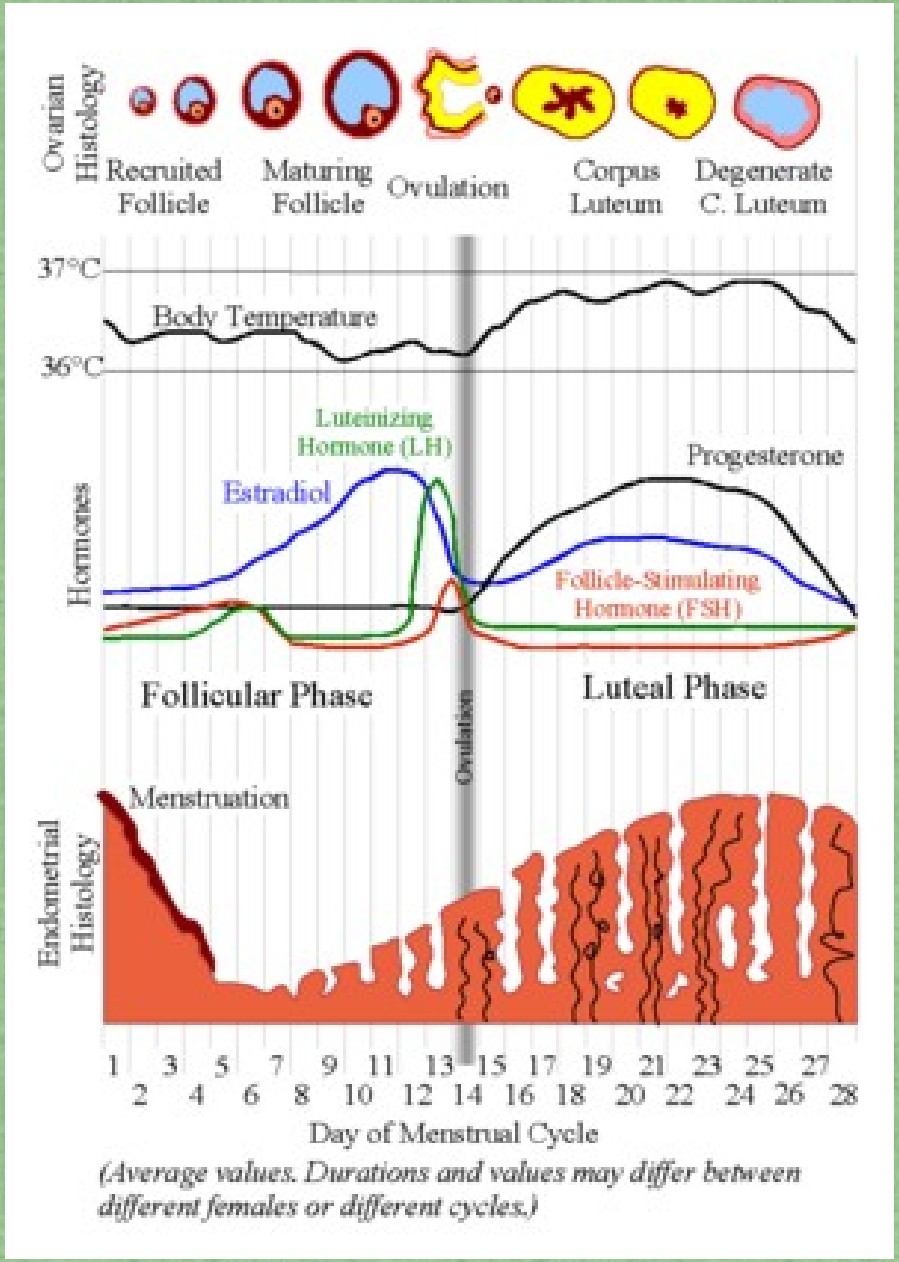
→May also ↑sensitivity to gonadotropins

- Luteal GnRH antagonist

→Induces luteolysis & prevents the FSH ↑

⇔Lower basal FSH and inhibin levels

⇔↓size and variability in the diameter of antral follicles



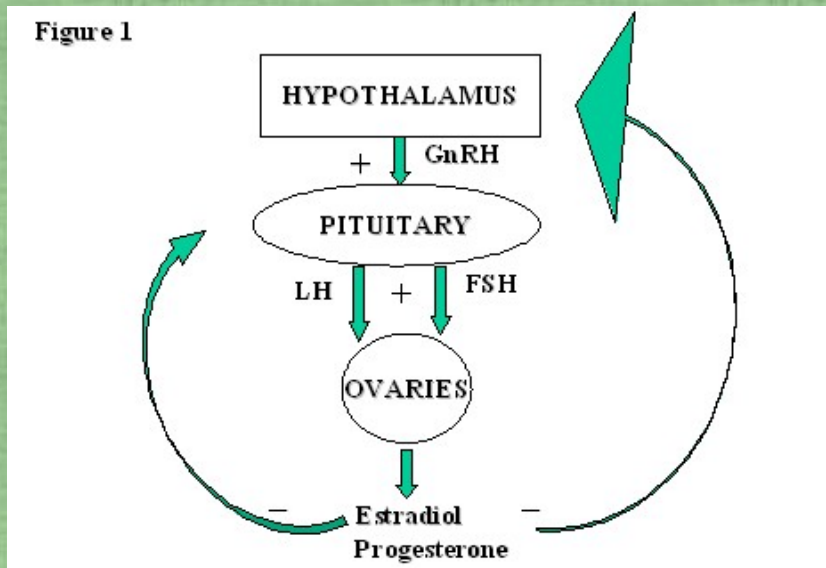
Aromatase inhibitors (AIs)

- Recognized by Mitwally et al.
- Few studies so far have used in low responders

- *Aromatase (in Fibroblasts, Osteoblasts, liver, breast):*

⇨ *Androstendione → estrone*

⇨ *Testosterone → Estrodiol*



Aromatase inhibitors (AIs)

- Central mechanism: E2 ~~negative feedback~~ hypothalamus

→Augment follicular growth$_k$

→Release endogenous gonadotropins (↑FSH) ⇔ r-FSH *chemically different (carbohydrate moiety)*

- Peripheral mechanism:

→Accumulation of intra-follicular androgen substrate

⇨↑FSH receptors expression ` intraovarian factors

(Gn surge attenuating factor ⇔ premature LH surge)

→↑ **Response to gonadotropins**

Aromatase inhibitors

- Alternative ovulation-induction agents
- Alone or adjunct to gonadotropins
- Without apparent adverse effect on endometrium (as antiestrogen therapies/ Clomifene citrate)

- AIs + r-FSH in IVF cycles → ↓the total dose of gonadotropins → ↓cost of IVF (also ↓OHSS)

- Letrozole/antagonist protocol (LA) ⇔ luteal E2/GnRH antagonist protocol (LPG)

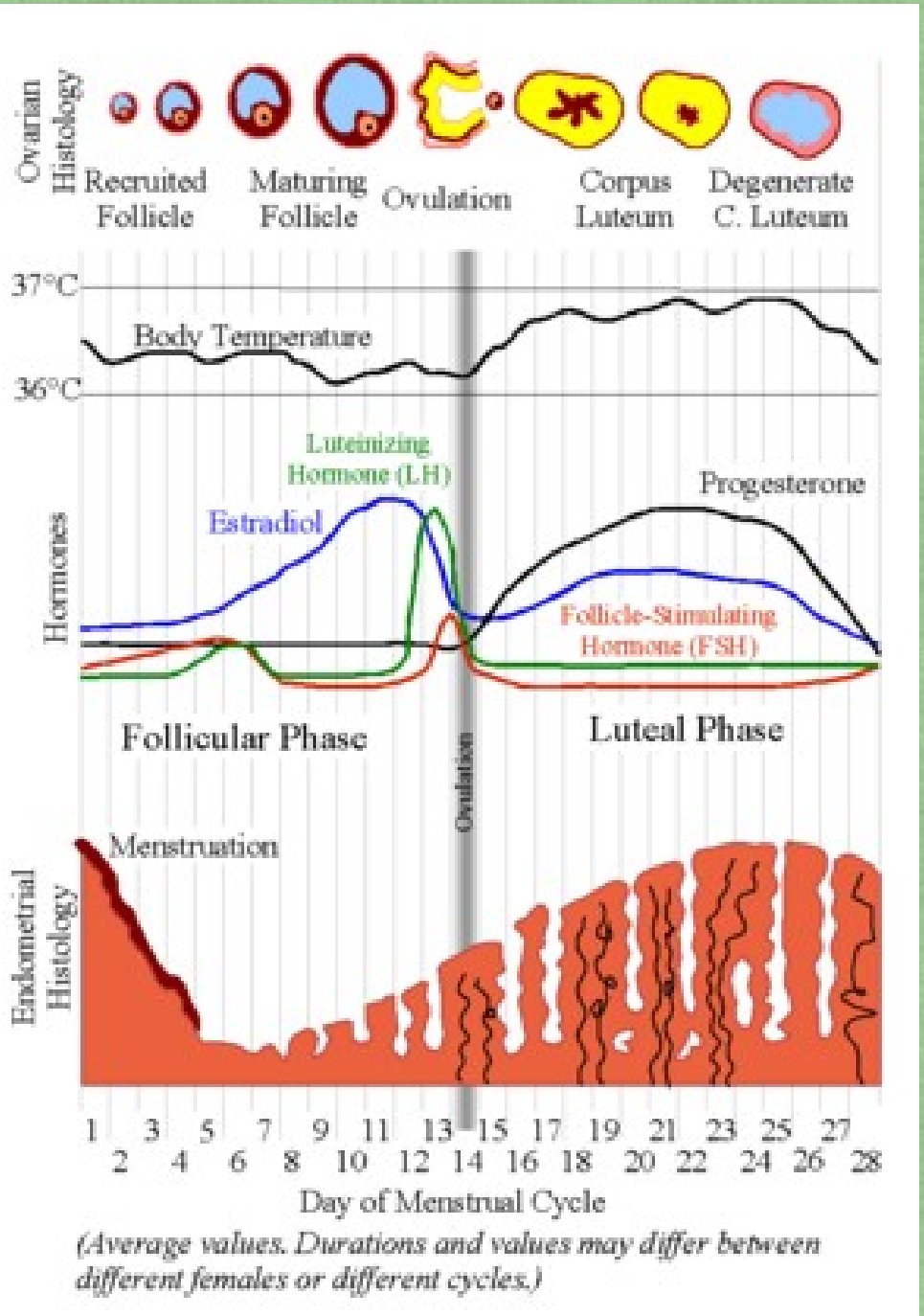
✓ in women who had exhibited low ovarian response in prior IVF attempts

MATERIALS AND METHODS

Patients

- Retrospective cohort study
- University of Connecticut institutional review board
- January 2009 ~ October 2010
- 99 low-responder patients, < 42 year old
  - ≧ 2 prior ovarian stimulation cycles at a starting dose of gonadotropins ≧ 300 IU → < 5 oocytes
  - One prior cycle cancellation due to low follicular recruitment (after 10 days of stimulation, ≤3 follicles, ≥15 mm in diameter)

- Prior failed cycles: GnRH agonist down-regulation, GnRH antagonist, and microdose leuprolide
- No prior ovarian OP or exposure to C/T or R/T
- Flexible antagonist protocol
  - Luteal E2 patch and GnRH antagonist (LPG)
  - Early follicular letrozole with no luteal pretreatment (LA)
- Each patient → single cycle → no crossover
- Assignment of protocol as physician's discretion



(Average values. Durations and values may differ between different females or different cycles.)

Stimulation Protocols

LPG group (n=52)

Previous cycle

- Day 10 after the LH surge → Initiated Transdermal E2 *(Vivelle Dot 0.1 mg; Novartis, Miami, FL)* every other day
- 11th day → began daily administration of ganirelix acetate *(Ganirelix; Organon Pharmaceuticals, Roseland, NJ)*, 0.25 mg SC for 3 consecutive days

Ensuing menses

- Day 2 → Check FSH, LH, E2 levels, baseline echo
- Remove last E2 patch

- Start ovarian stimulation (High-dose gonadotropins)
  - → *Average of* 450 IU r-FSH *(Gonal F; Serono, Rockland, MA)*
  - → 150 IU of hMG *(human menopausal gonadotropin, Menopur; Ferring Pharmaceuticals, Tarrytown, NY)*
- Lead follicle ≥13 mm or if E2 >300 pg/mL
  - → Restart Ganirelix (prevent a premature LH surge)
  - → *continued until the day of hCG administration*
- ≥3 lead follicles with ≥17-mm mean diameter
  - → hCG 5,000-10,000 IU SC (*human chorionic gonadotropin*)

Stimulation Protocols

LA group (n=47)

Spontaneous menstruation

- Day 2: Initiate Letrozole *(Femara; Novartis, East Hanover, NJ)* 5 mg/day → continued for 5 days
- Day 5: commence 450 IU r-FSH and 150 IU hMG
- Start ganirelix as LPG protocol
- criterion for hCG: ≥2 follicles, ≥20-mm diameter

after hCG

- 35 hrs → TVOR *(Transvaginal oocyte retrieval)*
  → Oocyte insemination or ICSI (intracytoplasmic sperm injection) as indicated
- 3rd Day → all embryos were transferred
- Luteal phase supplementation:

→ Progesterone 50 mg IM daily

  - From the evening after oocyte retrieval
  - until negative pregnancy test or confirmed clinical pregnancy (IUP with FHB)

- Primary outcome measure
  - Ongoing pregnancy rate (>20 weeks' gestation) per started cycle
- Secondary outcome measures:
  - Cancellation rate
  - Number of oocytes retrieved and transferable embryos
  - Implantation and clinical pregnancy rates

Statistical Analysis

- Statistical Package for the Social Sciences (release 17.0; SPSS Inc., Chicago, IL)
- Student's t-test -- comparison of continuous variables
- Chi-square or Fisher's exact test -- comparison of proportions
- $P < .05$ -- considered statistically significant
- Data were expressed as mean standard deviation

RESULTS

- 41x in LA (47x) group (87.2%) & 43x in LPG (52x) group (82.7%) had ≥ one prior cycle cancellation due to poor follicular recruitment
- Patients with no prior cycle cancellations had ≥ two preceding IVF cycles with retrieval of < five oocytes and no pregnancies

TABLE 1

Letrozole/antagonist (LA) versus luteal-phase estradiol/gonadotropin-releasing hormone antagonist (LPG) in poor responders: demographic and clinical characteristics of study participants.

	LA (n = 47)	LPG (n = 52)	*P* value
Age (y)	39.1 ± 2.8	39.2 ± 0.2	.51
BMI (kg/m^2)	26.6 ± 7.0	26.7 ± 5.9	.90
Day–3 FSH (mIU/mL)	10.7 ± 5.0	9.5 ± 3.8	.27
Day–3 LH (mIU/mL)	4.9 ± 1.9	5.1 ± 2.2	.49
Day–3 E_2 (pg/mL)	46.3 ± 18.6	40.9 ± 25.2	.22
History of FSH ≥12 (%)	34 (16/47)	17.3 (9/52)	.06
No. of prior IVF cycles	4.6 ± 1.8	3.3 ± 1.8	< .01
No. of prior canceled cycles	1.8 ± 1.2	1.1 ± 0.8	< .01

- 36x (76.6%) in LA underwent a prior ovarian stimulation using the LPG protocol

TABLE 2

Letrozole/antagonist (LA) versus luteal-phase estradiol/ gonadotropin-releasing hormone antagonist (LPG) in poor responders: COH response in study participants.

	LA (n = 47)		LPG (n = 52)	P value
FSH at start of COH	9.2 ± 2.8	>	4.07 ± 3.0	< .01
Stimulation days	11.1 ± 2.6		11.3 ± 3.3	.88
Total gonadotropins (IU)	4,388 ± 1,703	<	6,193 ± 1,018	< .01
Peak E_2 (pg/mL)	675 ± 458	<	1256 ± 799	< .01
Cancellation rate (%)	(26) 55.3 (26/47)		36.5 (19/52) (19)	.06
Canceled cycles due to poor ovarian response (%)	29.8 (14/47)		25 (13/52)	.6
Canceled ET after retrieval (%)[a]	10.6 (5/47)		7.7 (4/52)	.6
Canceled cycles due to premature LH surge (%)	14.9 (7/47)		3.8 (2/52)	.06

TABLE 3

Letrozole/antagonist (LA) versus luteal-phase estradiol/gonadotropin-releasing hormone antagonist (LPG) in poor responders: in vitro fertilization outcomes.

	LA (n = 47)		LPG (n = 52)	*P* value
No. of oocytes retrieved	6.1 ± 3.0		7.9 ± 4.8	.08
No. of mature oocytes	3.8 ± 2.4	<	6.6 ± 4.3	< .01
Maturation rate (%)	64	<	83	< .01
No. of 2PN oocytes	3.0 ± 2.3	<	5.3 ± 4.1	< .01
Fertilization rate	69		71	.9
No. of embryos transferred	2.2 ± 1.0		2.4 ± 1.4	.85
Implantation rate (%)	16.7		16.3	.96
Clinical pregnancy rate				
Per started cycle (%)	25.5 (12/47)		26.9 (14/52)	.88
Per ET (%)	50 (10/20)		42.4 (14/33)	.59
Ongoing pregnancy rate				
Per started cycle (%)	19.1 (9/47)		13.5 (7/52)	.44
Per ET (%)	40 (8/20)		21.2 (7/33)	.14
Pregnancy loss rate (%)	25 (3/12)		50 (7/14)	.18

- In the LA group
- 2x → pregnancy after intrauterine insemination
- 3x multifetal gestation (2x twins, 3x triplets)
- 38x not achieve an ongoing pregnancy
  - 31x referred to donor oocyte program or opted for no further treatment
  - 7x decided to attempt an additional IVF cycle → 6/7 were canceled

DISCUSSION

- Poor response to COH → ↓follicular response in quantity → retrieved lower number of oocytes

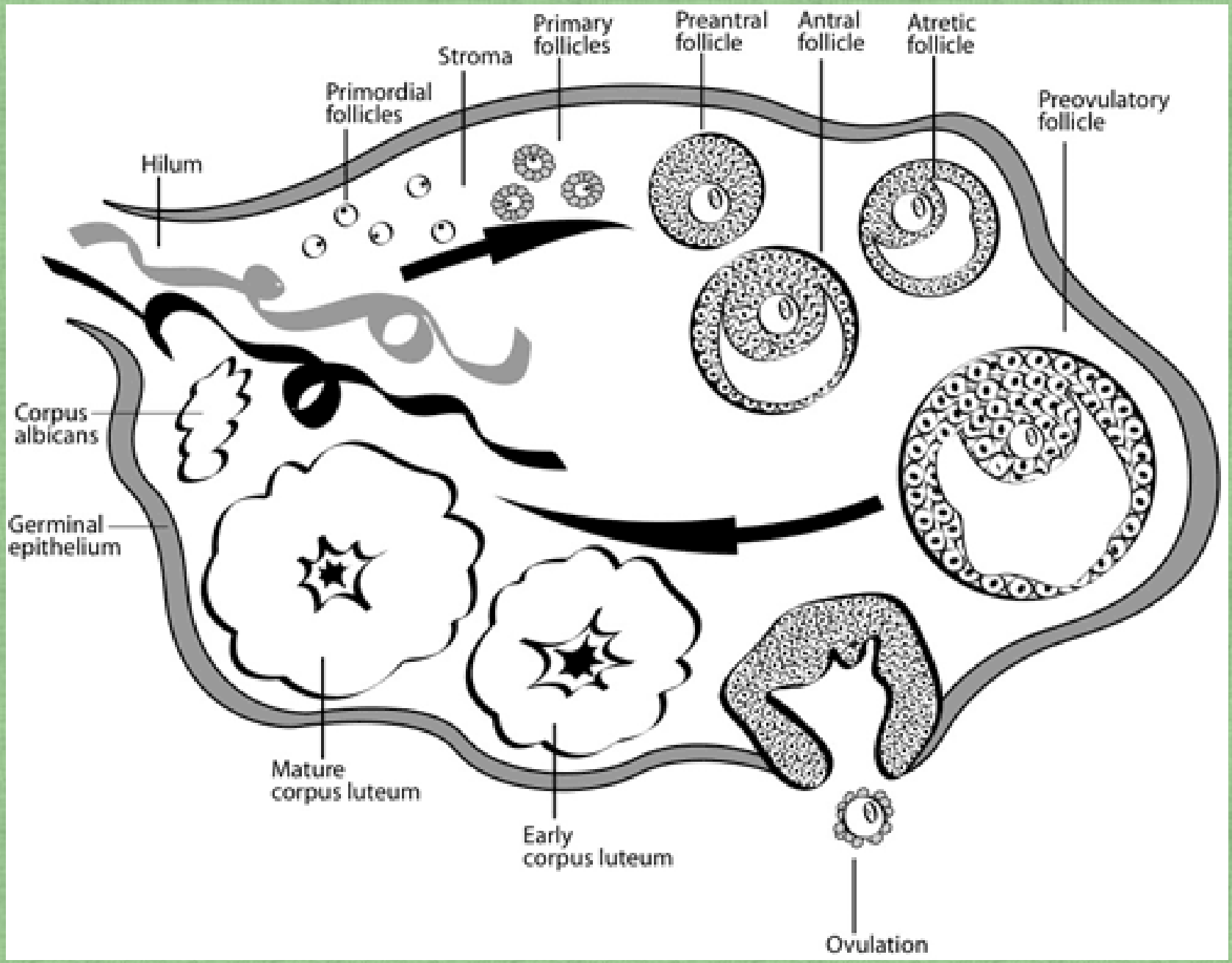
⇨ A major concern in assisted reproduction

⇨ The best treatment option remains controversial

- Luteal synchronization of follicular growth → ↑ yield oocyte … . *deZiegler et al.*
- Use of luteal E2/antagonist → ↓cancellation rate, ↑number of retrieved oocytes and embryos transferred… *Dragisic et al.*

Androgen

- Stimulates theca/granulosa cell proliferation & inhibits apoptosis → ↑preantral & small antral follicles
- Accumulation of follicular androgens → ↑FSH-R gene expression or stimulate IGF-I (insulin-like growth factor 1) system → may act in synergy with FSH → promote follicular steroidogenesis → ↑follicular sensitivity
- Some reports: before FSH treatment → Transdermal testosterone → ↑ovarian response


Primary follicles
Preantral follicle
Antral follicle
Atretic follicle
Stroma
Primordial follicles
Preovulatory follicle
Hilum
Corpus albicans
Germinal epithelium
Mature corpus luteum
Early corpus luteum
Ovulation

Letrozole

- 3rd generation highly selective non-steroidal AI *use in postmenopausal women with breast cancer*
- Competitively binding to the heme of the cytochrome P450 subunit of aromatase

→ Androstenedione → E2

⇨ ↑intraovarian androgens

→Profound effect on early follicle growth

→May up-regulate androgen-receptor gene expression in preantral and antral follicles

⇨ ↓serum [E2]

→May limit (cumulative [E2] → negative effect → oocyte quality & endometrial receptivity)

→Maintaining an adequate follicular development and estrogen biosynthesis

Study for Letrozole co-treatment

- Improved response to FSH stimulation
- ↑number of oocytes retrieved and implantation rate
- ↓mean total dose of gonadotropins
- ↓cancellation rate
- ↓cost of achieving a clinical pregnancy
- ↓dose of gonadotropins and terminal E_2

Letrozole/antagonist ⇔ microdose flare

- Previous study: ↓ongoing pregnancy rate ⇨ ***broad definition of poor response (suspected poor responder)***
- Recent large retrospective study:
  - → ↑ fertilization rate, implantation, cancellation rate
  - → Similar PR per started cycle

In this study

- Letrozole (LA) ⇔ luteal E2/GnRH antagonist (LPG) in women with known prior low response
- 5 mg/day x 5 days since MC D2 ⇔ 2.5 mg/day

  ⇨Intrinsic potency of letrozole: 2.5 mg/day → inhibit 97% estrogen (on nonstimulated granulosa cells)

  ⇨(actively dividing granulosa cells → need higher dose of AI → aromatization attenuation)

  ⇨ *One study for women undergoing COH*

- Started gonadotropins: 3 days after initiation of letrozole → allow the release of endogenous gonadotropins before initiation of exogenous stimulation ⇔ *(most of the other studies: started gonadotropins simultaneously with letrozole)*

- Administration of hCG: 2 follicles → ≥20 mm ⇔ *(All prior studies: 17or18 mm diameter without reported ↑ proportion of immature oocytes)* → still ↓Metaphase II oocytes

Premature LH surge

- Trend toward ↑ incidence (LH ≥ 10 mIU/mL): LA vs. LPG (14.9% vs. 3.8%) ⇔ *(not addressed in most studies)*
  - Normal responder: Letrozole → ↑ median [LH]
  - ↑ In AI protocols (tends to occur at lower [E2])
  - Ovaries with diminished ovarian reserve → prone to a premature LH surge (presumably due to ↓ GnRH-attenuating factor/GnSAF production)

∴ An early start and possibly a higher dose of the **antagonist** should be considered when using letrozole

Safety issues

- ↑risk of congenital cardiac malformations
  - Reassuring data *among a large number of children born to women treated with letrozole*: no such ↑in the overall rates of congenital malformations or chromosomal abnormalities
  - In this study → discontinued letrozole on day 6 or ≥1 week before ET (half-life 45 hours)

LA protocol

- ↓Gonadotropins used and E2 levels
- ↓Metaphase II oocytes (despite give hCG at lead follicle → 20mm, similar to previous study)

A trend toward... (lack of a statistically significant)

- ↑Cancellation rate (possibly due to inclusion of more severe poor responders)
- ↓Miscarriage rate (possible improvement in endometrial receptivity or oocyte quality)
- ↑Ongoing pregnancy rate per ET

- Non statistic significance between the ongoing pregnancy rates → May be type II error – (not powered enough to detect a difference of 20% in the ongoing pregnancy rate per ET between the 2 groups)

Conclusion

- Notable to identify a subgroup of low responders *(who benefit from AI + antagonist-based protocol)*
- Showed reasonable IVF outcomes of letrozole/gonadotropins for COH in low responders
- Using letrozole may require optimization → avoid a premature LH surge & ↑the yield of mature oocytes
- Need prospective randomized trials with adequate power to test the efficacy of AI-based protocols ⇔ other interventions in low responders

THANK YOU FOR LISTENING