Low respondence of ovarian stimulation

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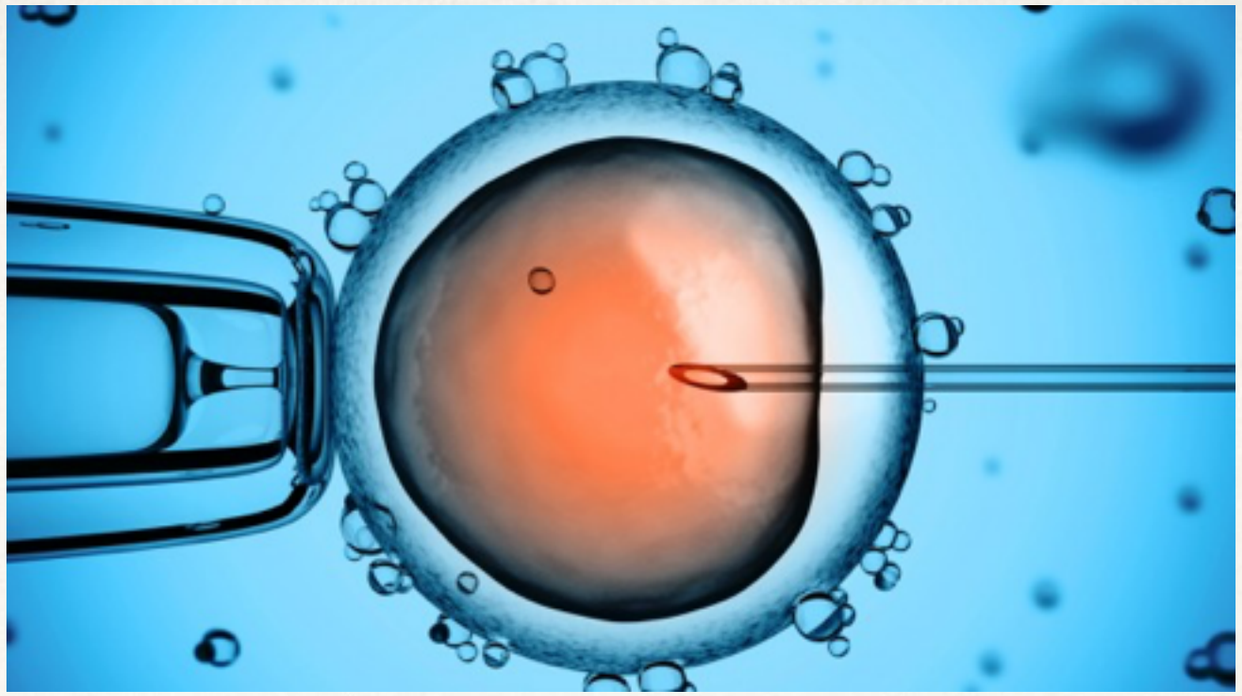

“Is there anything new?”

–Why is this topic so controversial and so current?

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Poor Ovarian Response (POR)

- Definition
- Assessment
- Strategies

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Definition : POR

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- A systematic review of 47 RCTs revealed 41 different definitions of POR (1)
- To standardize the definition of POR, Ferraretti et al. (2) proposed new criteria, known as the "Bologna criteria," based on three conditions:
  - 1) advanced maternal age (R40 years) or any other POR risk factor;
  - 2) a previous incident of POR; and
  - 3) a low ovarian reserve test in terms of antimullerian hormone (AMH) and antral follicle count (AFC).
- Two of these three criteria are required for a POR diagnosis.
- In addition, two cycles with POR after maximal stimulation are sufficient to classify a patient as a poor responder even in the absence of the other criteria mentioned.

Polyzos NP, Devroey P. A systematic review of randomized trials for the treat- ment of poor ovarian responders: is there any light at the end of the tunnel? Fertil Steril 2011;96. 1058–61.e7.
Ferraretti AP, la Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011;26:1616–24.

A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

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- New definition of "low prognosis" patients:

1) Introduces two new categories of impaired response:

   a. A "suboptimal response," defined as the retrieval of four to nine oocytes, which is associated, at any given age, with a significantly lower live birth rate compared with normal responders i.e., those with 10–15 oocytes (4).

   b. A "hyporesponse," in which a higher dose of gonadotropins and more prolonged stimulation are required to obtain an adequate number of oocytes (more than three) (5).

2) Combines "qualitative" and "quantitative" parameters, namely:

   a. The age of the patient and the expected aneuploidy rate.

   b. Biomarkers and functional markers (i.e., AMH and AFC).

Fertil Steril, Article in press, 2016.

Personalize treatment protocols

a. Using different GnRH analogue regimens.

b. Detecting polymorphisms of gonadotropins and their receptors.

c. Tailoring the FSH starting dose.

d. Personalizing gonadotropin doses (i.e., FSH monotherapy or LH-containing drugs).

e. Evaluating special regimens, including oocyte/embryo accumulation to maximize outcomes.

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Fertil Steril, Article in press, 2016.

Assessment

- Basal FSH
- AMH
- Inhibin B
- Basal estradiol
- AFC
- Ovarian volume
- Ovarian vascular flow
- Ovarian biopsy
- Clomiphene citrate challenge test
- Exogenous FSH ovaria reserve test
- GnRH agonist stimulation test
- Multivariate prediction models

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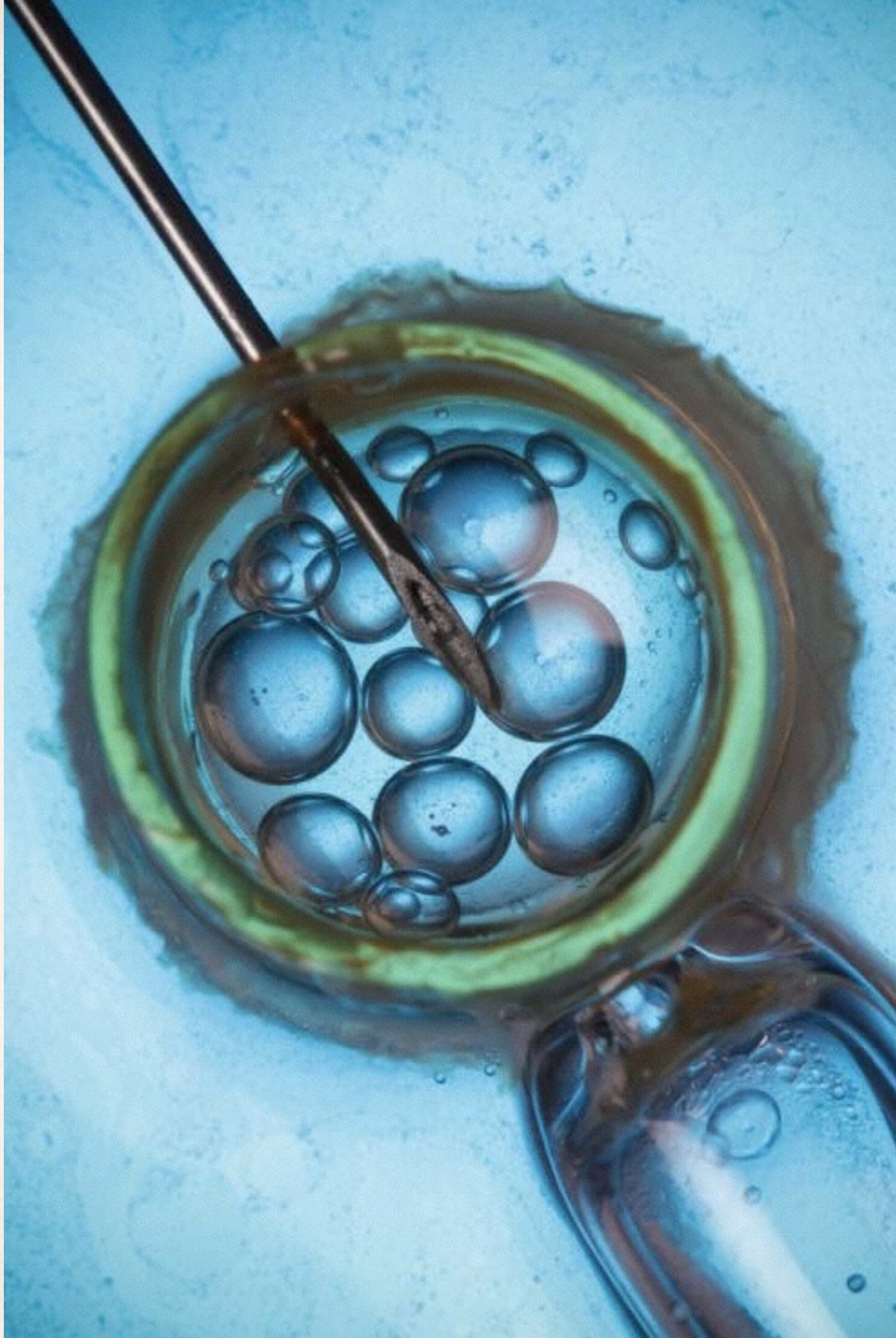

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Summary of the value of screening tests of ovarian reserve.

		Poor response		Non-pregnancy				
Test	**Cutpoint**	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**Reliability**	**Advantages**	**Limitations**
FSH	10–20 IU/L	10–80	83–100	7–58	43–100	Limited	Widespread use	Reliability Low sensitivity
AMH	0.2–0.7 ng/mL	40–97	78–92	[a]	[a]	Good	Reliability	Limit of detectability Two commercial assays Does not predict non-pregnancy
AFC	3–10	9–73	73–100	8–33	64–100	Good	Reliability Widespread use	Low sensitivity
Inhibin B	40–45 pg/mL	40–80	64–90	[a]		Limited		Reliability Does not predict non-pregnancy
CCCT (day-10 FSH)	10–22 IU/L	35–98	68–98	23–61	67–100	Limited	Higher sensitivity than basal FSH	Reliability Limited additional value to basal FSH Requires drug administration

Note: Laboratories ELISA.
[a] Insufficient evidence.

Practice Committee. Ovarian reserve testing. Fertil Steril 2015.

Summary of tests of ovarian reserve

FSH, AMH, AFC, Inhibit B, CCCT

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Strategies for poor ovarian response

Modifications of ovarian stimulation protocols
Other management options

Modifications of ovarian stimulation protocols

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- Medications
  - Gonadotropin
  - GnRH agonist
  - GnRH antagonist
- Protocol
  - DuoStim
  - Microflare/mini IVF/natural cycle
  - Combination GnRH agonist and antagonist
- Adjuvant therapy
  - Estradiol priming
  - Growth hormone
  - Androgens
  - Aspirin
- Alternative treatment
  - Traditional chinese medicine
  - Acupuncture

Medications

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- Gonadotropins
  - Higher starting doses of gonadotropins (450 IU and 600 IU)
  - Long acting gonadotropins (corifollitropin alfa)
  - uFSH
  - Luteal FSH start/late start/early (D1) start

Protocol

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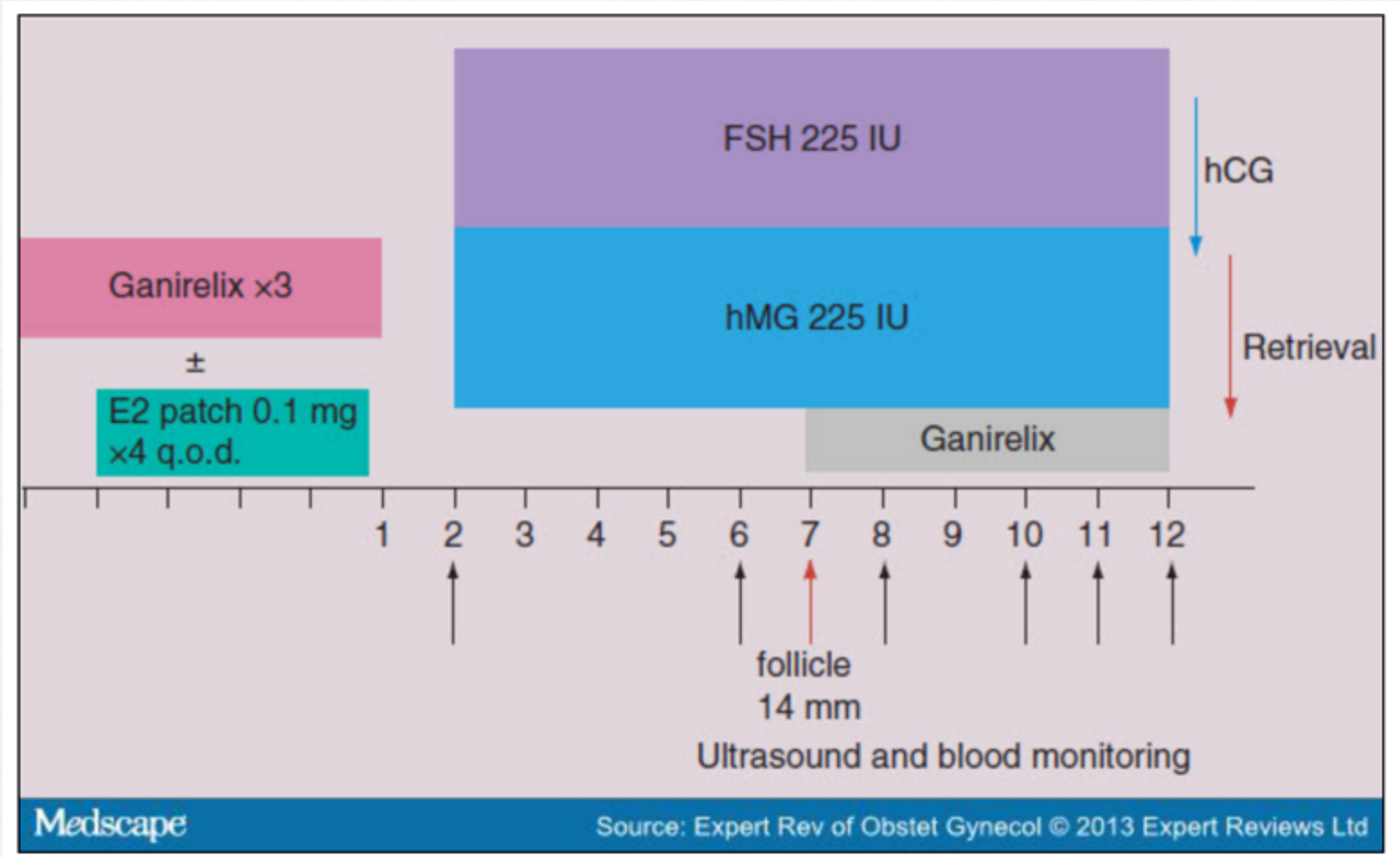
- Natural cycle with or without minimal stimulation
- FSH/hMG only (no agonist or antagonist)
- DuoStim
- GnRH agonists
  - Combination with GnRH antagonists
  - Stop protocol : to lower or to stop the dose of GnRH agonist during luteal phase
  - Decreasing the duration of GnRH agonist use
    - short and ultrashort /mini IVF/micro dose flareup regimens
- GnRH antagonists
  - Initiated during mid-late follicular phase

Luteal Estradiol GnRH antagonist Protocol



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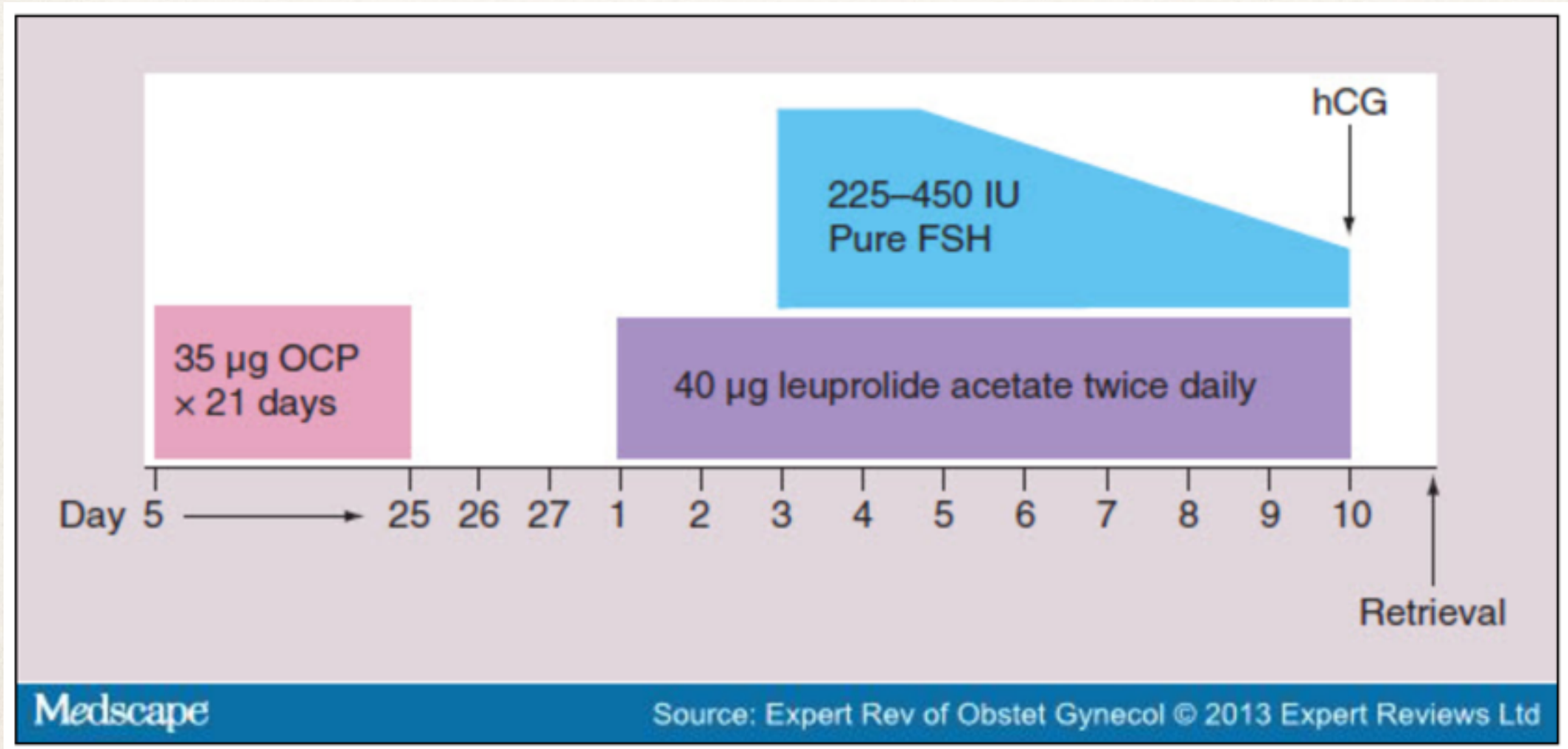
Oral Contraceptive pill/Microdose GnRH agonist Protocol



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Adjuvant therapies

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- Estradiol in luteal phase
  - With or without the simultaneous use of GnRH antagonist
- rLH with rFSH
- Growth hormone (GH) or GH-releasing factor
- Androgens :
  - Oral DHEA before ovarian stimulation
  - Transdermal testosterone
- Low aspirin
- Aromatase Inhibitors (Letrozole)
- Clomiphene Citrate
- Pyridostigmine
- Oral L-arginine
- Dexamethasone
- hCG
- Metformin

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human reproduction update

Trends in 'poor responder' research: lessons learned from RCTs in assisted conception

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Overall, the majority of published trials on POR suffer from methodological flaws and are, thus, regarded as being high-risk for bias. The same trials have used a variety of definitions for their poor responders and a variety of interventions for their head-to-head comparisons. Not surprisingly, discrepancies are also evident in the findings of trials comparing similar interventions. Based on the identified deficiencies, this novel type of 'methodology and clinical' review has introduced custom recommendations on how to improve future experimental research in the 'poor responder' population.

Table III Interventions with at least one RCT indicating benefit in reproductive outcomes.

Intervention	Significant outcome	Number of RCTs showing benefit	Number of RCTs showing no benefit
Estrogen add-back for luteal support	Live birth	**1 RCT** Kutlusoy *et al.* (2014)	**1 RCT** Aghahosseini *et al.* (2011)
rLH 4-day treatment followed by rFSH treatment during long protocol	Live birth	**1 RCT** Ferraretti *et al.* (2014)	**None**
DHEA supplementation	Ongoing pregnancy	**1 RCT** Moawad and Shaeer (2012)	**4 RCTs** Wiser *et al.* (2010) Artini *et al.* (2012) Kara *et al.* (2014) Yeung *et al.* (2014)
Antagonist flexible protocol (compared with microdose flare protocol)	Ongoing pregnancy	**1 RCT** Lainas *et al.* (2008)	**8 RCTs** Akman *et al.* (2001) Martinez *et al.* (2003) Malmusi *et al.* (2005) Schmidt *et al.* (2005) De Placido *et al.* (2006) Demirol and Gurgan (2009) Kahraman *et al.* (2009) Davar *et al.* (2013)
Day 2 embryo transfer (compared with Day 3)	Ongoing pregnancy	**1 RCT** Bahceci *et al.* (2006)	**None**
Long protocol (compared with antagonist protocol)	Clinical pregnancy	**1 RCT** Prapas *et al.* (2013)	**7 RCTs** Cheung *et al.* (2005) Marci *et al.* (2005) Tazegul *et al.* (2008) Kim *et al.* (2009) Shahrokh Tehrani Nejad *et al.* (2008) Kim *et al.* (2011) Sunkara *et al.* (2014)
Follicular flushing	Clinical pregnancy	**1 RCT** Mok-Lin *et al.* (2013)	**1 RCT** Levens *et al.* (2009)
Day 4 FSH start (compared with Day 1 FSH start) during antagonist protocol	Clinical pregnancy	**1RCT** Baerwald *et al.* (2012)	**None**
Transdermal testosterone	Clinical pregnancy	**1 RCT** Kim *et al.* (2011)	**2 RCTs** Massin *et al.* (2006) Fabregues *et al.* (2009)
Luteal phase FSH start	Clinical pregnancy	**1 RCT** Kucuk *et al.* (2008)	**2 RCTs** Kucuk and Sozen (2007) Kansal Kalra *et al.* (2008)
Addition of rLH mid-stimulation (compared with FSH dose increase)	Clinical pregnancy	**1 RCT** Ruvolo *et al.* (2007)	**2 RCTs** De Placido *et al.* (2001) De Placido *et al.* (2005)
High FSH dose (300 IU/day) (compared with 150 IU/day)	Clinical pregnancy	**1 RCT** Klinkert *et al.* (2005)	**None**

rLH/rFSH, recombinant LH/FSH.

Table IV Key clinical facts and trends in 'poor responder' research.

- The most popular criterion for defining 'poor responders' in RCTs has been low ovarian response at previous stimulation
- The most popular cut-off value for defining previous low response is 'less or equal to three retrieved oocytes'
- The most popular tests used in RCTs to define diminished ovarian reserve are AFC and FSH, followed by age and AMH
- Most research interventions were applied before/during controlled ovarian hyperstimulation
- The most popular stimulation protocols investigated in 'poor responder' research are the antagonist protocol, the microdose flare protocol and the long down-regulation protocol
- RCTs on popular protocols for poor responders have reported conflicting results with regard to oocyte yields and reproductive outcomes
- Only 1 in 10 RCTs has reported statistically significant differences in reproductive outcomes
- No 'positive' intervention is supported by more than one 'positive' RCT

Papathanasiou et al. , HRU Vol.22, No.3 pp. 306–319, 2016

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Conclusions

"The management of patients with impaired or poor ovarian response (POR) remains a controversial and complex clinical issue. "