# Ovarian Stimulation in Poor Responders:
## *Protocols that do not help and may help*

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# Background

- Incidence of poor ovarian response : 9-24%
  *(Surrey et al., 2000)*
- Possible association with:
  - Advanced age *(Akande et al., 2002)*
  - Previous ovarian surgery *(Nargund et al., 1995)*
  - High BMI *(Crosignani et al., 1994; Loh et al ., 2002)*
  - Early ovarian ageing *(Nikolaou & Templeton, 2003)*
- Unexpected poor ovarian response *(Keay et al.,1997)*

# Management of poor responders

Treatment of poor responders has been attempted with various methods in retrospective ,prospective, studies

using comparative and non-comparative designs

Most studies are underpowered and solid, useful conclusions are difficult to be drawn

There is a need for an evidenced based approach in the problem of treament of poor responders

# Materials and methods

Search strategy:

- MEDLINE *(1966 to November 2006)*
- EMBASE *(1988 to November 2006)*
- Cochrane Central Register of Controlled Trials *(Cochrane Library Issue 1, 2007)*
- **Keywords** :("poor" OR "low" OR "slow" OR "inadequate" OR "suboptimal") AND ("response" OR "responder" OR "ovarian reserve")
- No language limitations
- Hand-searching

# Materials and methods

## Data extraction

- Demographic
  - type of study
  - number of patients included
  - definition of poor ovarian response
- Methodological
  - randomization method
  - allocation concealment
- Procedural
  - type of intervention examined
  - type and protocol of ovarian stimulation
- Outcome data
  - clinical or ongoing pregnancy rate
  - live birth

# Materials and methods

## Inclusion criteria:

a) Prospective parallel two -arm
b) Randomized controlled trial
c) Full manuscript

## Exclusion criteria:

a) Quasi-randomization methods
   *(sequential numbers, date of birth, allocation by week day)*
a) Participation of patients more than once in studies

# Materials and methods

Definition of poor ovarian response:

- Variable
- Retrospective vs. Prospective

# Interventions to enhance IVF outcome in poor responders

- Addition of :

1. Growth hormone (GH) or GH-releasing factor (GHRF)
2. Pyridostigmine
3. Transdermal testosterone
4. Aspirin
5. L-arginine
6. Aromatase inhibitors

- Modifications of the long GnRH-a protocol

- Short versus long GnRH agonist protocol

# Interventions to enhance IVF outcome in poor responders

- GnRH antagonist protocol versus:

1. GnRH –a protocols
2. No pituitary suppression
3. Natural cycle

- Modifications of ovarian stimulation
- Intracytoplasmic sperm injection (ICSI)

# Addition of Growth Hormone (GH) or GH-releasing factor (GHRF)

## Background

- GH enhances:

  gonadotrophin effects on granulosa cells

  *(Lanzone et al., 1992)*

- GHRF enhances :
  - gonadotrophin-induced steroidogenesis
  - cyclic adenosine monophosphate formation (cAMP)

  *(Doldi et al., 1996)*

# Growth hormone for in vitro fertilization

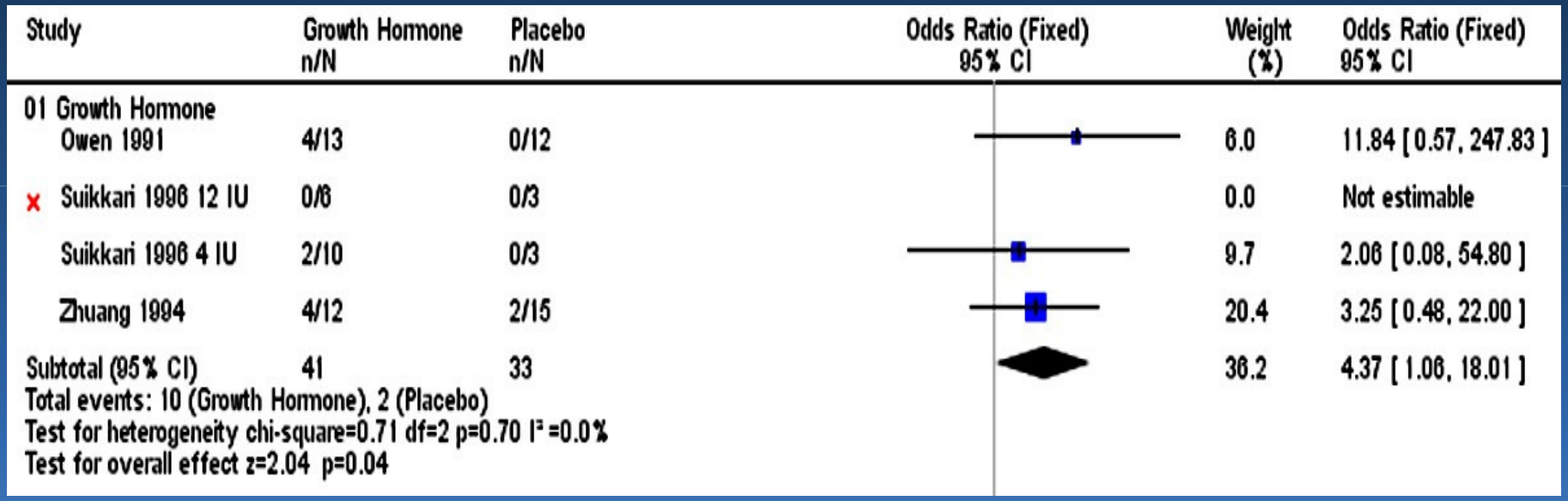
*(Harper et al. , 2003)*

| Study | N | Intervention | Outcome |
|---|---|---|---|
| Bergh et al.,1994 | 18 | Addition of GH | Live birth |
| Dor et al., 1995 | 14 | Addition of GH | Live birth |
| Owen et al., 1991 | 25 | Addition of GH | Live birth |
| Suikkari et al.,1996 | 22 | Addition of GH | Live birth |
| Zhuang et al.,1994 | 27 | Addition of GH | Live birth |
| Howles et al.,1999 | 196 | Addition of GHRF | Live birth |

# Growth hormone for in vitro fertilization

*(Harper et al., 2003)*

## GH Addition and live birth




OR: **4.37**

(CI 95% 1.06 to 18.01)

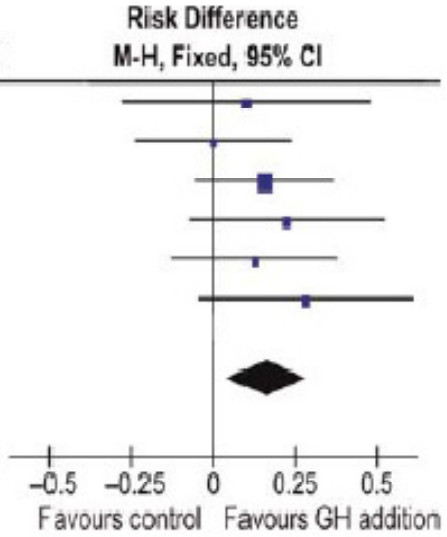
# GH in IVF: *Clinical Pregnancy Rate*

***Kolibianakis et al, Hum Reprod Update, 2009***

| Study or Subgroup | GH Events | GH Total | Control Events | Control Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bergh et al., 1994 | 3 | 10 | 2 | 10 | 12.2% | 0.10 [-0.28, 0.48] |
| Dor et al., 1995 | 0 | 7 | 0 | 7 | 8.5% | 0.00 [-0.24, 0.24] |
| Kucuk et al., 2007 | 10 | 31 | 5 | 30 | 37.2% | 0.16 [-0.06, 0.37] |
| Owen et al., 1991 | 4 | 13 | 1 | 12 | 15.2% | 0.22 [-0.07, 0.52] |
| Suikkari et al., 1996 | 2 | 16 | 0 | 6 | 10.6% | 0.13 [-0.13, 0.38] |
| Zhuang et al., 1994 | 5 | 12 | 2 | 15 | 16.3% | 0.28 [-0.04, 0.61] |
| **Total (95% CI)** | | **89** | | **80** | **100.0%** | **0.16 [0.04, 0.28]** |
| Total events | 24 | | 10 | | | |

Heterogeneity: $Chi^2 = 2.71$, $df = 5$ ($P = 0.75$); $I^2 = 0\%$

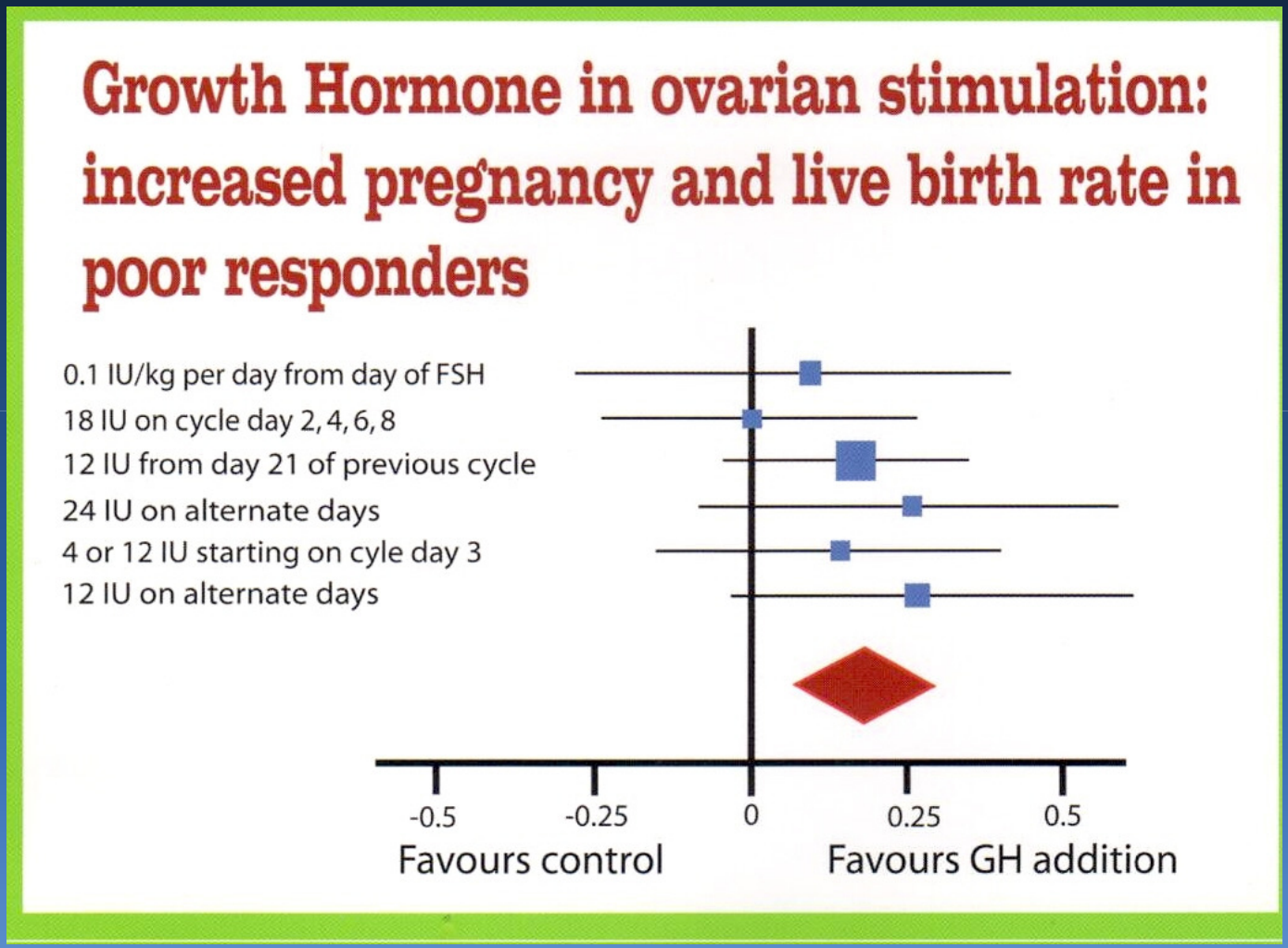
Test for overall effect: $Z = 2.65$ ($P = 0.008$)




**Rate Difference +16%**
**95% CI +4 to +28**

# GH in IVF: *Clinical Pregnancy Rate*

***Kolibianakis et al, Hum Reprod Update, 2009***




**Rate Difference +16%**
**95% CI +4 to +28**

# Growth hormone for in vitro fertilisation

*(Harper et al. , 2003)*

GHRF Addition:

- Single study *(Howles et al., 1999)*

- Addition of GHRF vs. No addition

  *Live birth rate:* 5.2% vs. 4.0%

  *Rate difference:* 1.2% (95% CI: -5.3 to +8.1)

# Growth hormone for in vitro fertilisation

*(Harper et al. , 2003)*

## Conclusions

- GH Addition: Beneficial effect on the probability of live birth
- GHRF Addition: No beneficial effect

# Addition of Pyridostigmine

Background

- Acetylcholinesterase inhibitor
- Increase GH secretion by enhancing the action of acetylcholine

*(Delitala et al., 1988)*

# Addition of Pyridostigmine

- Relevant study: *Kim et al ., 1999*
- N: 70 patients
- Protocol: GnRH agonist protocol and gonadotrophins
- Definition of poor response : < 3 oocytes retrieved and/or a minimum requirement of 50 ampoules of gonadotrophins in a previous failed IVF attempt
- Outcome: ongoing pregnancy / delivery rate

# Addition of Pyridostigmine
## (*Kim et al., 1999)*

Addition of pyridostigmine vs. no addition:

*Ongoing pregnancy/delivery rate:* 8.6% vs. 22.9%

*Rate difference :* -14.3%  (95% CI:-31.4 to +3.2)

# Addition of Pyridostigmine
## (*Kim et al., 1999*)

Conclusion:

Addition of pyridostigmine

does not improve the ongoing pregnancy / delivery rate

in poor responders undergoing IVF

# Addition of transdermal testosterone

## Background

- Identification of androgens receptors by immunochemistry in the human ovary *(Suzuki et al., 1994)*
- Androgens play a critical role on follicular growth *(Ryan et al.,1968)*
- Convertion of androgens into estrogens by the aromatase activity of the granulosa cells *(Harlow et al., 1988; Shaw et al., 1989)*

## Rationale:

- beneficial effect on the number of small antral follicles
- improve the ovarian sensibility to FSH

# Addition of transdermal testosterone

- Relevant study: Massin et al.,2006
- N: 53 patients
- Protocol: GnRH-a/recombinant FSH (rFSH)
- Definition of poor response :E2 <1200 pg/ml on the day of HCG administration, < 5 follicles retrieved, FSH > 12 IU/L, E2 > 70 pg/ml and inhibin B < 45 pg/ml on day 3 of a spontaneous cycle.
- Outcome : Delivery rate

# Addition of transdermal testosterone

Massin et al.,2006

Addition of transdermal testosterone vs. placebo

*Delivery rate:* 11.1% vs. 3.8%

*Rate difference:*7.3% (95% CI:-9.4 to +24.5)

# Addition of transdermal testosterone

Massin et al.,2006

## Conclusion:

Testosterone addition

in poor responders treated by IVF

does not appear to result in an increased probability of pregnancy

# Addition of Aspirin

## Background:

- Beneficial effect of the addition of low-dose in:

  - patients with low uterine blood flow undergoing thawed ET

    *(Wada et al., 1994)*

  -oocytes donation recipients with a thin endometrium

    *(Weckstein et al.,1997)*

## Rationale:

- impaired ovarian blood flow

  (*Battaglia et al ., 2000)*

# Addition of Aspirin

- Relevant study: Lok et al., 2004
- N: 60 patients
- Protocol: GnRH-a/HMG
- Definition of poor response : recruitment of fewer than 3 mature follicles (≥17mm) in previous IVF attempt or presence of repeated high basal levels of FSH (>10IU/L)
- Outcome : clinical pregnancy rate

# Addition of Aspirin
## *(Lok et al., 2006)*

Addition of Aspirin vs. placebo

*Clinical pregnancy rate: 3.33%* vs. 6.77%

*Rate difference:* -3.33% (95% CI:-18.24 to +10.85)

# Addition of Aspirin
## *(Lok et al., 2006)*

Conclusion

A beneficial effect of low-dose aspirin

in poor responders undergoing IVF

is not currently supported

# Addition of L-arginine

## Background

- Increased vascularization appears to play a critical role in the selection, growth and maturation of follicles in both natural and IVF cycles

*(Weiner et al.,1993)*

- NO might participate in periovulatory vasodilatatory modulation of the ovarian blood flow in the rat

*(Ben-Shlomo, 1994)*

# Addition of L-arginine

## Background

- NO play a role in follicular maturation and ovulation.

*(Anteby et al., 1996)*

- L-arginine is involved in the formation of NO either by a calcium dependent or a cytokine-inducible NO synthase.

*(Moncada et al., 1991)*

# Addition of L-arginine

- Relevant study: Battaglia et al.,1999
- N: 34 patients
- Protocol: flare-up GnRH-a/pFSH
- Definition of poor response : at least one previous cycle cancellation due to E2<1100 pmol/l and/or < 3 follicles recruited by day 8
- Outcome : cumulus-oocyte complexes (COCs)
  pregnancy rate

# Addition of L-arginine

Battaglia et al.,1999

Addition of L-arginine vs. placebo

- *COCs rate*: 4.1 ± 1.9 vs. 1.6 ± 0.5
- *WMD*: 2.5 (95% CI: 1.53 to 3.47)

- *Pregnancy rate* : 17.6% vs. 0%
- *Rate difference*: 17.6% (95% CI: -4.0 to +45.0)

# Addition of L-arginine

Battaglia et al.,1999

## Conclusion

Addition of L-arginine: no beneficial effect

# Addition of aromatase inhibitors

- Background:

  The selective inhibition of aromatase:

  - prevents the overall production of estrogens
    their negative feedback effects on the hypothalamus- hypophysis axis
    -results in an increase of pituitary production of FSH
    *Simpson et al .,2000)*

    -may increase the production follicular androgens,
    which might improve follicular sensitivity or stimulate IGF- 1

    *(Giudice et al., 1992; Palter et al., 2001)*

# Addition of aromatase inhibitors

-induces ovulation in anovulatory PCOS women

*(Mitwally and Casper, 2000)*

-increases ovarian sensitivity to gonadotrophins rendering it an attractive option for poor responders

*(Mitwally and Casper, 2002)*

# Addition of aromatase inhibitors

- Relevant study: Goswami et al .,2004
- N:38 patients
- Protocol: long GnRH-a/rFSH protocol
- Definition of poor response : No clear definition
- Outcome : pregnancy rate

# Addition of aromatase inhibitors

Goswami et al .,2004

Addition of aromatase inhibitors vs.placebo

*Pregnancy rate/ cycle*: 23.1% vs. 24.0%

*Rate difference*: -0.9% ( 95% CI -25.4 to +29.0)

# Addition of aromatase inhibitors

Goswami et al .,2004

Conclusion

Letrozole addition

does not improve clinical pregnancy rate

in poor responders undergoing IVF

# Modifications of the long GnRH-a protocol

- Background:

different dosages of GnRH agonist

different protocols for GnRH agonist administration

have been used to enhance pregnancy rates in patients with poor ovarian response.

# Modifications of the long GnRH-a protocol

- Relevant study: Dirnfeld et al.,1999
- N: 63 patients
- Protocol: standard long luteal protocol versus a stop agonist long protocol.

  In the stop agonist protocol administration of GnRH-a was initiated in the midluteal phase and was stopped upon adequate down-regulation.

- Relevant study: Garcia-Velasco et al.,2000
- N: 70 patients
- Protocol: "stop" versus "non-stop" protocol

  i) non-stop protocol: GnRH-a long protocol/high doses of FSH+HMG or (ii) stop protocol: GnRH-a initiated in midluteal phase of the previous cycle and was stopped with the onset of menses, FSH+HMG doses similar to the non stop protocol

# Modifications of the long GnRH-a protocol

Dirnfeld et al.,1999

- Definition of poor response :
- ≤ 4 mature oocytes retrieved in at least one previous IVF cycle and/or a previous low response to COH, as evidenced by a peak E2 level of<2.000 pmol/L
- Outcome : ongoing pregnancy rate

Garcia-Velasco et al.,2000

- Definition of poor response :
- development of less than three follicles ≥18mm in diameter in a previous IVF attempt and presence of basal FSH concentration <12IU/ml
- Outcome : pregnancy rate

# Modifications of the long GnRH-a protocol

*-Dirnfeld et al.,1999*

Stop agonist protocol vs. standard long protocol

*Ongoing pregnancy rate* : 5.0% vs. 2.6%

*Rate difference*: 2.4% ( 95% CI -9.1+14.1)

*-Garcia-Velasco et al.,2000*

Non- stop vs. stop protocol

*Pregnancy rate :* 13.9% vs. 17.6%

*Rate difference:* 3.7% ( 95% CI -21.4 to +13.7)

# Modifications of the long GnRH-a protocol

Dirnfeld et al.,1999 Garcia-Velasco et al.,2000

## Conclusion

The modifications of the long agonist protocol described do not enhance the probability of pregnancy over the conventional long protocol

# Short versus long protocol

- Background:

- Suppression of premature LH surge: A matter of debate

- Short protocol:

  promotes follicular growth by taking advantage of the flare-up effect of GnRH-agonist on pituitary gonadotrophin release

- Long protocol:

  results in a more coordinated follicular growth.

# Short versus long protocol

2 relevant studies

# Short versus long protocol

- Relevant study: Weissman et al .,2003
- N:60 patients
- Protocol:

  Short protocol: a high dose of GnRH-a for 4 days, followed by standard GnRH-a dose

  Long protocol: a standard GnRH-a dose was used until pituitary down-regulation, following by halving the GnRH-a dose

- Definition of poor response: presence of fewer than 5 oocytes retrieved or three or fewer follicles of 16mm or larger developed on the day of cycle cancellation, or serum E2 level < 500pg/ml on the day of HCG administration
- Outcome:clinical pregnancy rate

# Short versus long protocol

- Relevant study: Dirnfeld et al.,1991
- N: 54 patients
- Protocol: short and long GnRH-a protocol
- Definition of poor response : at least one previous cancelled cycle due to a peak E2<300 pg/ml or early LH rise when the largest follicle had a diameter <16mm or serum progesterone <1.2 ng/ml during the follicular phase
- Outcome : pregnancy /cycle

# Short versus long protocol

- *Weissman et al .,2003*

Mini-dose long protocol vs. modified short protocol

*Clinical pregnancy rate/ started cycle*: 22,6% vs 3,4%

p=0.053

- *Dirnfeld et al.,1991*

Short vs.long protocol

*Pregnancy rate/ started cycle:* 7.69% vs. 28.57%

*Rate difference:* -20.88% ( 95% CI: -40.18 to +0.3)

# Short versus long protocol

- *Weissman et al .,2003* *Dirnfeld et al.,1991*

Conclusion

The two protocols appear to yield the same results

in poor responders undergoing IVF

# GnRH antagonist (GnRH-ant) versus GnRH-a protocols

- Background:

GnRH antagonist prevent the suppression of endogenous gonadotrophin secretion at the stage of follicular recruitment

*(Craft et al., 1999; Tarlatzis et al., 2003).*

# GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

*Griesinger et al., 2006*

**Table 1.** Main characteristics of randomized controlled trials (RCT) on patients with expected, or history of, poor response.

| *Reference* | *Sample size (ITT)* | *Randomization* | *Criteria for 'poor response'* | *Agonist protocol* | *Antagonist protocol* | *Gonadotr-ophin type* |
|---|---|---|---|---|---|---|
| *Full publication* | | | | | | |
| Akman *et al.*, 2001 | 48 | True, allocation concealed | Previous cycle: bFSH >15 IU/l or E2 (dHCG) <500 pg/ml or COC <4 (leuprolide), | Short, flare-up pretreatment with OCP[a] | Flexible, multiple dose (cetrorelix) | HMG + uFSH |
| Martinez *et al.*, 2003 | 44 | True, allocation concealed | Previous 'poor response' (triptorelin), | Short, flare-up OCP pretreatment | Fixed, multiple dose (cetrorelix), OCP pretreatment | rFSH + HMG |
| Cheung *et al.*, 2005 | 66 | True, allocation concealed | Repeated bFSH > 10 IU/l or previous cycle with <3 COC | Long, luteal (buserelin), OCP pretreatment | Fixed, multiple dose (cetrorelix), OCP pretreatment | rFSH |
| Marci *et al.*, 2005 | 60 | True, allocation concealed | Previous cycle: E2 (dHCG) <600 pg/ml and <3 COC | Long, luteal (leuprolide) | Flexible, multiple dose (ganirelix) | rFSH |
| Malmusi *et al.*, 2005 | 60 | True, allocation concealment unclear | Previous cycle: <5 COC or no ovarian response when ≥300 IU FSH for ≥15 days | Short, flare-up (triptorelin) | Flexible, multiple dose (ganirelix) | rFSH |
| Schmidt *et al.*, 2005 | 48 | True, allocation concealed | Previous cycle: E2 (dHCG) ≤850 pg/ml and/or ≤4 COC and bFSH <13 mIU/ml | Short, flare-up (leuprolide), OCP pretreatment[a] | Flexible, multiple dose (ganirelix) | rFSH + HMG |
| De Placido *et al.*, 2006 | 133 | True; allocation not concealed | ≥37 yrs or bFSH ≥9 IU/l, regular cycle | Short, flare-up (triptorelin) | Flexible, multiple dose (cetrorelix) | rFSH + rLH |
| *Abstract* | | | | | | |
| Mollo *et al.*, 2005 | 116 | Randomization method not described | bFSH >9 IU/l and/or >37 yrs | Short, flare-up (decapeptyl) | Flexible, multiple dose (ganirelix) | rFSH + uHCG |

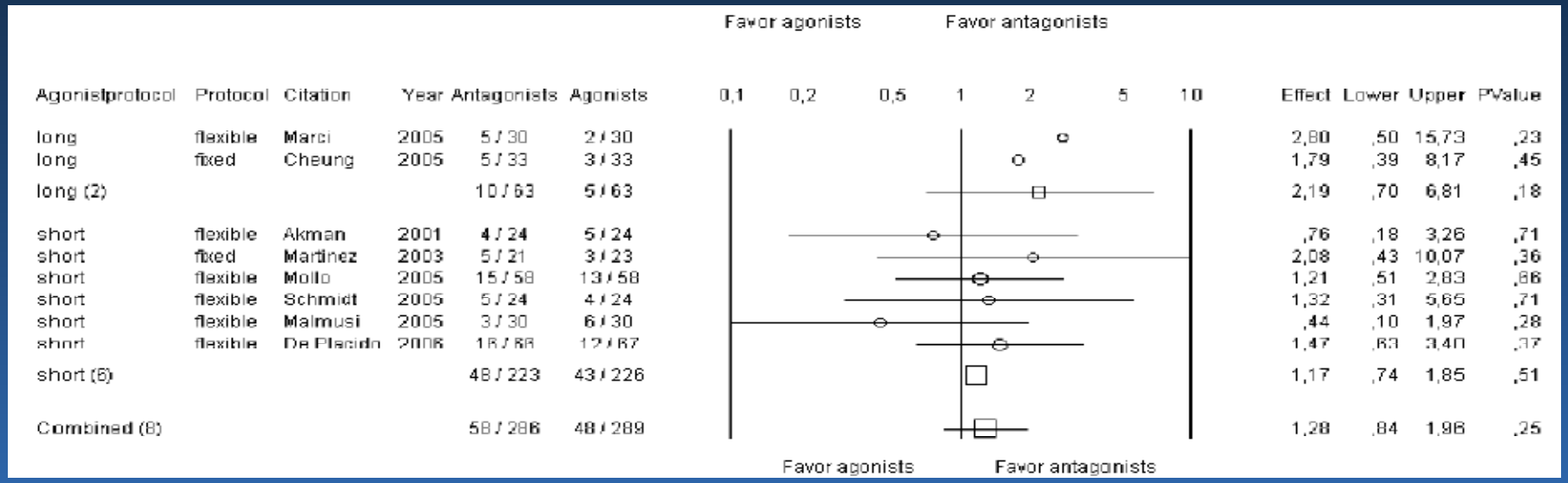
## GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

*Griesinger et al., 2006*

- Relevant studies:8
- Total N: 575 patients
- Protocols: 2 studies→ long agonist protocol
  6 studies → flare-up protocol
- Definition of poor response:
  In the majority of studies →"inappropriate ovarian response" during a previous stimulated cycle.
  Only in two studies→ age of the patients and the basal FSH concentrations used as criteria
- Outcome: clinical pregnancy rate
  COCs

# GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

*Griesinger et al., 2006*




| Agonistprotocol | Protocol | Citation | Year | Antagonists | Agonists | Effect | Lower | Upper | PValue |
|---|---|---|---|---|---|---|---|---|---|
| long | flexible | Marci | 2005 | 5 / 30 | 2 / 30 | 2,80 | ,50 | 15,73 | ,23 |
| long | fixed | Cheung | 2005 | 5 / 33 | 3 / 33 | 1,79 | ,39 | 8,17 | ,45 |
| long (2) | | | | 10 / 63 | 5 / 63 | 2,19 | ,70 | 6,81 | ,18 |
| short | flexible | Akman | 2001 | 4 / 24 | 5 / 24 | ,76 | ,18 | 3,26 | ,71 |
| short | fixed | Martinez | 2003 | 5 / 21 | 3 / 23 | 2,08 | ,43 | 10,07 | ,36 |
| short | flexible | Mollo | 2005 | 15 / 58 | 13 / 58 | 1,21 | ,51 | 2,83 | ,66 |
| short | flexible | Schmidt | 2005 | 5 / 24 | 4 / 24 | 1,32 | ,31 | 5,65 | ,71 |
| short | flexible | Malmusi | 2005 | 3 / 30 | 6 / 30 | ,44 | ,10 | 1,97 | ,28 |
| short | flexible | De Placido | 2006 | 16 / 68 | 12 / 67 | 1,47 | ,63 | 3,40 | ,37 |
| short (6) | | | | 48 / 223 | 43 / 226 | 1,17 | ,74 | 1,85 | ,51 |
| Combined (8) | | | | 58 / 286 | 48 / 289 | 1,28 | ,84 | 1,96 | ,25 |

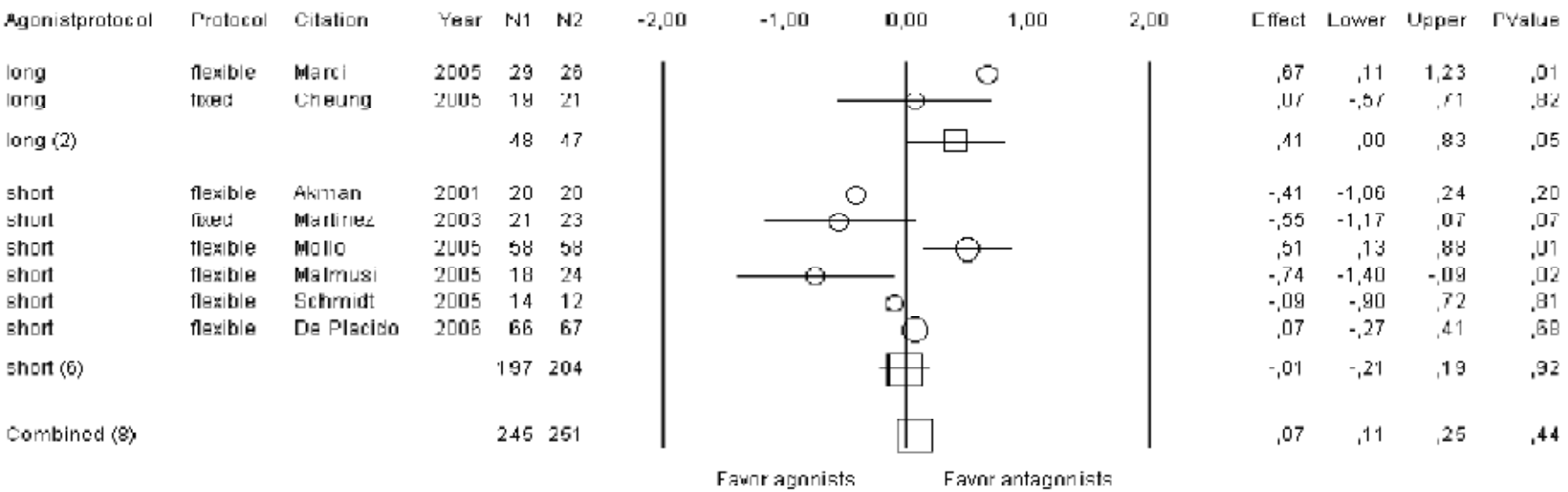
Agonist vs.antagonist
Clinical pregnancy rate

OR=1.28

(95% CI: 0.84 -1.96)

# GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

*Griesinger et al., 2006*




- Long agonist group vs. GnRH-ant group

  COCs

  SDF 0.41 (95 % CI:0.0-0.83,P=0.05)

GnRH-antagonists in ovarian stimulation for IVF
in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

*Griesinger et al., 2006*

## Conclusion

No difference in pregnancy rates appears to exist between GnRH analogues in poor responder patients

# GnRH-ant versus no pituitary suppresion

- Relevant study: Akman et al.,2000
- N: 40 patients
- Protocol: GnRH-ant/FSH+HMG vs FSH+HMG
- Definition of poor response : at least two previous IVF attempts with low response due to the one of the following reasons: baseline FSH concentrations >15mIU/ml, E2 on the day of HCG < 500pg/ml, or fewer than four oocytes retrieved
- Outcome : ongoing pregnancy rate

# GnRH-ant versus no pituitary suppresion

Akman et al.,2000

GnRH antagonist group vs. control group

*Ongoing pregnancy rate:* 5.0% vs.15.0%

*Rate difference*: 10.0% ( 95% CI: -31.44 to +11.02)

# GnRH-ant versus no pituitary suppresion

Conclusion

The addition of GnRH antagonists to ovarian stimulation

does not offer any benefit

in poor responder patients undergoing IVF

# GnRH-ant versus natural cycle

- Background:

the use of natural cycle IVF in poor responder patients as alternative to COH and oocyte donation:

→less invasive

→ less costly

# GnRH-ant versus natural cycle

- Relevant study: Morgia et al .,2004
- N: 129 patients
- Protocol: natural cycle versus a GnRH-ant protocol
- Definition of poor response : retrieval of three or fewer oocytes in a previous attempt or cancellation of the cycle because of no follicular development
- Outcome : pregnancy rate

# GnRH-ant versus natural cycle

Morgia et al .,2004

Natural cycle and the GnRH-ant group

*Pregnancy rate*: 1.7% vs. 2.86%

*Rate difference*: 1.16% (95% CI: -8.3 to +6.4)

# GnRH-ant versus natural cycle

Morgia et al .,2004

## Conclusion

No beneficial effect of natural cycle

# Modifications of ovarian stimulation

- High vs standard dose of FSH
- High vs decremental dose of FSH

# Modifications of ovarian stimulation

- Relevant study: Cedrin-Durnerin et al., 2000
- N: 96 patients
- Protocol: high fixed dose of gonadotropins versus a decremental dose in a short mini-dose GnRH-a protocol
- Definition of poor response : retrieval of fewer of five oocytes in a previous IVF cycle or elevated baseline FSH or E2 levels on cycle day 3
- Outcome : pregnancy rate

- Relevant study: Klinkert et al .,2005
- N: 52 patients
- Protocol: higher starting dose of gonadotrophins during a long GnRH –a protocol
- Definition of poor response : the presence of fewer than four oocytes retrieved or fewer than three follicles developed on the day of cycle cancellation
- Outcome :ongoing pregnancy rate

# Modifications of ovarian stimulation

- *Cedrin-Durnerin et al., 2000*
  Decremental group vs.high fixed dose group

  *Pregnancy rate*: 6.25% vs. 8.33%
  *Rate difference*: 2.08 (95% CI: -14.03 to +9.64)

- *Klinkert et al .,2005*
  Standard dose of FSH vs.  double dose

  *Ongoing pregnancy rate:* 7.69% vs. 3.85%
  *Rate difference:* 3.84 ( 95% CI: -12.19 to +20.60)

# Modifications of ovarian stimulation

*Cedrin-Durnerin et al., 2000* *Klinkert et al .,2005*

## Conclusion

A high fixed-dose gonadotrophin regimen

does not improve the pregnancy rate

in poor responder patients

# Modifications of ovarian stimulation

## Background:

B) The antral follicles are present in late follicular phase of the ovarian cycle and initiation of their further development occurs under the action of the premenstrual FSH rise

*(Gougeon et al, 1996)*

## Rationale:

Earlier administration of FSH might ↑ the number of recruited follicles by opening the recruitment window in the late luteal phase of the preceding cycle

# Modifications of ovarian stimulation

- Relevant study: Rombauts et al., 1998
- N:40 patients
- Protocol: initiating FSH during the luteal phase
- Definition of poor response : retrieval of three to six oocytes in the last FSH stimulated IVF or GIFT cycle.
- Outcome : COCs

# Modifications of ovarian stimulation

Rombauts et al., 1998

- Luteal initiation of FSH vs. follicular initiation of FSH

  *Number of oocytes retrieved/cycle* :

  median: 4.5, range: 2-12 vs. median: 6, range: 1-10

# Modifications of ovarian stimulation

Rombauts et al., 1998

## Conclusion

The administration of FSH in the luteal phase

has no beneficial effect on the total number of oocytes retrieved

in poor responder patients

# Intracytoplasmic sperm injection (ICSI)

## Background

Available evidence is not able to demonstrate

whether ICSI is more efficacious than conventional IVF

in poor responder patients

*(Van Steirteghem 1993)*

# Intracytoplasmic sperm injection (ICSI)

- Relevant study: Moreno et al.,1998
- N: 104 patients
- Protocol: long GnRH-a protocol/HMG+FSH.
- Fertization method: ICSI or IVF
- Definition of poor response: retrieval of six or fewer follicles in a previous cycle.
- Outcome : pregnancy rate

# Intracytoplasmic sperm injection (ICSI)

Moreno et al.,1998

IVF vs. ICSI

*Pregnancy rate* : 17.3% vs. 21.1%

*Rate difference*: -3.8% ( 95% CI -18.9 to +11. 4)

# Intracytoplasmic sperm injection (ICSI)

Moreno et al.,1998

## Conclusion

Pregnancy rates
are not dependent on the fertilization
method in poor responders,
however more studies are necessary

# CONCLUSIONS

- The management of poor responders still represents a challenge for the clinician, which is further complicated by the variations in the definition of poor ovarian response
- With the exception of GH co-administration, none of the examined approaches appears to be beneficial
- Due to the low incidence of poor ovarian response, evaluation of the interventions proposed is usually performed in single, underpowered studies, which might not allow the detection of the true effect of an intervention