

## The Role of adjuvant medical therapies

ESHRE SIG Maribor 27<sup>th</sup> February 2009

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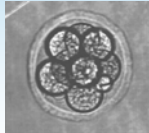
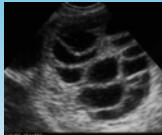
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## Adjuvant treatments in IVF practice

- **Drugs used in addition to standard regimens**
- **During Ovarian stimulation**
  - Enhance Ovarian response
- **Peri-implantation**
  - Increase embryo implantation
- Published studies relate to Controlled Ovarian Stimulation



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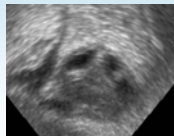
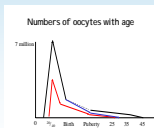
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## Poor ovarian response

- Defining Poor response

"Failure to develop a **sufficient** number of mature follicles to proceed to oocyte retrieval or yielding only a **few** oocytes following ovarian stimulation"



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### Adjuvant therapies used during ovarian stimulation

- **Established poor responder**

- Growth Hormone
  - Howles et al 1999 RCT
  - Kiyoi et al 2008 Meta analysis
- L-Arginine (no benefit)
- Pyridostigmine
- DHEA
- Letrozole
- Testosterone

- **General IVF population**

- Glucocorticoids
- Aspirin

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### Established poor responders - adjuvant Pyridostigmine Kim et al 1999

- **Rationale**

- Acetylcholinesterase inhibitor
- GH secretion enhanced

- **RCT Double blind**

- Tubal (n=70)
- Significantly more:
  - oocytes
  - embryos
  - trend toward higher pregnancy rate (9/35vs 4/35)

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### Established poor responders - adjuvant Letrozole (Mitwally & Casper 2002)

- **Rationale**

- aromatase inhibitor (used in breast cancer treatment )
- androgen accumulates
- Increases sensitivity to FSH

- **Observational cohort study**

- Poor responders IUI (n=12)
- Significantly more
  - follicles
  - less gonadotrophin requirement

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**Adjuvant Testosterone** (Balasch et al 2006)

- Observational cohort study
- Third cycle (n=25) normal basal FSH
- 2 previous poor responses
  - <3 follicles 14mm after 8-9 days stimulation
  - Or < 2 follicles 18mm or less after further 4-5 days
- Step down protocol (450, 300, 150, 150iu FSH then individualised)
- 20% repeat cancellation
- 30% clinical pregnancy/OR
- Transdermal

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**Adjuvant corticosteroids in infertility practice**

- **Synthetic steroids**
  - Therapeutic use
  - Differ in pharmacodynamics
  - Dose and duration dependent side effects
- Alone (1950's)
- Clomifene (1960's)
- Gonadotrophins (1960's)
- IVF without GnRHa (1980's)
- IVF (1990's )
  - During ovarian stimulation
  - Embryo implantation
  - Prevention of OHSS

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**Adjuvant – dexamethasone** (Keay et al 2001)

- RCT
  - twin centre
  - n=290
  - <40 yrs
- Day of stimulation to OR
  - 1mg dexamethasone vs placebo

	Dex n=145	Placebo n=145
Cancellation Poor response	2.8 <sup>†</sup>	12.4 <sup>†</sup>
Cancellation Over response	4.0	2.1
Clinical pregnancy rate	27 <sup>††</sup>	18 <sup>††</sup>

<sup>†</sup> P<0.05  
<sup>††</sup> P<0.005

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**Adjuvant – prednisolone** (Fridstrom *et al* 1999)

- RCT
  - n=20
  - PCOS
- Day of stimulation to OR
  - 10mg prednisolone vs placebo
  - During stimulation until night prior to oocyte retrieval
- Intrafollicular androgen profiles
  - Trend toward higher follicle number
  - Shorter duration of stimulation

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**General IVF population – Low-dose aspirin for in vitro fertilisation** (Poustie *et al* 2007)

- Rationale
  - based on APA outcome
  - increase follicular blood flow
- Conclusion
  - Not currently recommended

Low-dose aspirin versus placebo or no treatment Outcome Clinical pregnancy rate.




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**Adjuvant medical therapies and Ovarian response**

- None of adjuvant therapies show consistent benefit
- Controversy over use of Aspirin
- Poor response
  - No intervention shown to be useful (Shanbhag *et al* 2007)
- Cochrane protocol 2008 (Pandian Z, Keay SD, Bhattacharya S)
  - Glucocorticoid during ovarian stimulation

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### Adjuvant medical therapies– implantation

- **Implantation failure**
  - Various interventions
- **Assisted hatching**
- **PGS**
- **Glucocorticoids**
  - Immune modulator
  - Alters cytokine expression and excess Nk cell activity
  - Reduce endometrial inflammation

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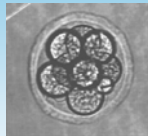
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### Peri-implantation Adjuvant steroids – Cochrane review

- Boomsma CM, Keay SD, Macklon NS 2007
- Peri-implantation Glucocorticoid administration for Assisted reproductive technology cycles
- **Primary outcome measure**
  - Livebirth rate per couple
- **Secondary outcome measures**
  - Ongoing pregnancy rate per couple
  - Pregnancy rate per couple



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### Peri-implantation Glucocorticoid administration for Assisted reproductive technology cycles

- Truly randomised trials included
  - N=13
- 1759 participants
- **Glucocorticoid used**
  - Methyl prednisolone 4mg or 16mg
  - Prednisolone 5mg , 7.5mg ,10mg ,15mg or 60 mg/day
  - Dexamethasone 0.5mg or 1mg /day
- **Prevention of OHSS**
  - Hydrocortisone
  - Prednisolone 30mg decreasing in luteal phase

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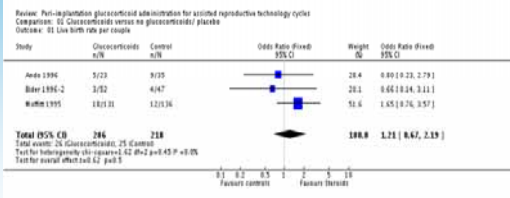
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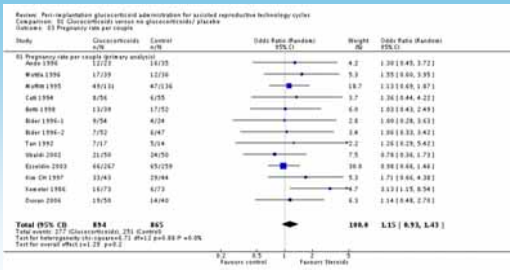
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## Live birth rate per couple



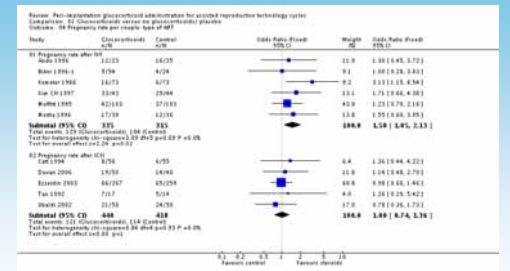
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## Pregnancy rate per couple



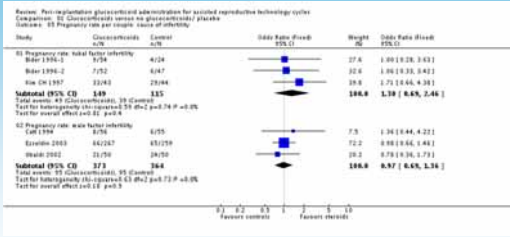
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## Pregnancy rate per couple – IVF and ICSI separately

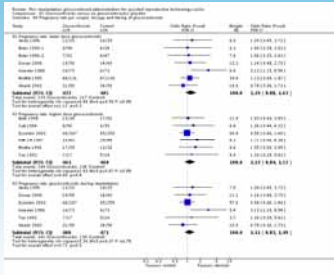


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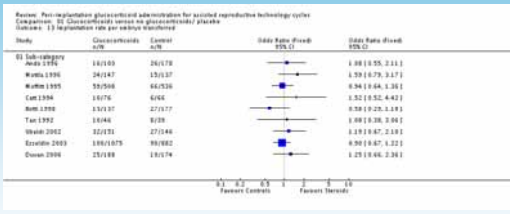
## Cause of infertility



## Dosage and timing of administration



## Implantation rate



### Summary – Peri-implantation

- **No clear evidence for routine peri-implantation glucocorticoids in ART cycles.**
- **Limited (borderline) evidence that it may benefit IVF patients (without ICSI)**
- **Paucity of evidence in:-**
  - Unexplained infertility
  - Recurrent implantation failure
  - Women with high numbers of uterine Nk cells
- **Studies to date in unselected populations**

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### Adjuvant medical therapies

- Cannot currently recommend adjuvant medical therapy
- Studies predominantly in controlled ovarian hyperstimulation cycles
- Definitions of poor response and implantation failure important

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