# ESHRE CAMPUS 2009
# ARTIFICIAL INSEMINATION: AN UPDATE

**Genk, December 13-15, 2009**

## Intrauterine insemination discussed by the ESHRE Capri Workshop Group

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# IUI CYCLES PERFORMED IN EUROPE

| | | 2001 | 2002 | 2003 | 2004 |
|---|---|---|---|---|---|
| Sperm Donor Partner | Cycles (x 1000) | 53 | 79 | 83 | 98 |
| | Pregnancies (%) | 13 | 11 | 12 | 12 |
| | Singleton births (%) | 89 | 89 | 87 | 87 |
| | Multiple births (%) | 11 | 11 | 13 | 13 |
| | Cycles (x 1000) | 14 | 15 | 17 | 18 |
| | Pregnancies (%) | 16 | 16 | 16 | 18 |
| | Singleton births (%) | 90 | 90 | 89 | 88 |
| | Multiple births (%) | 10 | 10 | 11 | 11 |

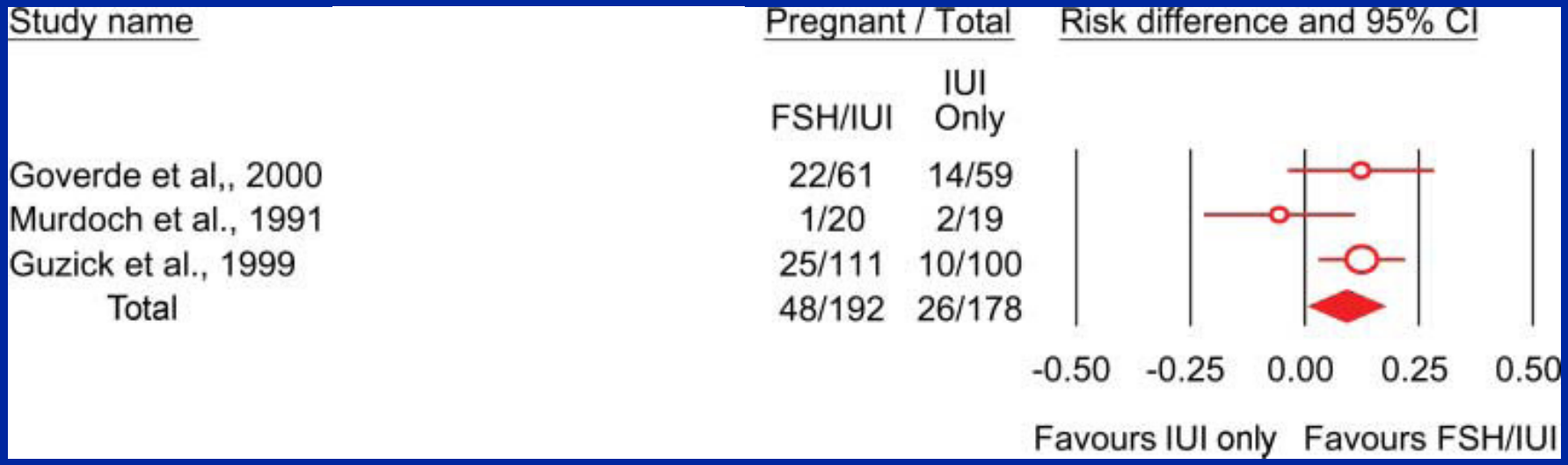
*(Andersen et al., 2005-2008)*

# MAIN INDICATION FOR IUI: UNEXPLAINED INFERTILITY

Categories of unexplained infertility:

- 20% of couples after the initial work-up
- 20-40% of couples with mild male subfertility
- 50% of those in whom conventional treatments have failed

# LIVE BIRTH RATE PER COUPLE FOLLOWING IUI WITH OR WITHOUT OVARIAN STIMULATION




*(Verhulst et al., 2006)*

# PREGNANCY RATES ASSOCIATED TO IUI: THREE LARGE CLINICAL STUDIES

| Study | Rate x cycle (%) | | | |
|---|---|---|---|---|
| | Women treated No. | Pregnancy | Twin | Triplets |
| Guzick et al., 1999 (RCT) | 932 | 12 | 20 | 7 |
| Gleicher et al., 2000 (retrospective) | 1494 | 13 | 20 | 9 |
| Dickey et al., 2005 (retrospective) | 2272 | 19 | 19 | 4 |

# THE RISK OF MULTIPLE PREGNANCY

- Perinatal mortality: 7 times higher for triplets and 5 times higher for twins

  *(Fisk and Trew, Lancet 1999)*

- Cerebral palsy: 48 times more frequent in triplets and 8 times in twins

  *(Petterson et al., B.M.J., 1993)*

# FEWER TRIPLETS WITH LOWER DOSE FSH (≤ 75 IU/DAY) AND CYCLE CANCELLATION

| Study | PR per cycle | Triplets/All pregnancies |
|---|---|---|
| Balasch et al., 1994 | 12.8% | 0/12 |
| Cohlen et al., 1998 | 13.2% | 0/21 |
| Sengoku et al., 1999 | 14.3% | 0/7 |
| Goverde et al., 2000 | 8.7% | 0/31 |
| Ragni et al., 2004 | 20.0% | 0/13 |
| Gerli et al., 2004 | 12.3% | 0/17 |
| Papageorgiou et al., 2004 | 10.4% | 1/266 |
| Tur et al., 2005 A | 10.1% | 1/149 |
| Tur et al., 2005 B | 14.0% | 5/207 |
| Ragni et al., 2006 | 9.2% | 0/116 |
| Total | - | 7/839 |
| **Studies with cancellation criteria** | **10.2%** | **2/613** |

# THEORIES

OLD
- The higher the number of released oocytes the higher the chance of conception

NEW
- High ovarian responsivity reflects the release of higher quality oocytes

# IUI: NUMBER OF STIMULATED FOLLICLES VS PREGNANCY RATE

Meta-analysis of 11599 cycles

| Follicle No. | % increase of PR vs monofollicular cycles |
|---|---|
| 2 | 1.6 |
| 3 | 2.0 |

*(Van Rumste et al., H. R.U., 2008)*

# ONE OR MORE FOLLICLES FOR IUI CYCLES?

- If the growth of 1-2 follicles would be associated with the expected fecundity, mono-ovulation will be the goal for the future IUI
- There is a need of RCTs

# IUI: CLINICAL CONDITIONS AFFECTING SUCCESS RATES

- Age of the female partner
- Duration of subfertility
- Abnormal spermiogram

*(Steures et al., 2004)*

# PREMATURE LH SURGE DURING FSH STIMULATION WITH AND WITHOUT ANTAGONISTS

- Patients: 203 women with unexplained infertility
- Mild ovarian stimulation: median FSH dose 550-600 IU

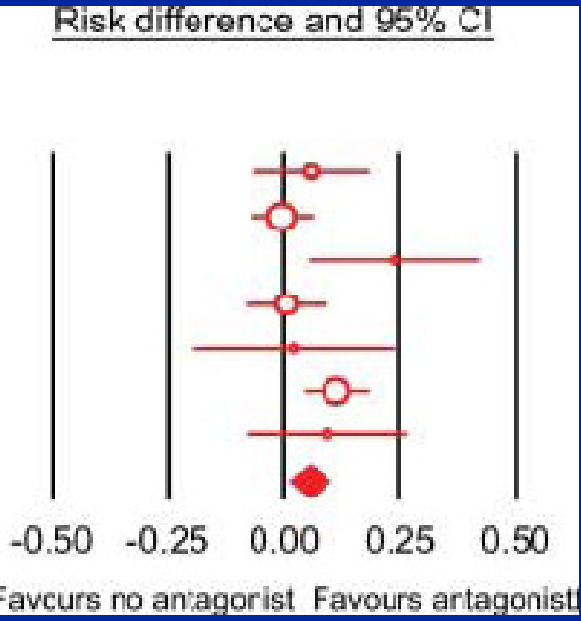
| Group | A | B |
|---|---|---|
| Antagonist | Ganirelix | Placebo |
| Cycles | 103 | 100 |
| LH surge % | **3.9** | **28.0** |
| Ongoing PR % | **12.6** | **12.0** |

- Premature luteinization is one of the consequences of the poor quality follicle

*(Lambalk et al., HR, 21, 632-639, 2006)*

# ONGOING P.R. PER COUPLE WITH ONE CYCLE OF FSH/IUI WITH AND WITHOUT GnRH ANTAGONIST

| Study name | Pregnant / Total | |
|---|---|---|
| | FSH/IUI + GnRH Antagonist | FSH/IUI alone |
| Allegra et al., 2007 | 8/52 | 5/52 |
| Crosignani et al., 2007 | 15/148 | 16/151 |
| Gomez et al., 2005 | 15/39 | 6/41 |
| Lambalk et al., 2006 | 13/103 | 12/100 |
| Ragni et al., 2001 | 3/19 | 3/22 |
| Gomez et al., 2008 | 38/184 | 17/183 |
| Lee et al., 2008 | 6/31 | 3/30 |
| Total | 98/576 | 62/579 |




NNT: 20 antagonist cycles for one additional pregnancy

# LUTEAL SUPPORT: IS IT NECESSARY IN STIMULATED IUI CYCLES?

- Luteal support is necessary during induction of ovulation in hypophysectomized patients
- Women undergoing IUI stimulated cycles are not totally hypogonadotropic
- Exogenous HCG persists for at least 10 days and at that time the embryo is secreting the endogenous hormone

# IUI: FACTORS INVOLVED IN BALANCING EFFICACY AND SIDE EFFECTS

- The chance of spontaneous pregnancy
- Ovarian stimulation aimed to the growth of one or more follicles
- Cycle cancellation if there are more than two dominant follicles

# PREGNANCY RATE PER CYCLE AND NUMBER NEEDED TO TREAT (NNT) PER CYCLE

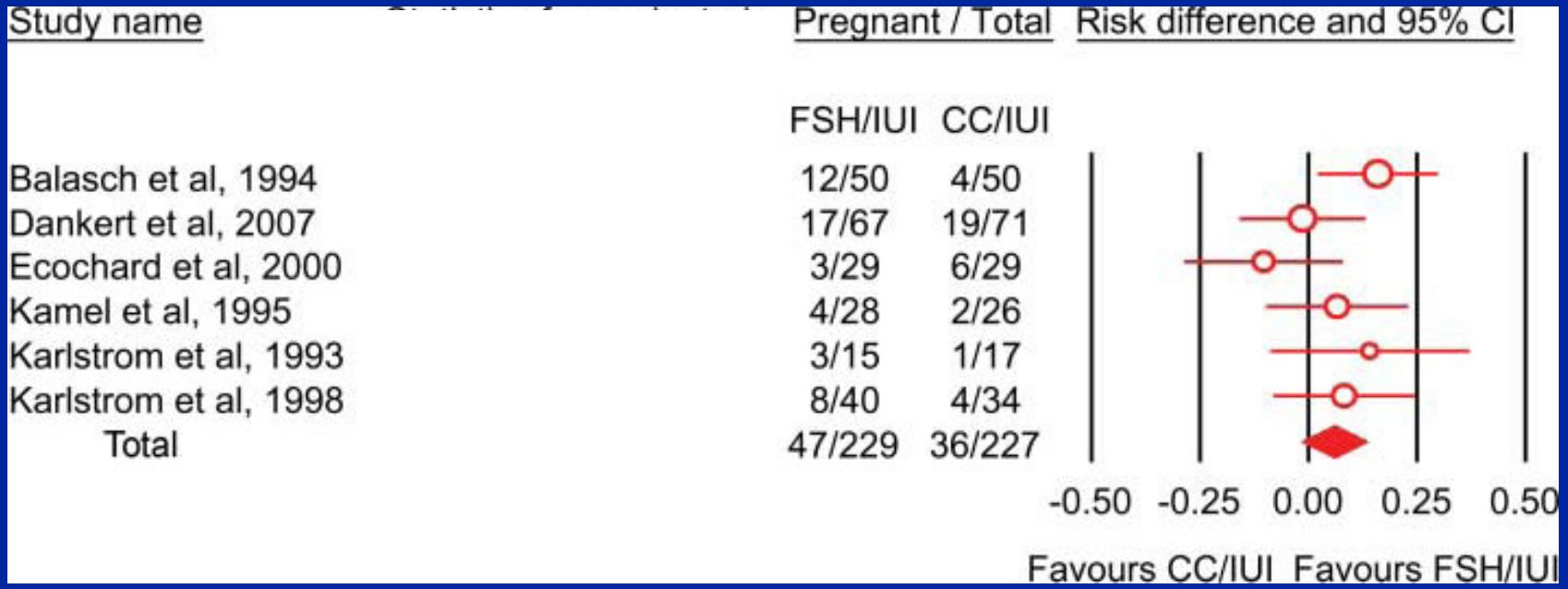
| Treatment | Pregnancy rate per cycle | NNT 95 % CI | Source |
|---|---|---|---|
| IUI | 5 | 32 (12-46) | Guzick et al., 1999, Steures et al., 2007 |
| FSH/IUI | 12 | 11 (9-16) | Guzick et al., 1999 |
| IVF | 31 | 4 (3-7) | Hughes et al., 2004 |

# IVF MAKE-UP FOR THE BIRTHS LOST BY POSTPONING CONCEPTION

| Woman's age | IVF make-up |
|---|---|
| From 30 to 35 | 50% |
| From 35 to 40 | 30% |

*(The ESHRE Capri Workshop Group, HRU, 11, 261-276, 2005)*

# PREGNANCY RATES FOLLOWING IUI COMBINED WITH OVARIAN STIMULATION USING EITHER ANTI-ESTROGEN OR FSH




Prior to IVF, IUI with clomiphene stimulation is cheap and many couples will conceive

*(Cantineau et al., 2007)*

# CONCLUSIONS - 1

- In good prognosis couples, the live birth rate is better without treatment
- IUI is widely used with infertility diagnoses other than bilateral tubal obstruction, severe male infertility and severe ovulation defects
- The good success rate recently associated with mild stimulated IUI cycles must be confirmed by large trials

# CONCLUSIONS - 2

- Prevention of premature LH surges and luteal phase support do not appear major requirements in IUI cycles
- Although IUI treatment is cheaper and less demanding IVF is the most effective treatment for infertility
- There is a need for management trials to evaluate the order of treatment and overall effectiveness of treatment strategies in more clinical and cost settings.