IUI in the treatment of male infertility – a tale in two parts

ESHRE Campus workshop

Thessaloniki

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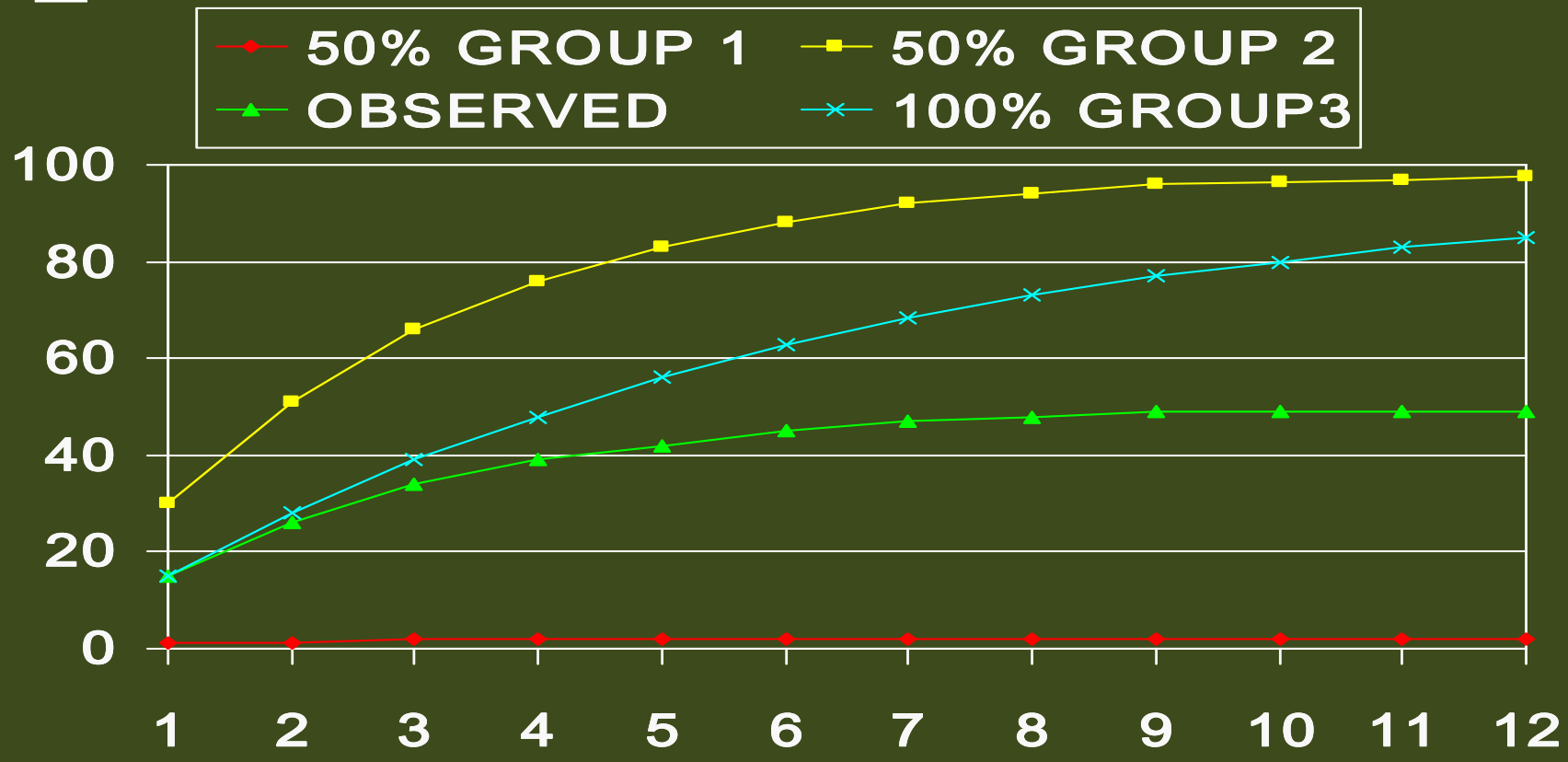
IUI in male infertility – Part 1

IUI – introduction – what we have always known to be true

- **Indications**:
  - → Unexplained infertility: ?
  - → (Minimal endometriosis): ?
  - → Cervical infertility: +++
  - → Mild male infertility: ?
- **Mode of action**:
  - → Not etiological but “chance-increasing” treatment
  - → Timing, localization, sperm preparation, ± stimulation
  - → Doubles chances of pregnancy (10->20% or 5->10% but also 1->2%)
  - → Population treated = bimodal (the ones for whom IUI will work and the ones for whom it will not…) -> maximum nr of cycles = 4 to 6

IUI – Success rates – how to interpret (why max 4 to 6 cycles?)

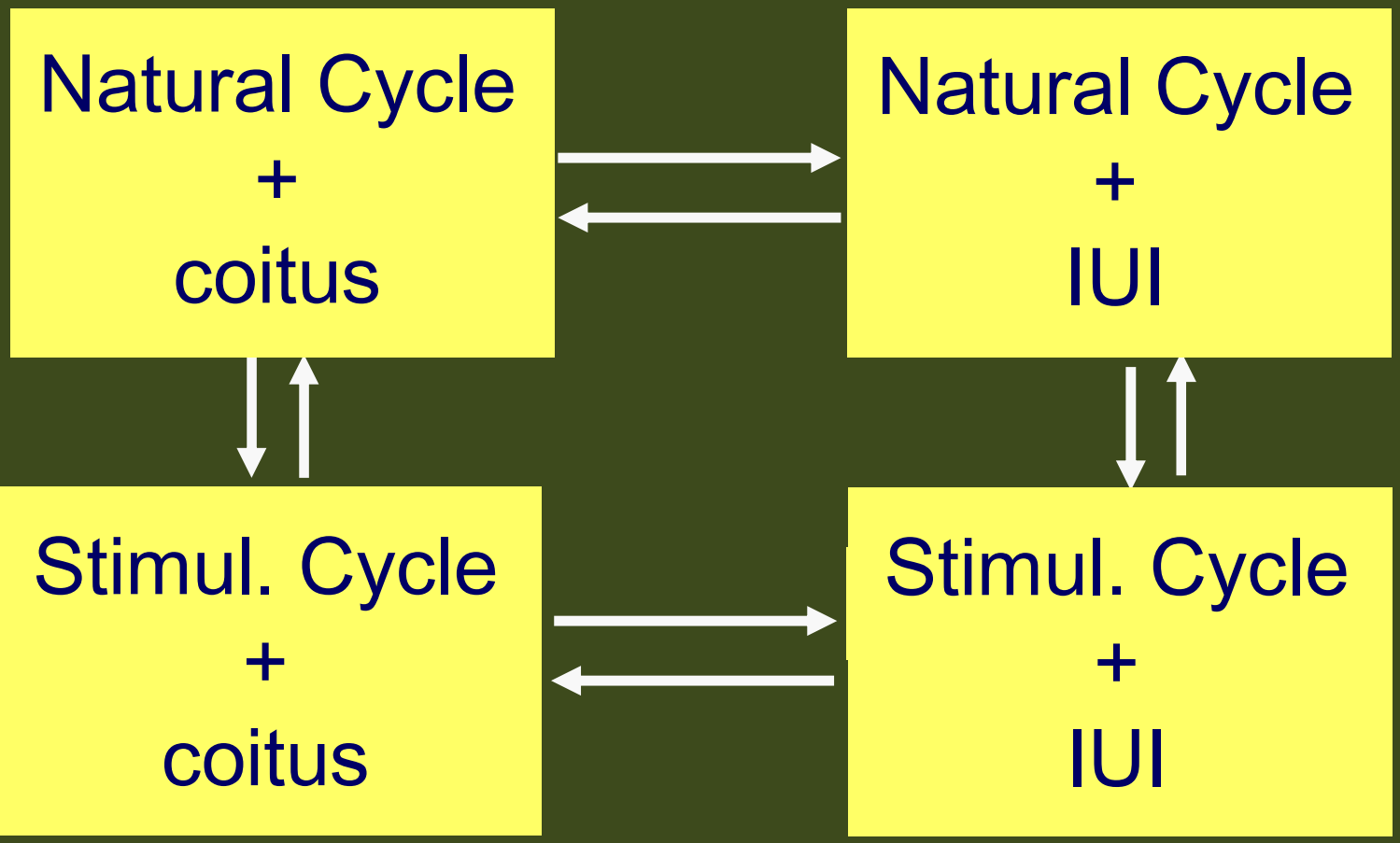


P(GROUP 1) = 30% pregnancy/cycle
P(GROUP 2) = 0 % pregnancy/cycle
P(GROUP 3) = 15% pregnancy/cycle

IUI – technical aspects

- → Sperm preparation mandatory (>< contractions, infection risk)
- → Technique: centrifugation, swim-up or density gradient centrifugation? no evidence
- → Inseminate all or only motile sperm? no evidence
- → Sperm quality? > 3-5-10 million motile sperm?
- → Intracervical, IUI (0.2-0.5 ml) or FSP (4ml)?
  - IUI superior to intracervical with frozen sperm
  - FSP superior tot IUI in unexplained infertility only
- → Timing? 2 inseminations no better than 1

IUI vs intercourse? Natural vs stimulated cycle?



IUI – male infertility – Guidelines?

- NICE: IUI is used to manage male factor infertility where semen is of sufficient quality for there to be two to five million motile sperm available after sperm preparation. However, the specific semen criteria for the use of IUI vary from clinic to clinic.
- When compared with timed intercourse, IUI was associated with increased pregnancy rates per cycle in both natural cycles (pooled OR 2.5, 95% CI 1.6 to 3.9, based on six RCTs) and stimulated cycles (pooled OR 2.2, 95% CI 1.4 to 3.6, based on seven RCTs). No difference was found between pregnancy rates in stimulated and unstimulated IUI cycles (OR 1.8, 95%CI 0.98 to 3.3, based on four RCTs). However, it is recognised that stimulated IUI carries a risk of multiple pregnancy.

IUI – male infertility – NICE Recommendations

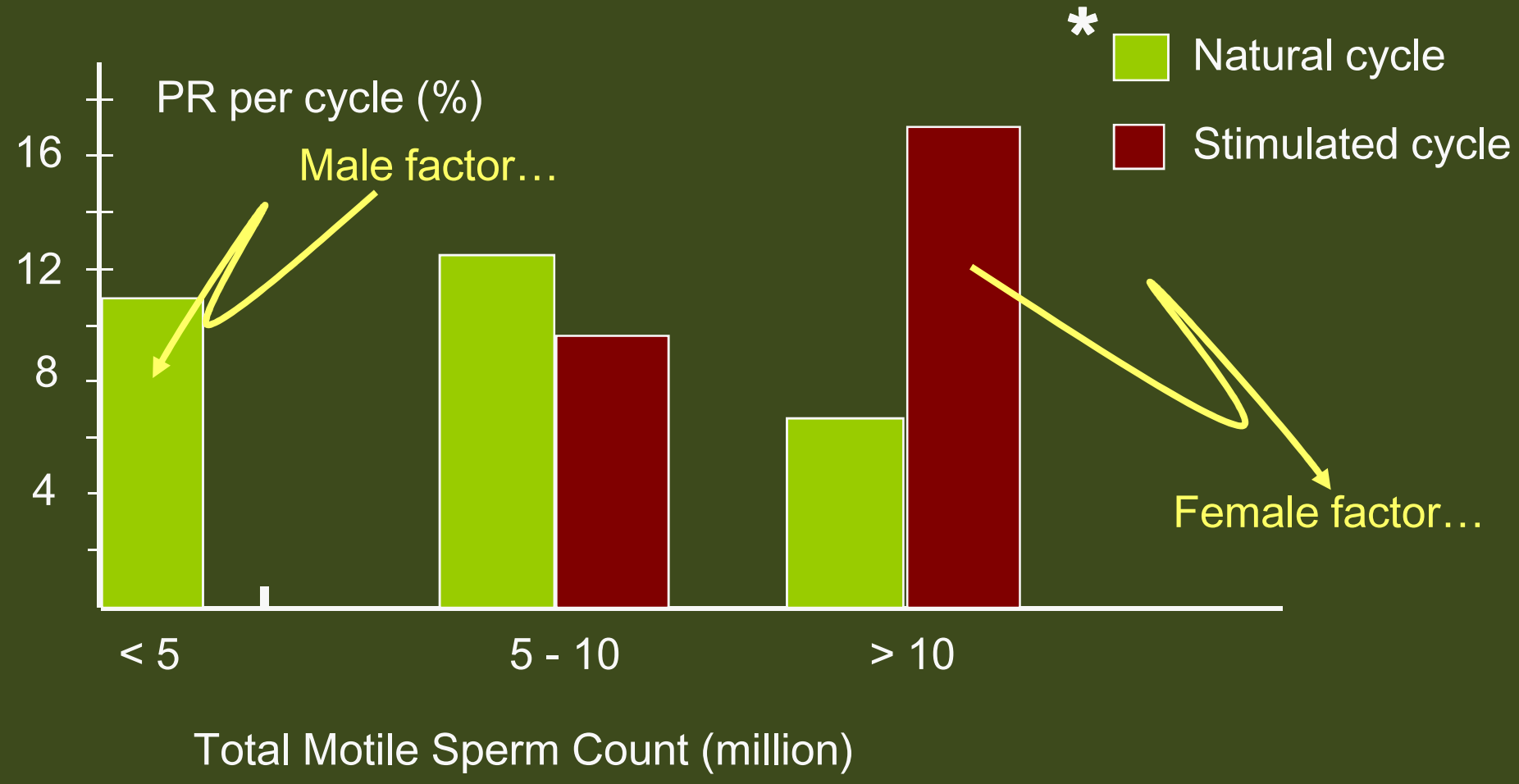
- Couples with mild male factor fertility problems, (unexplained fertility problems or minimal to mild endometriosis) should be offered up to six cycles of intrauterine insemination because this increases the chance of pregnancy.
- Where intrauterine insemination is used to manage male factor fertility problems, ovarian stimulation should not be offered because it is no more clinically effective than unstimulated intrauterine insemination and it carries a risk of multiple pregnancy.
- Where intrauterine insemination is undertaken, single rather than double insemination should be offered.

Tournaye, Curr Opin Obs Gyn 18(3), 2006, 253-259

- IUI applied in natural cycles is an efficient technique for remedying male subfertility. COH is not beneficial unless the native semen sample shows a total motile count above 10 million spermatozoa.

- Depending on the woman's age, at least three and a maximum of six IUI cycles can be proposed. If no pregnancy is obtained, the next step would be IVF or ICSI.

Cohlen, HR 1998;13(6):1553-8: influence of sperm quality – IUI with or without stimulation



Risks of IUI

- Infections
- Multiple pregnancies (MP)

Type stim.	cycles	% MP	% HOMP
CC/HMG (a)	593	5	0.0
75/250 IU HMG (b)	2560	6.2	1.4
150 IU HMG (a)	1528	19	3.2
150/225 IU HMG (a)	1500	21	4.5
Analog/HMG (a)	259	31	8.5

(a) Nan et al. Hum Reprod 1994;9:2022–6.
(b) Fino et al. Fertil Steril 2005;84(Suppl 1):S312.

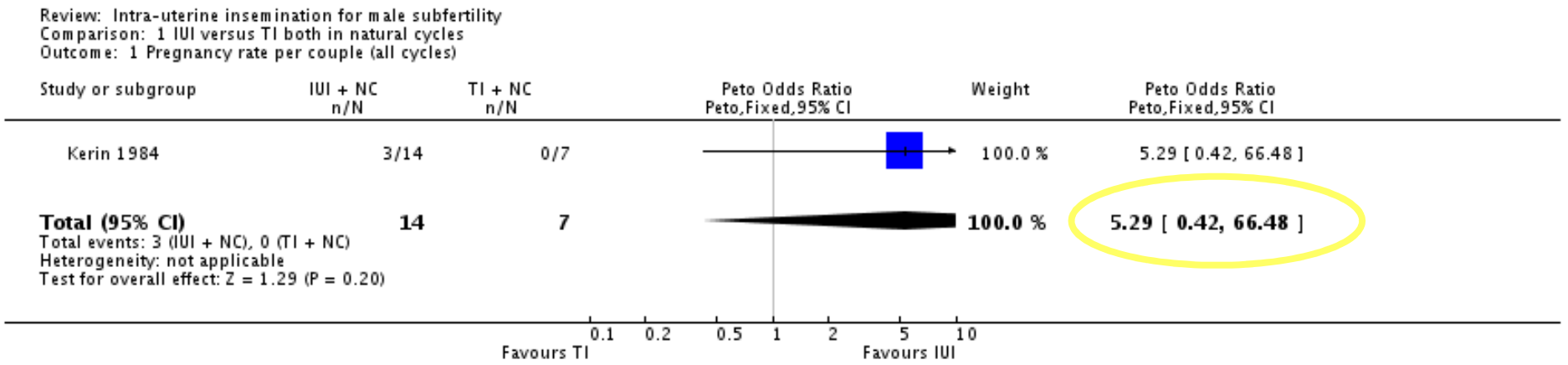
IUI in male infertility – Part 2

IUI – male infertility – Recent evidence

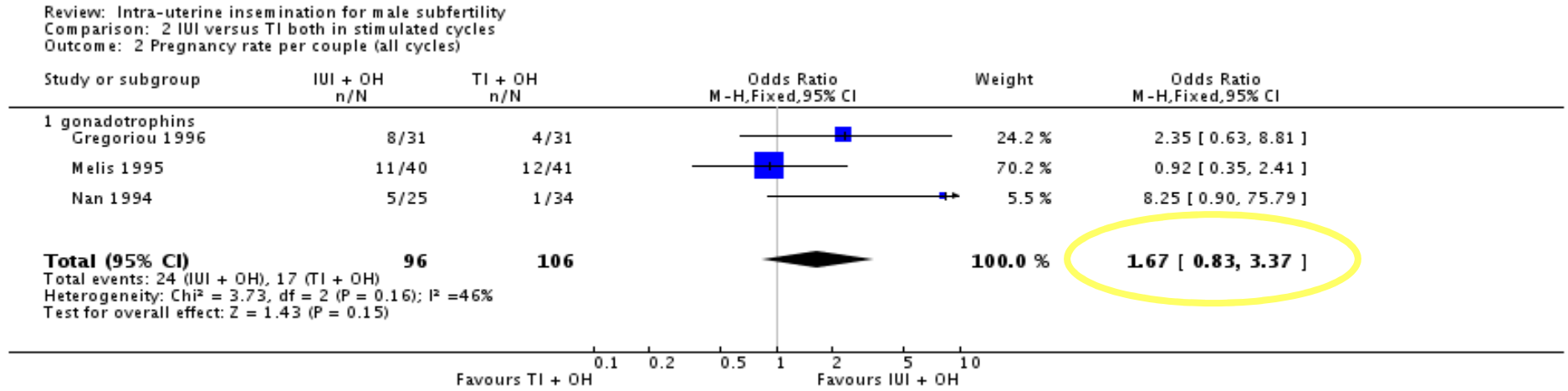
- Hypothesis: IUI increases the chances of pregnancy in case of mild male infertility. In natural or in stimulated cycles? Compared to timed intercourse or “ordinary intercourse”?

- Answer: Bensdorp A, Cohlen BJ, Heineman MJ, Vanderkerchove P. Intra-uterine insemination for male subfertility. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD000360. DOI: 10.1002/14651858.CD000360.pub4

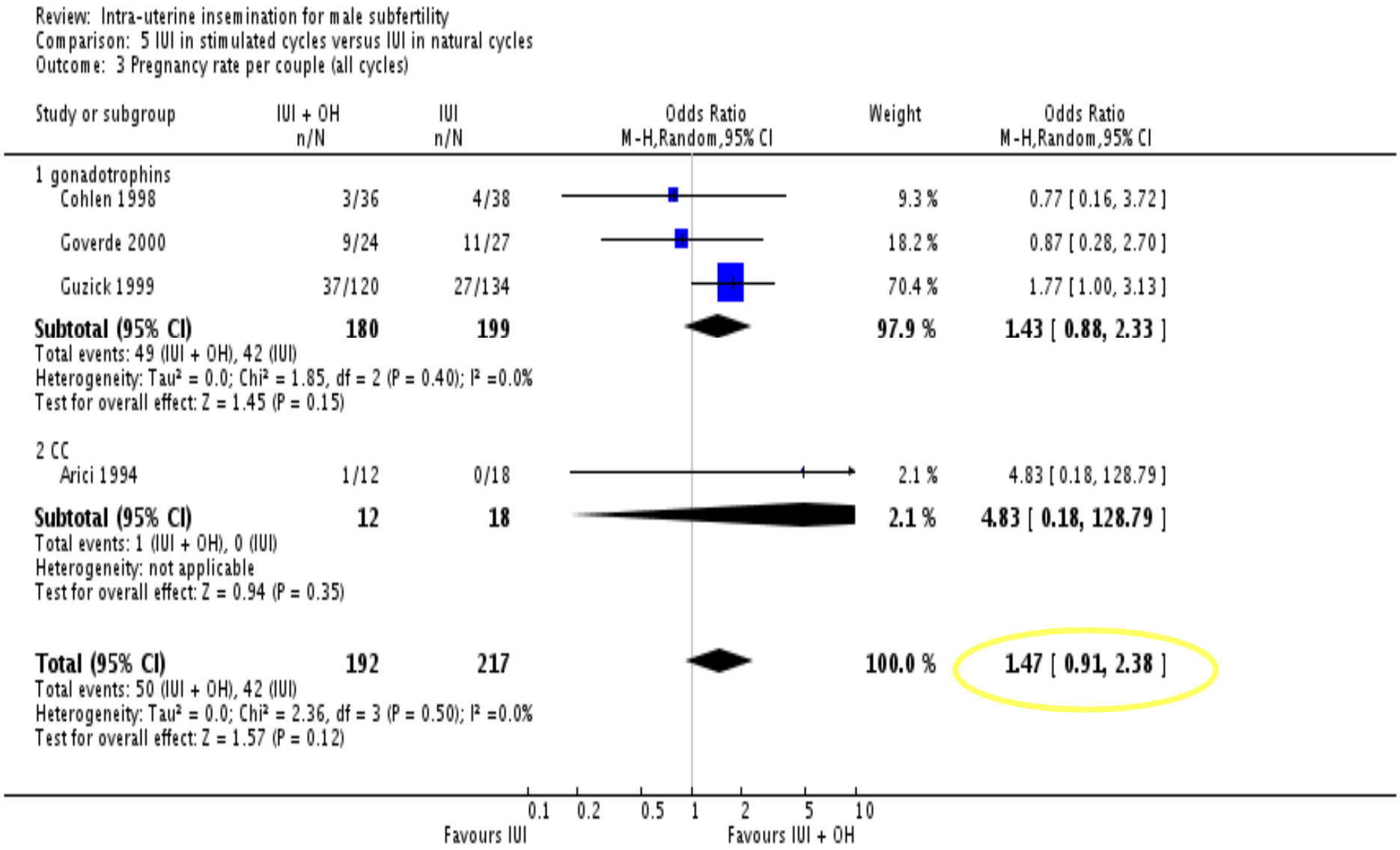
Natural cycle: IUI vs timed intercourse: PR/couple



Stimulated cycle: IUI vs timed intercourse: PR/couple



IUI: Natural vs Stimulated cycle: PR/couple



IUI – male infertility – Recent evidence

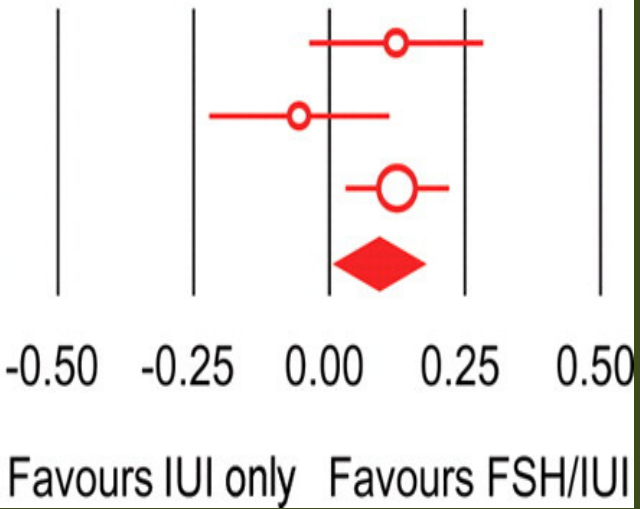
Conclusion: There was insufficient evidence of effectiveness to recommend or advise against IUI with or without OH above TI, or vice versa. Large, high quality randomised controlled trials, comparing IUI with or without OH with pregnancy rate per couple as the main outcome of interest are lacking. There is a need for such trials since firm conclusions cannot be drawn yet.

IUI – stimulation ? Protocols ?

- GnRH antagonists (>< premature LH surge, better timing): not superior !
- Luteal support? Not needed !
- Clomiphene citrate ~ FSH
- FSH: more multiple pregnancies!

Live birth rate per couple following IUI with or without FSH ovarian stimulation (Verhulst et al., 2006)

Study name	Statistics for each study			Pregnant / Total	
	Risk difference	Lower limit	Upper limit	FSH/IUI	IUI Only
Goverde et al,, 2000	0.123	-0.039	0.286	22/61	14/59
Murdoch et al., 1991	-0.055	-0.223	0.113	1/20	2/19
Guzick et al., 1999	0.125	0.028	0.223	25/111	10/100
Total	0.089	0.014	0.164	48/192	26/178

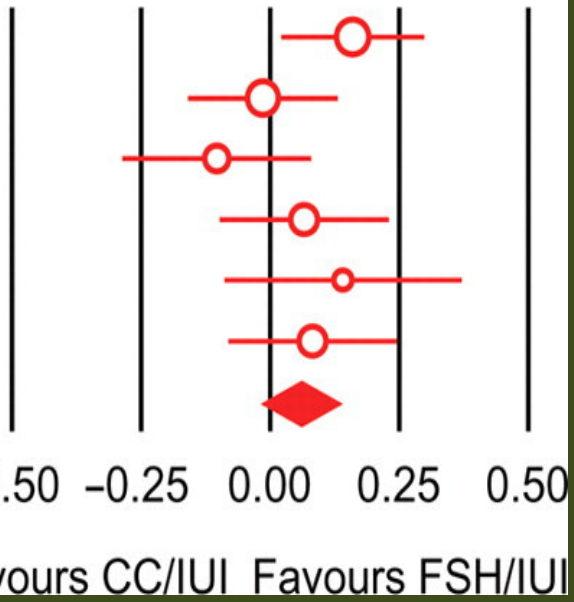


The ESHRE Capri Workshop Group, Hum Reprod Update 2009 15:265-277; doi:10.1093/humupd/dmp003

Human Reproduction Update

Pregnancy rates following IUI combined with ovarian stimulation using either anti-estrogens or FSH

Study name	Statistics for each study			Pregnant / Total	
	Risk difference	Lower limit	Upper limit	FSH/IUI	CC/IUI
Balasch et al, 1994	0.160	0.020	0.300	12/50	4/50
Dankert et al, 2007	−0.014	−0.160	0.133	17/67	19/71
Ecochard et al, 2000	−0.103	−0.288	0.081	3/29	6/29
Kamel, 1995	0.066	−0.099	0.231	4/28	2/26
Karlstrom et al, 1993	0.141	−0.090	0.372	3/15	1/17
Karlstrom et al, 1998	0.082	−0.082	0.247	8/40	4/34
Total	0.057	−0.010	0.125	47/229	36/227



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Human Reproduction Update

HRU 2009;15(3): 265-77. Intrauterine insemination.ESHRE Capri Workshop Group.

Registered IUI in Europe				
	2001	2002	2003	2004
IUI partner				
Countries	15	16	18	19
Cycles	52 939	78 505	82 834	98 388
Pregnancies (%)	6696 (12.6)	8961 (11.4)	9995 (12.1)	12 216 (12.4)
Singleton births (%)	5826 (88.8)	6553 (88.7)	3880 (86.9)	10 499 (86.9)
Multiple births (%)	732 (11.2)	831 (11.3)	585 (13.1)	1582 (13.1)
IUI donor				
Countries	15	17	16	15
Cycles	14 185	14 779	16 743	17 592
Pregnancies (%)	2307 (16.3)	2327 (15.7)	2620 (15.6)	3108 (17.7)
Singleton births (%)	1980 (89.6)	1928 (90.0)	2283 (88.6)	2686 (88.2)
Multiple births (%)	230 (10.4)	215 (10.0)	294 (11.4)	360 (11.8)

HRU 2009;15(3): 265-77. Intrauterine insemination.ESHRE Capri Workshop Group.

- Timed intercourse >< ordinary intercourse (OI)
- IUI probably not superior to OI
- Cheap, simple, widely used, but not effective???
- Cheap??? Cost-effectiveness as calculated by a mathematical model (Pashayan et al., BMC Health Serv Res (2006) 6:80): for IVF alone, unstimulated IUI followed by IVF and stimulated IUI followed by IVF were £12 600, £13 100 and £15 100 per live birth, respectively -> for couples with unexplained infertility and mild male factor, a primary offer of an IVF cycle was both cheaper and more cost-effective than starting with IUI or stimulated IUI followed by IVF

HRU 2009;15(3): 265-77. IUI Capri Workshop Group: Results

- Stimulated IUI is ineffective in male infertility and the effect on other diagnoses is small
- With clomiphene citrate and IUI, the most common IUI protocol, pregnancy rates average 7% per cycle
- FSH ovarian stimulation and IUI treatment is only modestly better than observation only with pregnancy rate 12% per cycle but multiple birth rates averaging 13%
- Mildly stimulated (1–2 follicles) cycles might reduce the cost and multiple birth rates but may require more cycles of treatment
- Prevention of premature LH surges and luteal phase support do not appear to be major requirements in IUI cycles.

HRU 2009;15(3): 265-77. IUI Capri Workshop Group: Conclusions

- 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.
- Differences in sperm preparation and IUI methodology do not have profound effects on the success rate.
- Prior to using IVF, IUI with clomiphene ovarian stimulation is relatively cheap and many couples will conceive and not require IVF.
- There is a need for more placebo-controlled trials of CC/IUI, including trials to determine the optimal length of treatment.

HRU 2009;15(3): 265-77. IUI Capri Workshop Group: Conclusions

- IUI in stimulated cycles was effective only in patients with more than 3 years duration of infertility but is associated with a significant rate of higher-order multiple births.
- The good success rate recently associated with mild stimulated IUI cycles must be confirmed by large trials.
- 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 on the patient, 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.

What next ?

- The better the prognosis of the couple, the more likely OI will be equally effective as IUI, with or without stimulation.
- The worse the prognosis of the couple, the more likely IVF will be more effective.
- Place for IUI in the future?
  - → In places were IVF is not affordable / reimbursed / available?
  - → Balanced against risks for OHSS, multiples, other risks and complications after IVF/ICSI?
  - → Longer period of expectant management, but than straight to IVF?
- Need for “management trials”

Thank you for your attention !