Subfertility & prognostic factors & intrauterine insemination

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Subfertility

- Most of patient attending with the desire of childbearing are subfertile and although rate of their monthly contraception reduce, they can spontaneously conceive

"ESHRE Capri Group 1996"

  - Cost analysis of treatment and adverse effect of ovarian stimulation should be taken into account prior to advanced treatment during the management of these patients
  - Prior to using IVF which is an expensive and invasive method, appropriate treatment could be planned.

IUI

STOP-GAP treatment in unexplained infertility,

as an empirical treatment

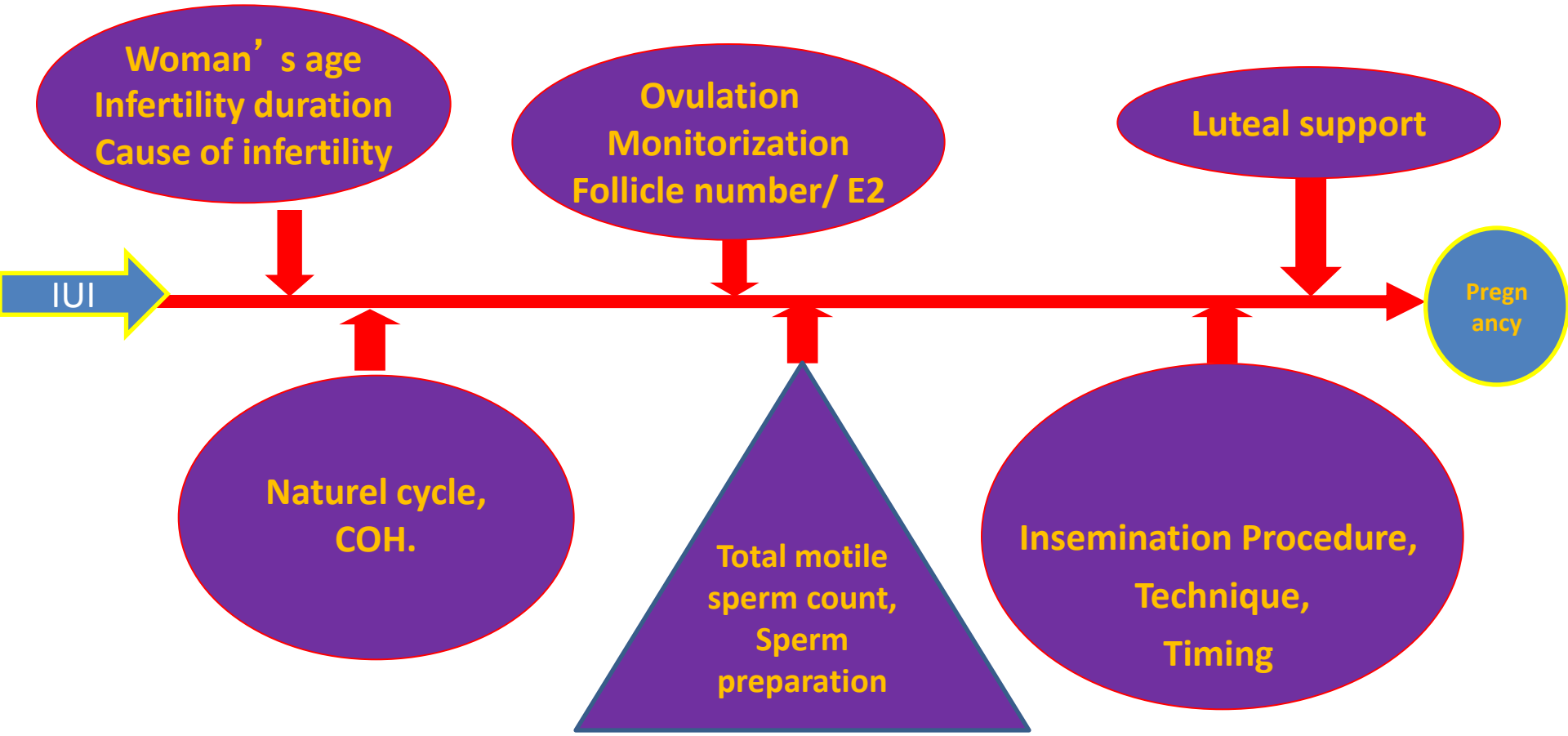
instead of expectant manegement or before IVF

IUI cycles performed in Europe using partner's semen (Andersen et al.,) Human Reprod 2009

<40 age	2005 year
Cycle	120613
Pregnancy	**12.6 %**
Single	87.9 %
Twin	11.1 %
Triplet	1.1%

>40 age	2005 year
Cycle	8295
Pregnancy	**7.4 %**
Single	94.4 %
Multiple	4.9 %
Triplet	0.7 %

Predictive factors for pregnancy after intrauterine insemination



Ocmbelet W, RBM Online 2014

IUI-Kümülatif gebelik oranı %5-20

Kadın yaşı >40

İnfertilite süresi uzadıkça

Ciddi male faktör varlığında

Başarı ↓

Merviel P, Fertil Steril 2010
Harris ID, Fertil Steril 2010

Assessment and treatment for people with fertility problems:

NICE guideline

Table 1. Cumulative probability of conceiving a clinical pregnancy by the number of menstrual cycles

Age category, years	Pregnant after 1 year (12 cycles), %	Pregnant after 2 years (24 cycles), %
19–26	92	98
27–29	87	95
30–34	86	94
35–39	82	90

From NICE guideline 156. Cumulative probability of conceiving a clinical pregnancy by the number of menstrual cycles attempting to conceive in different age categories (assuming vaginal intercourse occurs twice per week) (Reproduced with permission: Dunson DB, Baird DD, Colombo B [2004]. Increased infertility with age in men and women. Obstetrics and Gynecology 103: 51–6).

Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature

The woman's age was the strongest predictor of success in all indications, with an ongoing pregnancy rate per couple of 38.5% for the under 30s and 12.5% for the over 40s

Clinical and ongoing pregnancy rates per couple and the frequency of twin pregnancies for woman in different age groups.

Age	No. of couples (%)	Clinical pregnancy/couple % (n)	Ongoing pregnancy/couple % (n)	Twin pregnancy/clinical pregnancy % (n)
≤30	135 (38.2)	44.4 (60)	38.5 (59)	20 (12)[a]
31–35	145 (41.2)	40 (58)	31.7 (46)	10.3 (6)[b]
36–40	57 (16.1)	33.3 (19)	26.3 (15)[a]	5.2 (1)
>40	16 (4.5)	25 (4)	12.5 (2)[b]	0
Total	353	39.9 (141)	34.5 (122)	13.5 (19)

[a,b] Indicates significant difference at $P<.05$.

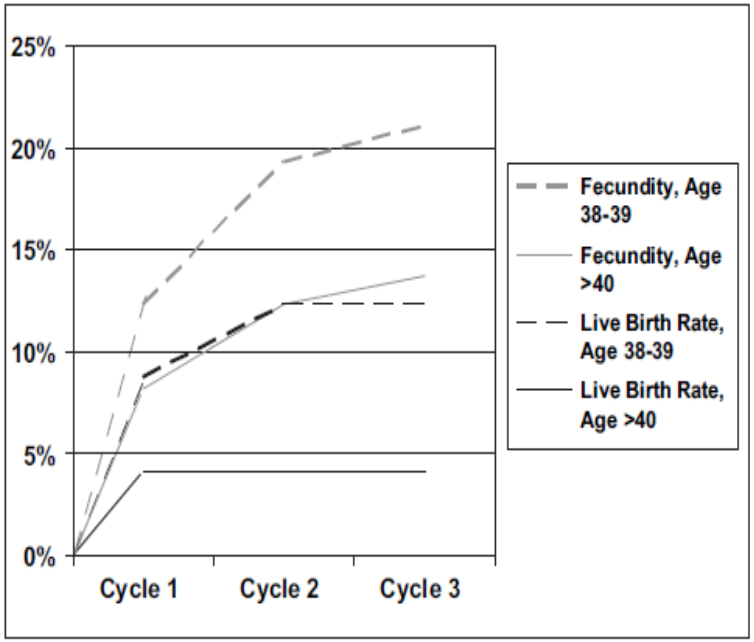
Merviel. Pregnancy and IUI. Fertil Steril 2010.

Merviel P, Fertility and Sterility 2010

Poor success of gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination for older women

FIGURE 1

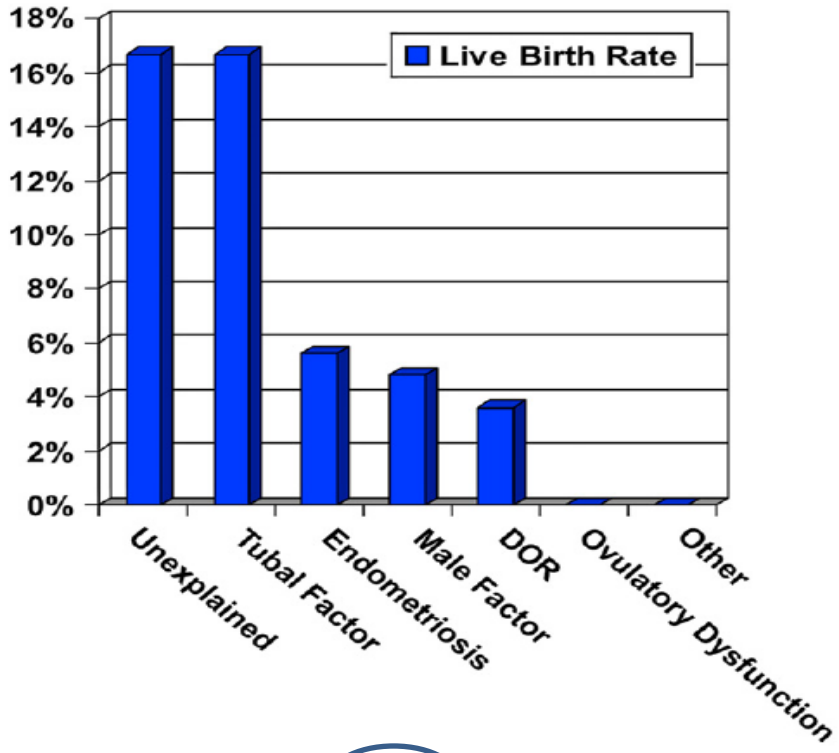
Reverse Kaplan-Meier curve showing the live birth rates and fecundity rates by cycle stratified by age.



Harris. Poor birth rates with IUI after 40. Fertil Steril 2010.

FIGURE 2

Live birth rates stratified by diagnosis.



Harris. Poor birth rates with IUI after 40. Fertil Steril 2010.

Harris, Fertil Steril 2010

Assessment and treatment for people with fertility problems:

NICE guideline

- Women <40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where ≥6 are by intrauterine insemination), should be offered 3 full cycles of IVF.
- One full cycle of IVF should offered if a women is aged 40–42 years provided they have never previously had IVF treatment, there is no evidence of low ovarian reserve and there has been a discussion of the implications of IVF and pregnancy at this age
- An earlier referral for specialist consultation is appropriate when the woman is aged ≥36 years, there is a known cause of infertility, or a history of predisposing factors. People at risk of infertility because of planned treatment (for example, for cancer), should be offered referral to a fertility specialist.

Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome

Table II. Intrauterine insemination pregnancy rate according to female characteristics and sperm parameters (after preparation)

	Pregnancies/cycle (%)
Age (years)[a]	
<40	98/713 (13.7)
⩾40	4/98 (4.1)
Infertility duration (years)[b]	
⩽6	92/646 (14.2)
>6	10/165 (6.1)
Infertility aetiology[c]	
Unexplained	63/413 (15.3)
Male factor	27/229 (11.8)
Endometriosis	9/138 (6.5)
Ovarian dysfunction	3/31 (9.7)
Type of infertility	
Primary	52/457 (11.4)
Secondary	50/354 (14.1)
Sperm count ($\times 10^6$/ml)	
<5	6/84 (7.1)
5–10	12/91 (13.2)
>10	84/636 (13.2)
Progressive motility (%)	
<40	6/63 (9.5)
⩾40	96/748 (12.8)

[a]$P = 0.007$; [b]$P = 0.005$; [c]$P = 0.05$.

Table III. Intrauterine insemination pregnancy rate according to number of follicles, thickness of endometrium and number of treatment cycle

	Pregnancies/cycle (%)
Number of follicles (>16 mm)[a]	
1	10/177 (5.7)
2	36/265 (13.6)
3	32/196 (16.3)
⩾4	24/173 (13.9)
Thickness of endometrium (mm)	
<6	3/27 (11.1)
6–10	87/683 (12.7)
>10	12/101 (11.9)
Number of treatment cycle[b]	
1	51/283 (18.0)
2	26/228 (11.4)
3	15/160 (9.4)
4	7/73 (9.6)
⩾5	3/67 (4.5)

[a]$P = 0.013$; [b]$P = 0.007$.

Huttunen SN, Human Reproduction, 1999

Ovarian stimulation protocols

- Anti- oestrogens
  - Clomiphene citrate
  - Aromatase inhibitors
- Gonadotrophins
- Combinations
- Gonadotrophins with GnRH antagonists (flexible or variable)

The ESHRE Capri Workshop Group1

- 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.

Human Reproduction Update 2009

Assessment and treatment for people with fertility problems:

NICE guideline

- Oral ovarian stimulation agents (such as clomiphene citrate, anastrozole, or letrozole) should not be given to women with unexplained infertility

Three points???

- Is FSH/IUI superior to no treatment?
- Is FSH/IUI superior to CC/IUI?
- Is FSH/IUI superior to IUI alone ??

FSH/IUI is better than expectant management ?

ESHRE Capri Workshop Group

- Duration of infertility less than 2-3 years’ ‘*at least among patients with unexplained infertility*’, FSH/IUI (4.3%) is no better than expectant management (4.6%)
- But has a modest better effect with FSH-IUI for patients, more than 3 years duration of infertility; “12% ---3%”. There would be one additional pregnancy for every 11 cycles of FSH/IUI compared with control cycles.

Guzick 1999.Steures 2006

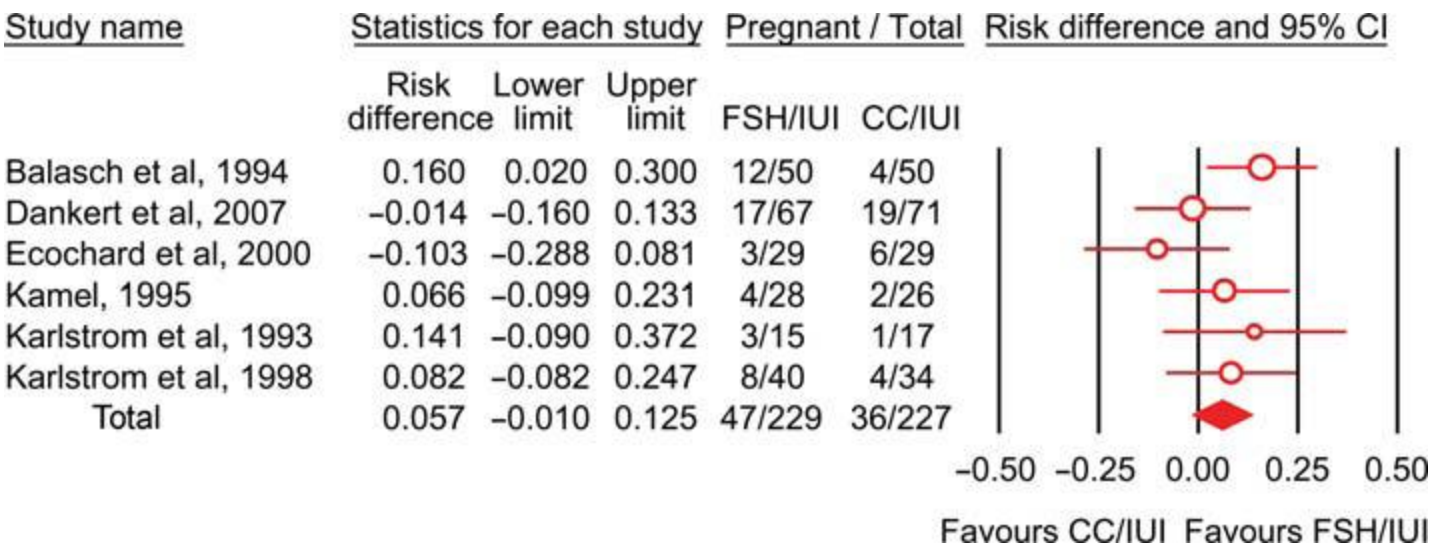
- Duration of infertility is an important prognostic factor!!!!

Human Reproduction Update 2009

Pregnancy rates following IUI combined with ovarian stimulation using either anti-estrogens or FSH. Live birth rates could not be assessed

Is FSH/IUI superior to CC/IUI?

7 trials, 556 couple with unexplained infertility, mild male factor and mild endometriosis FSH/IUI treatment has better pregnancy rate (%5.7) but not statistically significant



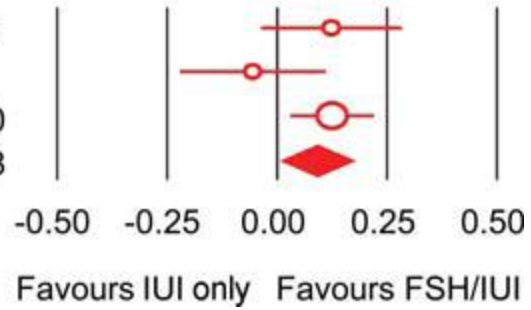
Cantineau et al., 2007.

Live birth rate per couple following IUI with or without FSH ovarian stimulation

Is FSH/IUI superior to IUI only ??

FSH/IUI treatment is better than IUI alone with live birth There would be one additional pregnancy for every 12 cycles of FSH/IUI in unexplained infertility

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



Verhulst et al., 2006

Follicle number

- The presence of three or more dominant follicles (%16.3) is associated with a two- to three-fold increase in pregnancy rates compared with monofollicular growth (%5.7)

  Huttunen SN 1999, Tomlinson 1996,Hughes 1998, Erdem A 2008

- Although multifollicular growth is a good prognostic factor, it is not considered as an advantage due to the risk of increasing frequency of multiple pregnancy and it is adopted to a cause of cycle cancellation

  NICE National Institute for Clinical Excellence,**2004**

- **According to regulations, >2 follicles measuring >16 mm is the indication of cycle cancellation in Turkey**

Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature

The "ideal" stimulation cycle allows for the recruitment of at least two follicles measuring >16 mm, with an E2 concentration >500 pg/mL on the day of hCG administration.

Clinical and ongoing pregnancy rates per cycle and the frequency of twin pregnancies for the groups classified according to the E_2 concentration and the number of follicles >16 mm on the day of triggering.

	No. of cycles (%)	Clinical pregnancy %/cycle (n)	Ongoing pregnancy %/cycle (n)	Twin pregnancies/clinical pregnancies % (n)
E_2 concentration on the day of triggering or the LH peak:				
<500 pg/mL	845 (90.3)	12.9 (109)	11 (93)[a]	9.2 (10)[a]
≥500 pg/mL	90 (9.7)	23.3 (20)	20 (18)[b]	35 (7)[b]
Total	935	13.8 (129)	11.1 (111)	13.2 (17)
No. of follicles >16 mm on the day of triggering or the LH peak:				
1	641 (63.7)	11.2 (72)	9.8 (63)[c]	5.5 (4)
2	309 (30.7)	17.5 (54)	14.5 (45)[d]	16.7 (9)
≥3	56 (5.6)	23.2 (13)	21.4 (12)	38.4 (5)
Total	1006	13.8 (139)	11.9 (120)	12.9 (18)

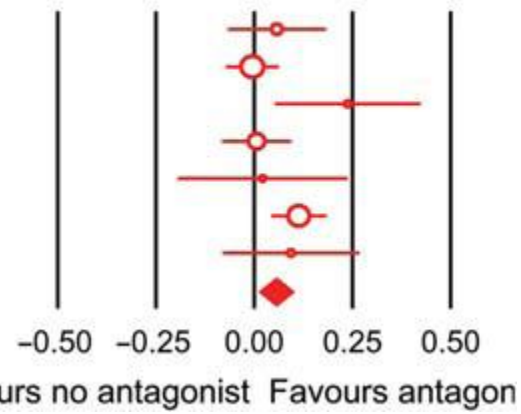
[a,b] Indicates significant difference at $P<.02$.
[c,d] Indicates significant difference at $P<.01$.

Merviel. Pregnancy and IUI. Fertil Steril 2010.

Merviel P, Fertil Steril, 2010

Ongoing pregnancy rate per couple with one cycle of FSH/IUI with and without GnRH antagonist treatment.

Study name	Statistics for each study			Pregnant / Total	
	Risk difference	Lower limit	Upper limit	FSH/IUI + GnRH Antagonist	FSH/IUI alone
Allegra et al., 2007	0.058	−0.069	0.184	8/52	5/52
Crosignani et al., 2007	−0.005	−0.074	0.064	15/148	16/151
Gomez et al., 2005	0.238	0.051	0.425	15/39	6/41
Lambalk et al., 2006	0.006	−0.084	0.097	13/103	12/100
Ragni et al., 2001	0.022	−0.196	0.239	3/19	3/22
Gomez et al., 2008	0.114	0.042	0.186	38/184	17/183
Lee et al., 2008	0.094	−0.082	0.269	6/31	3/30
Total	0.053	0.015	0.092	98/576	62/579



In seven RCTs, the average ongoing pregnancy rate was only 5.3% greater withGnRH antagonist treatment (95% CI: 1.5, 9.2). This means that it would take 20 cycles of GnRH antagonist administration to have one pregnancy more than without GnRH antagonist treatment Lambalk et al., 2006).

Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal sperm

TABLE 1

Relation of initial sperm quality to per-cycle pregnancy rate.

Sperm variable	No. of cycles	No. of pregnancies	Pregnancy rate per cycle (%)	*P* value*
Sperm concentration ($\times 10^6$/mL)				
<5	121	3	2.5	
5–10†	221	19	8.6	<.04
10–20	434	38	8.8	
20–40	794	83	10.4	
≥40	2,486	306	12.3	
Total sperm count ($\times 10^6$)				
<10	102	1	1.0	
10–20†	183	15	8.2	<.02
20–40	352	29	8.2	
40–80	647	55	8.5	
≥80	2,772	349	12.6	
Sperm motility (%)				
<20	80	1	1.2	
20–30†	194	7	3.6	
30–40	555	54	9.7	<.001
40–50	955	123	12.9	
≥50	2,272	264	11.6	
Percentage of sperm with normal forms†				
<5	11	0	0.0	
5–10†	34	3	10.7	NS
10–20	127	16	12.7	
20–30	248	29	11.7	
60	1,804	209	11.6	
≥60	1,719	175	10.2	
Total motile sperm count ($\times 10^6$)				
<5	175	4	2.3	
5–10†	193	16	8.3	<.02
10–20	402	33	8.2	
20–40	658	59	9.0	
≥40	2,626	337	12.8	

Note: NS = not significant.
* Threshold group versus less than threshold group.
† Threshold level.

Intrauterine insemination is effective therapy for male factor infertility when initial sperm motility is ≥30% and the total motile sperm count is ≥5 x 106

Dickey R, Fertil Steril, 1999

Effect of sperm morphology and number on success of intrauterine insemination

Intrauterine insemination used for treating male factor infertility has little chance of success when the woman is older than 35 years, the number of motile spermatozoa inseminated is <5 x 106, or normal sperm morphology is <30%.

Pregnancy rate in various age groups and various normal sperm counts.

Group	1	2	3	4	
No. of motile spermatozoa inseminated ($\times 10^6$)	<1	1-<3	3-<5	>5	
Cycles (n)	90	151	263	210	Total (N = 714)
Age (y)					
<25	110	1 (0.9%)	5 (4.5%)	12 (10.9%)	31 (28.2%)[a]	49
25-<30	168	0	3 (1.78%)	4 (2.38%)	10 (5.95%)	17
30-<35	200	0	1 (0.5%)	2 (1.0%)	8 (4.0%)	11
35-<40	236	0	0	0	2 (0.84%)	2

[a] $P=.001$, $\chi^2 = 13.23$.

Badawy. Success of intrauterine insemination. Fertil Steril 2009.

Pregnancy rate in various levels of normal sperm morphology and sperm counts.

	Group A	Group B	P[a]	χ^2
Normal morphology	<30% (417 cycles)	>30% (297 cycles)		
$<5 \times 10^6$ (504 cycles)	10/216 (4.62%)	18/143 (12.5%)	.01	6.39
$>5 \times 10^6$ (210 cycles)	19/201 (9.45%)	32/154 (20.77%)	.009	6.74
Total	29 (6.95%)	50 (16.83%)	.001	40.5

[a] Group A compared with group B.

Badawy. Success of intrauterine insemination. Fertil Steril 2009.

Badawy. Fertil Steril 2009.

Conclusion(s): An average total motile sperm count of 10 million may be a useful threshold value for decisions about treating a couple with IUI or IVF.

Clinical pregnancy rates and live birth rates of infertility treatments based on average total motile sperm counts in the ejaculate.

	Average total motile sperm count			
Treatment	<10 million	10–30 million	>30 million	χ^2 *P* value
No. of patients who got pregnant/total no. of patients (%)				
1st cycle of IUI	1/68 (1.5)	16/152 (10.5)	98/819 (12.0)	0.03
1st cycle of IVF	29/71 (40.9)	14/40 (35.0)	139/313 (44.4)	0.49
All cycles of IUI	5/214 (2.3)	42/502 (8.4)	274/2,763 (9.9)	
All cycles of IVF	37/99 (37.4)	18/59 (30.5)	167/393 (42.5)	
No. of live births/total no. of patients (%)				
1st cycle of IUI	1/68 (1.5)	13/152 (8.6)	62/819 (7.6)	0.15
1st cycle of IVF	24/71 (33.8)	11/40 (27.5)	120/313 (38.3)	0.35
All cycles of IUI	3/214 (1.4)	29/502 (5.8)	194/2,763 (7.0)	
All cycles of IVF	32/99 (32.3)	15/59 (25.4)	147/393 (37.4)	

Van Voorhis. Motile sperm count and IUI effectiveness. Fertil Steril 2001.

Van Voorhis, Fertil Steril 2001.

The effect of the average total motile sperm count on clinic-specific cost-effectiveness of infertility treatments.

	Average total motile sperm count				
	≤10 million		>10 million		
Procedure	No. of deliveries/ no. of cycles (%)	Cost per delivery ($)	No. of deliveries/ no. of cycles (%)	Cost per delivery ($)	Incremental* cost per delivery ($)[a]
Natural IUI	1/113 (0.8)	57,997	34/916 (3.7)	13,827	18,805
CC-IUI	2/79 (2.5)	22,248	111/1,567 (7.1)	7,951	9,290
hMG-IUI	0/22 (0)	—	78/782 (10)	19,092	21,274
All IUI	3/214 (1.4)	48,129	223/3,265 (6.8)	12,744	14,957
IVF cycles	32/99 (32.3)	32,869	162/452 (35.8)	28,639	29,551

[a] Calculated only for average total motile sperm count >10 million. This calculation assumes a 1% spontaneous pregnancy rate per cycle.

Van Voorhis. Motile sperm count and IUI effectiveness. Fertil Steril 2001.

TMS=>10.Mil., Dorpurev U , JMI, 2011

Semen quality and prediction of IUI success in male subfertility: a systematic review

- 55 studies were analysed.
- Sperm parameters most frequently examined were: (i) **inseminating motile count after washing: cut-off value between 0.8 and 5 million; (ii) sperm morphology using strict criteria: cut-off value 5% normal morphology; (iii) total motile sperm count in the native sperm sample: cut-off value of 5–10 million; and (iv) total motility in the native sperm sample: threshold value of 30%.**
- The results indicate a lack of prospective studies, a lack of standardization in semen testing methodology and a huge heterogeneity of patient groups and IUI treatment strategies.
- The literature did not reveal level 1 evidence on the relationship between sperm quality and IUI success.
- This structured review indicates that **IMC >1 million with IUI** is probably the best cost-effective treatment before starting IVF, irrespective of sperm morphology
- Despite the current ongoing debate concerning cost-effectiveness of IUI versus IVF in moderate male factor infertility, other factors might be important, such as the well-known differences between both strategies in risk profile and patient satisfaction

Ombelet W, RBM Online 2014

Semen preparation

- It is necessary to remove seminal plasma to avoid prostaglandin-induced uterine contractions and pelvic infection.
- There is not enough to randomized-controlled trials for systematically assesment of the best sperm preparation method.

Boomsma et al., 2007

Timing of insemination

- **Timing of insemination may be kept at 24 or 36 h after hCG injection**

- 24 h after LH surge
- hCG injection after LH surge has better pregnancy rate

Kosmas I Fertil Steril 2007

Fuh W Human reprod 1997

Single or double IUI

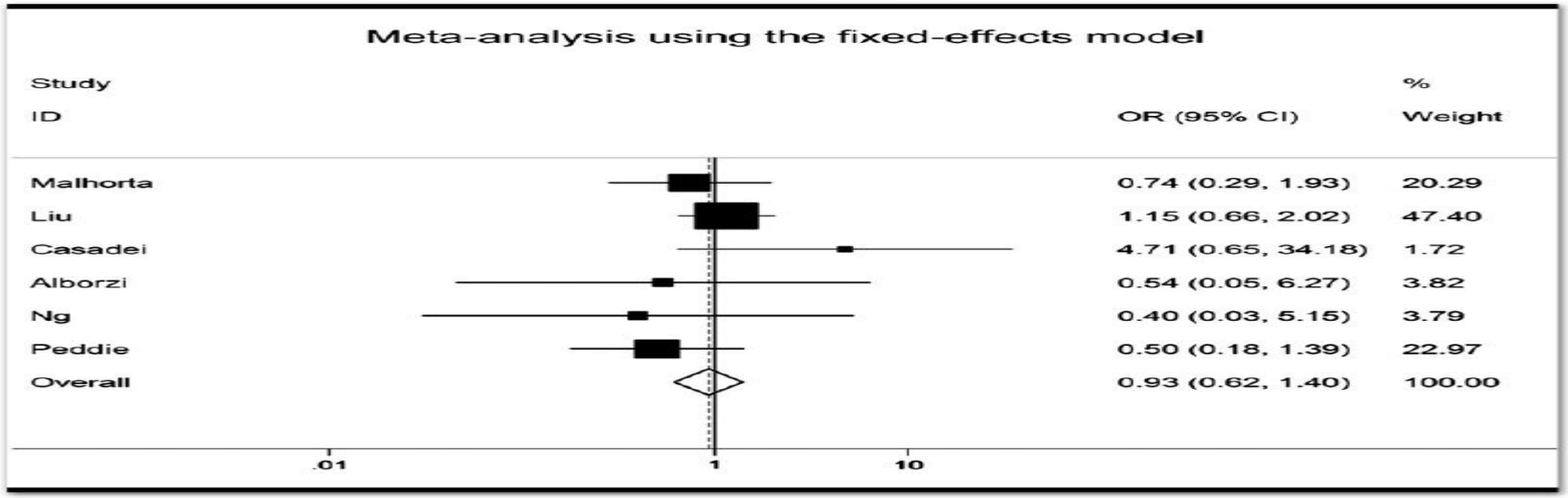
- Double IUI offers no clear benefit in the overall clinical pregnancy rate in couples with unexplained infertility.

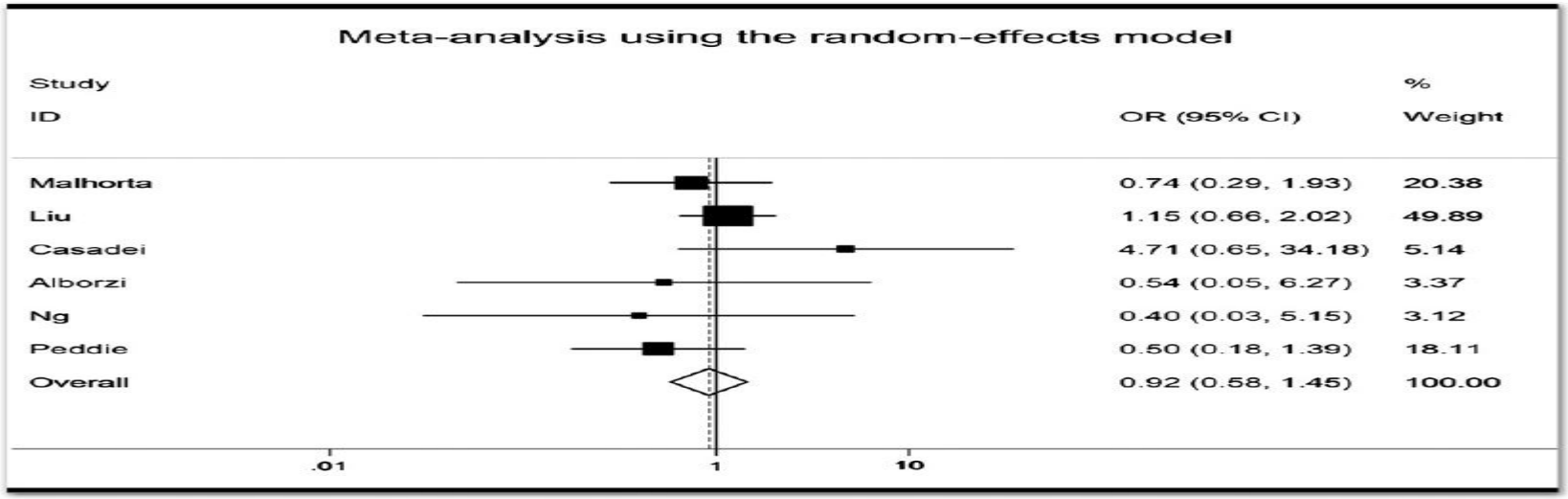
Polyzos Fertil Steril 2010

NICE Guidance Feb. 2004

Cantineau et al., 2003

Double versus single intrauterine insemination for unexplained infertility: a meta-analysis of randomized trials





Polyoz N, Fertil Steril 2010

The number of IUI cycles

- More than 80% of clinical pregnancies were obtained during the first three cycles, 95,5% of all pregnancies result from the first four cycles

Morshedi M et al, 2003

•The number of IUI cycles may be depends on woman age, duration of infertility and ovarian reserve, it would be 2 for some patients while it would be 6for others.

Custers M Human Reprod 2008

Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature

The best balance between cost and efficacy is found in the first three IUI cycles. At present, it is generally admitted that IUI should be limited to four or six cycles and that IVF should be performed in the event of failure.

Percentages of IUI and clinical and ongoing pregnancies per cycle in the first six cycles.

Cycle	No. of cycles	Clinical pregnancy %/cycle (n)	Ongoing pregnancy %/cycle (n)	Cumulative cancellation rate % (n)
1	353	16.4 (58)	15.0 (53)	—
2	245	12.2 (30)	10.6 (26)	18.3 (55)
3	156	16.0 (25)	13.4 (21)	43.0 (118)
4	121	10.7 (13)	7.4 (9)	52.1 (132)
5	86	9.3 (8)	7.0 (6)	64.7 (158)
6	61	11.5 (7)	11.5 (7)	74.3 (177)
7	8	0	0	96.5 (223)
8	5	0	0	97.8 (226)
9	3	0	0	98.7 (228)
Total	1038	13.5 (141)	11.7 (122)	

Note: After the sixth cycle (n = 16; 1.5% of all cycles), no pregnancies were observed. For clinical pregnancy rates, statistical differences were not significant for the first six cycles.

Merviel. Pregnancy and IUI. Fertil Steril 2010.

Merviel P, Fertil Steril, 2010

Where should IUI be done?

- It could be done at everywhere which provide optimal conditions

- It should be connection with andrology lab. It could ideally be done at department with andrology lab

Soft or hard catheter

- The type of catheter; soft or hard catheter; there is no significant difference in terms of pregnancy rates

Aou Setta Human Reprod.2006

Miller PB Fertil Steril 2005

Van der Poel N Cochrane 2010

- The type of catheter used was correlated with differing pregnancy rates, 15.3% per cycle for a soft catheter versus 7% for a hard catheter

Merviel Fertil Steril 2010

Soft versus firm catheters for intrauterine insemination (Review)

van der Poel N, Farquhar C, Abou-Setta AM, Benschop L, Heineman MJ

Analysis 1.1. Comparison 1 Soft versus firm catheters, Outcome 1 Live birth rate.

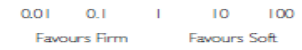
Review: Soft versus firm catheters for intrauterine insemination

Comparison: 1 Soft versus firm catheters

Outcome: 1 Live birth rate

Study or subgroup	Soft n/N	Firm n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Evenepoel 2007	4/53	11/52		11.2 %	0.33 [0.11, 0.99]
Fancsovits 2005	23/124	20/127		30.9 %	1.22 [0.63, 2.34]
Vermeylen 2006 (1)	39/270	39/270		57.8 %	1.00 [0.62, 1.62]
Total (95% CI)	**447**	**449**		**100.0 %**	**0.94 [0.65, 1.35]**

Total events: 66 (Soft), 70 (Firm)
Heterogeneity: $Chi^2 = 4.16$, $df = 2$ ($P = 0.12$); $I^2 = 52\%$
Test for overall effect: $Z = 0.34$ ($P = 0.74$)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Soft versus firm catheters, Outcome 2 Pregnancy rate.

Review: Soft versus firm catheters for intrauterine insemination

Comparison: 1 Soft versus firm catheters

Outcome: 2 Pregnancy rate

Study or subgroup	Soft n/N	Firm n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Evenepoel 2007	4/53	11/52		7.8 %	0.33 [0.11, 0.99]
Fancsovits 2005 (1)	23/124	20/127		21.4 %	1.22 [0.63, 2.34]
Miller 2005	11/49	8/51		9.3 %	1.55 [0.57, 4.18]
Segal 1998	5/34	0/17		2.5 %	5.11 [0.73, 35.48]
Vermeylen 2006 (2)	46/270	45/270		45.5 %	1.03 [0.65, 1.61]
Vutyavanich 2003	12/86	15/77		13.5 %	0.67 [0.29, 1.53]
Total (95% CI)	**616**	**594**		**100.0 %**	**1.00 [0.73, 1.35]**

Total events: 101 (Soft), 99 (Firm)
Heterogeneity: $Chi^2 = 8.63$, $df = 5$ ($P = 0.12$); $I^2 = 42\%$
Test for overall effect: $Z = 0.03$ ($P = 0.97$)
Test for subgroup differences: Not applicable

The Cochrane Library, 2010

Management after IUI

- Rest after procedure
- The effect of rest for 10-15 min after the IUI on pregnancy rate ⇨ *positive effect?*
- Intercourse on hCG day and 12- 24 h after IUI
- Luteal support: is it really necessary in stimulated IUI cycles?

Luteal phase support may improve pregnancy outcomes during intrauterine insemination cycles

Mohamed Ahmed Maher*

Luteal phase support with vaginal progesterone improved the success of intrauterine insemination cycles when recombinant follicle-stimulating hormone was used for ovulation induction

Table 3
Pregnancy outcomes for cycles with and without luteal phase support.

	Supported cycles (n=132)	Unsupported cycles (n=126)	Mean (95% CI)	p-Value
Total pregnancy rate/cycle (%)	49/132 (37.1%)	26/126 (20.6%)	2.27 (1.30–3.97)	0.004
Clinical pregnancy rate				
Per cycle (%)	39/132 (29.54%)	25/126 (19.84%)	1.79 (1.04–3.05)	0.07
Per patient (%)	39/71 (54.92%)	25/71 (35.21%)	1.56 (0.85–2.84)	0.016
Livebirth rate including multiple pregnancies				
Per cycle (%)				
Per patient (%)	25/132 (18.9%)	7/126 (5.5%)	3.4 (1.42–8.16)	0.001
	25/71 (35.2%)	7/71 (9.8%)	3.57 (1.95–8.78)	<0.001
Miscarriage rate				
Per cycle (%)	7/132 (5.3%)	7/126 (5.6%)	0.95 (0.32–2.79)	0.92
Per patient (%)	7/71 (9.9%)	7/71 (9.9%)	1.00 (0.33–2.99)	
Multiple pregnancy rate				
Per cycle (%)	4/132 (3%)	0 (0%)		0.04
Per patient (%)	4/71 (5.6%)	0 (0%)		0.04
Ectopic pregnancy rate				
Per cycle (%)	0 (0%)	3/126 (2.4%)		0.08
Per patient (%)	0 (0%)	3/71 (4.2%)		0.07

CI, confidence interval.
Chi-squared test.

Eurp j obst gyneco and reprod biol, 2011

Impact of luteal phase support on pregnancy rates in intrauterine insemination cycles: a prospective randomized study

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Department of Obstetrics and Gynecology, Gazi University School of Medicine, Ankara, Turkey

TABLE 2

Cycle characteristics of patients undergoing treatment with (study group) or without (control group) vaginal progesterone gel.

	Study group	Control group	
Duration of therapy (days)	8.7 ± 2.4	9.1 ± 3.1	NS
Total amount of gonadotropins (IU)	985.2 ± 511.3	937.9 ± 417.6	NS
No. of follicles 9–16 mm	2.9 ± 2.1	2.8 ± 2.1	NS
No. of dominant follicles (>16 mm.)	1.6 ± 0.6	1.5 ± 0.9	NS
Endometrial thickness on the day of hCG	10.9 ± 1.9	10.9 ± 2.0	NS
Total progressive motile sperm number after sperm preparation ($\times 10^6$/mL)	37.2 ± 45.6	48.8 ± 58.0	NS
Type of gonadotropin			NS
rec alpha	116	107	
rec beta	107	97	
Total pregnancy rate per cycle (%)	56/223 (25.1)	28/204 (13.7)	*P*=.002
Clinical pregnancy rate per cycle (%)	47/223 (21.1)	26/204 (12.7)	*P*=.028
Live birth rate per cycle (%)	39/223 (17.4)	19/204 (9.3)	*P*=.016
Clinical pregnancy rate per patient (%)	43/109 (39.4%)	25/105 (23.8%)	*P*=.01
Live birth rate per patient (%)	39/109 (35.8%)	19/105 (18.1%)	*P*=.003
Multiple pregnancy rate per cycle	3/223 (1.34%)	4/204 (1.96%)	NS

Erdem. Luteal support in IUI with gonadotropins. Fertil Steril 2009.

Luteal phase support in normo-ovulatory women stimulated with clomiphene citrate for intrauterine insemination: need or habit?

D. Kyrou*, H.M. Fatemi, H. Tournaye, and P. Devroey

Table II Treatment outcomes between the study groups.

	Progesterone group	No progesterone group	Difference, % (95% confidence interval)	*P*
Ongoing pregnancy rate (%)				
Intention-to-treat	17/234 (7.3)	19/218 (8.7)	−1.4 (−6.7, 3.6)	0.61
Per protocol	17/196 (8.7)	19/204 (9.3)	−0.6 (−6.4, 5.2)	0.82
Early pregnancy loss (%)				
Intention-to-treat	3/234 (1.3)	4/218 (1.8)	−0.5 (−3.5, 2.1)	0.72
Per protocol	3/196 (1.5)	4/204 (2.0)	−0.5 (−3.6, 2.7)	0.78
No. of pregnancies (%)				0.74/0.87
Singletons				
Intention-to-treat	16 (6.8)	17 (7.8)	−1.0 (−6.0, 3.9)	
Per protocol	16 (8.2)	17 (8.3)	−0.1 (−5.7, 5.4)	
Twins				
Intention-to- treat	1 (0.4)	2 (0.9)	−0.5 (−2.8, 1.6)	
Per protocol	1 (0.5)	2 (1.0)	−0.5 (−3.0, 2.0)	

Hum Reprod, 2010

Intrauterine insemination

The ESHRE Capri Workshop Group[1]

In summary, if IUI is used in spontaneous or in mildly stimulated (1–2 follicles) cycles there is no biological or empirical evidence that treatment with hCG or progesterone in the luteal phase is necessary or improves the pregnancy rate (Ragni *et al.*, 2001). Nevertheless the addition of progesterone, hCG and/or other substances became established clinical practice even in the absence of any robust evidence of effectiveness. Experience from induction of ovulation with gonadotrophins in hypophysectomized women had demonstrated that it was necessary to provide continued support in the form of hCG at least until the mid-late luteal phase (Lunenfeld, 2004). But women undergoing ovarian stimulation during IUI cycles are not totally hypogonadotrophic, even those cotreated with potent GnRH antagonists. Moreover, the half life of hCG is relatively long so that if at least 5000 IU are used for ovulation induction, biologically significant amounts persist for at least 10 days by which time the embryo is secreting hCG.

Human Reproduction Update, Vol.15, No.3 pp. 265–277, 2009

ECONOMY

- DIFFERENTIAL COST
- OPPORTUNITY COST
- SUNK COST

Cost analysis

For couples with unexplained and mild male factor subfertility, primary offer of a full IVF cycle is less costly and more cost-effective than providing IUI (of any modality) followed by IVF

IVF: £12 600

U-IUI + IVF: £13 100

S-IUI + IVF: £15 100

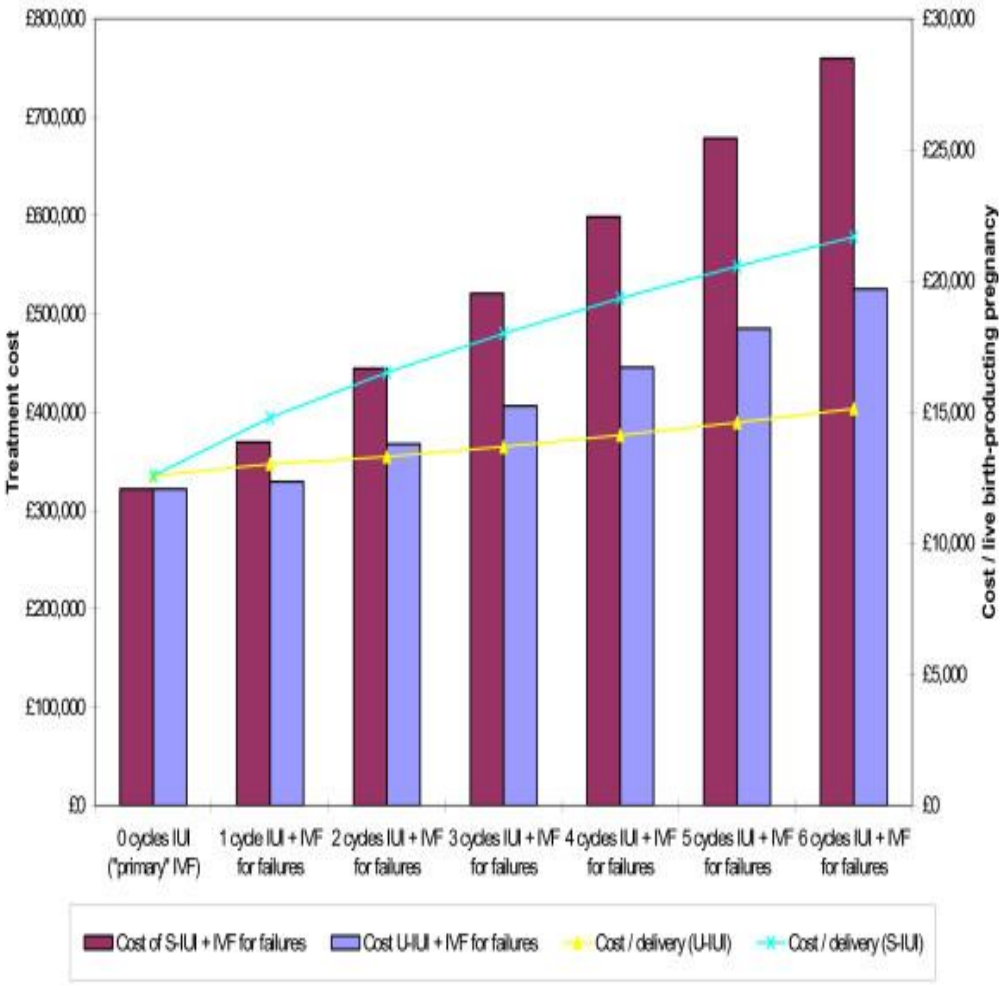
/ per live birth-producing pregnancy.

6 cycles of U-IUI + IVF = £ 174.200

" 54 additional IVF cycles, 14 live birth"

6 cycles of S-IUI + IVF= £438.000

"136 additional IVF cycles, 35 live birth"



Pashayan N, BMC 2006

Alternative treatment plan

- Standard management including , 3 cycles of CC/IUI …..3 cycles of FSH /IUI …up to 6 cycles of IVF
- Alternative protocol, accelerated, 3 cycles of CC /IUI …. *No FSH/IUI* ….

  up to 6 cycles of IVF

When IVF is affordable, IUI is unnecessary ?

- Clinical pregnancy; 65% in the accelerated arm, 64% in, the standard arm,
- The median time to pregnancy was shorter in the accelerated arm.
- The average number of IVF cycles was 1.1 and 1.4 in the standard and accelerated arms,
- 2.642 dollar economic save per patient and 0.06 additional pregnancy in the accelerated arm, ***Reindollar et al., 2007***

YES!

- IVF may potentially be a premature choice in women younger ‘aged 35’ with an unexplained infertility, < 2 years duration

The ESHRE Capri Workshop Group1, *Human Reproduction Update 2009*

Summary…..

- IUI in stimulated cycles was effective only in patients with more than 2 years duration of infertility but is associated with a significant rate of higher-order multiple births
- Prevention of premature LH surges and luteal phase support do not appear major requirements in IUI cycles

- Differences in sperm preparation and IUI methodology do not have profound effects on the success rate.

- Although IUI treatment is cheaper and less demanding on the patient, IVF is the most effective treatment for infertility

NICE guideline 2014
The ESHRE Capri group Human Reprod 2009,
Merviel P, et all., Fertility and Sterility Vol. 93, No. 1, January 2010

Summary…..

- **The choice of patient is really important**

- **Woman's age…… <35-40**
- **Duration of infertility….=2-3-4... <6**

- **at least two follicles measuring >16 mm, E2 concentration >500 pg/mL on hCG day**

- **The number of motile spermatozoa inseminated is >5 x 106**
  - **1 million ??**
- **<u>The decision and number of IUI should be designated by woman 's age, ovarian reserve and duration of infertility, patients' request</u>**

THANK YOU

OB&GYN DEPARTMENT & IVF CENTER

Prof. Dr. C.Fıçıcıoğlu

Yrd.Doç.Dr.O.Akçın

Doç.Dr. Ü.Uslu

Bio. B.Şimşek

T.C. YEDİTEPE ÜNİVERSİTESİ
TIP FAKÜLTESİ

Teşekkürler...

Table 1 Overview of papers examining and reporting on the influence of sperm quality on IUI outcome (1982—2011).

Publication	Country	Couples (n)	Cycles (n)	Sperm parameter	Threshold	Type of study
Berker et al. (2012)	Turkey	338		Motility grade A/TMSC	>10 million if motility grade A=0	RA
Sun et al. (2012)	China	412	908	Morphology SC	≥5%	RA
Demir et al. (2011)	Turkey	212	253	TMSC	>10 million	RA
				Morphology SC	>4%	
Dorjpurev et al. (2011)	Japan	283	1177	TM	>30%	RA
				TMSC	>10 million	
Nikbakht and Saharkhiz (2011)	Iran	445	820	TMSC	5—10 million	POS
				IMC	>10 million	
				Morphology SC	≥5%	
Yang et al. (2011)	China	482		SCSA—DFI	<25%	POS
Youn et al. (2011)	China		383	CASA concentration	111 million	RA
				CASA motility grade AB	51.40%	
				CASA motility grade A	30.10%	
Castilla et al. (2010)	Spain			SCSA—DFI		Structured review
Merviel et al. (2010)	France	353	1038	TMSC	>5 million	RA
Tijani and Bhattacharya (2010)	UK			TMSC	>10 million	Structured review
Badawy et al. (2009)	Egypt	393	714	IMC	>5 million	POS
				Morphology WHO	>30%	
Haim et al. (2009)	France		248	Motility grade A	>10%	POS
De La Cuesta Benjumea et al. (2008)	Spain	183	500	IMC	>1.5 million	RA
Guven et al. (2008)	Turkey	232	255	Morphology SC	>4%	RA
Bungum et al. (2007)	Denmark		387	SCSA—DFI	≤30%	RA
Kdous et al. (2007)	Tunisia	138	206	IMC	>1.1 million	RA
Tay et al. (2007)	Malaysia	317	507	IMC/TMSC	>20 million	RA
Arslan et al. (2006)	USA	82	313	HZI	<30%	POS
Mehrannia (2006)	Iran	824	824	IMC	>10 million	RA
Grigoriou et al. (2005b)	Greece	615	1641	Morphology SC	>10%	RA
De La Cuesta et al. (2004)	Spain	168	430	IMC	>2 million	RA
Shibahara et al. (2004)	Japan	160	682	Morphology SC	>15.5%	POS
				CASA—RASP	≥25.5%	
van Weert et al. (2004)	the Netherlands			IMC	0.8—5 million	Meta-analysis
Wainer et al. (2004)	France	889	2564	IMC + Morphology WHO	>5 million/>30%	RA
Yalti et al. (2004)	Turkey	190	268	TM	>30%	RA
Zhao et al. (2004)	USA	431	1007	TM	>80%	RA
Makkar et al. (2003)	Hong Kong	292	600	IC	>20 million/ml	RA
				Morphology SC	≥7%	
				IMC	>1 million	
Ombelet et al. (2003)	Belgium			Morphology SC	>4%	Structured review
				IMC	>1 million	
Saucedo de la Llata et al. (2003)	Spain		787	Morphology WHO	>20%	RA
				IMC	>1 million	
Lee et al. (2002a)	China	209	244	Morphology SC	>4%	POS
Lee et al. (2002b)	Singapore	1479	2846	IMC	>1 million	RA
				TM	>30%	
Miller et al. (2002)	USA	438	1114	IMC	>10 million	POS
Hauser et al. (2001)	Israel	108	264	Morphology SC	>4%	POS
Khalil et al. (2001)	Denmark	893	2473	IMC	>5 million	RA
Montanaro Gauci et al. (2001)	South Africa		495	Morphology SC	>4%	RA

Ombelet W, RBM Online 2014

Publication	Country	Couples (n)	Cycles (n)	Sperm parameter	Threshold	Type of study
Van Voorhis et al. (2001)	USA	1039	3479	TMSC	>10 million	RA
				TM	>50%	
Van Waart et al. (2001)	South Africa			Morphology SC	>4%	Structured review
Branigan et al. (1999)	USA	414	1100	IMC	≥10 million	POS
				Sperm survival 24 h	≥70%	
Dickey et al. (1999)	USA	1841	4056	Motility grade AB	≥30%	RA
				TC	≥10 million	
				TMSC	≥5 million	
Stone et al. (1999)	USA		9963	TMSC	≥4 million	RA
				TM	≥60%	
Cohlen et al. (1998)	The Netherlands	74	308	TMSC	>10 million	POS/RCoT
Shulman et al. (1998)	Israel	160	544	Semen parameters	Not useful	RA
Van der Westerlaken et al. (1998)	The Netherlands	566	1763	IMC	>10 million	RA
Berg et al. (1997)	Germany	902	3037	IMC	>0.8 million	RA
Karabinus and Gelety (1997)	USA	193	538	Morphology SC	Not useful	RA
Ombelet et al. (1997a)	Belgium	373	792	IMC and Morphology SC	>1 million + >4%	RA
Burr et al. (1996)	Australia	163	330	Morphology SC	>10%	RA
				IMC	Not useful	
Campana et al. (1996)	Switzerland	332	1115	IMC	>1 million	POS
Huang et al. (1996)	China	939	1375	IMC	>5 million	POS
Ombelet et al. (1996)	Belgium	412	1100	Morphology SC	≥4%	RA
Matorras et al. (1995)	Spain	74	271	Morphology SC	Not useful	POS
Toner et al. (1995)	USA	126	395	IMC	>2 million	RA
				Morphology SC	>4%	
Brasch et al. (1994)	USA	546	1205	IMC	>20 million	RA
Francavilla et al. (1990)	Italy	86	411	Morphology WHO	>50%	RA
				TMSC	>5 million	
Horvath et al. (1989)	USA	232	451	IMC	>1 million	RA

Ombelet W, RBM Online 2014

Assessment and treatment for people with fertility problems:

NICE guideline

A woman's age should be used as an initial predictor of her overall chance of success through natural conception.

Table 2. Cumulative probability of conceiving a clinical pregnancy by the number of cycles of insemination

Woman's age, years	ICI using thawed semen (Schwartz *et al* 1982)[2]		Woman's age, years	ICI using fresh semen (van Noord-Zaadstra *et al*, 1991)[3]		Woman's age, years	IUI using thawed semen (HFEA data and personal communication)	
	6 cycles	12 cycles		6 cycles	12 cycles		6 cycles	12 cycles
<30	50%	70%	<31	58%	76%	—	—	—
30–34	43%	62%	31–35	50%	71%	<35	63%	86%
>34	33%	54%	>35	39%	55%	35–39	50%	75%

ICI = intracervical insemination. IUI = intrauterine insemination. From NICE guideline 156.

Effect of sperm morphology and number on success of intrauterine insemination

Intrauterine insemination used for treating male factor infertility has little chance of success when the woman is older than 35 years, the number of motile spermatozoa inseminated is <5 106, or normal sperm morphology is <30%.

Pregnancy rate in various normal sperm counts.

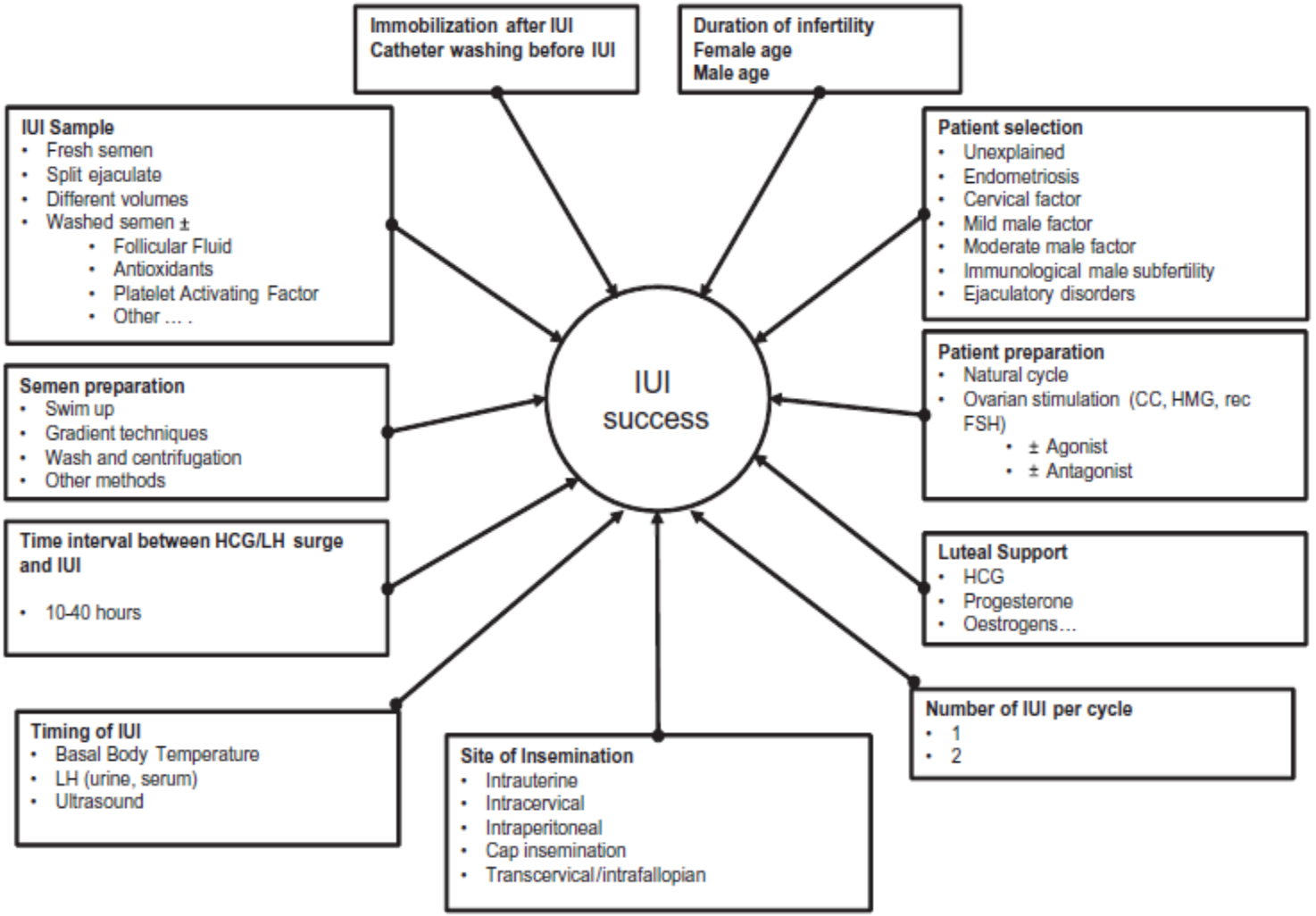
	Group 1	Group 2	Group 3	Group 4	Total	χ^2	*P*
No. of motile spermatozoa inseminated ($\times 10^6$)	<1	1–<3	3–<5	>5			
Cycles (n)	90	151	263	210	714		
Pregnancies (n)	1	9	18	51	79		
Pregnancies per cycle (%)	1.11	5.96	6.84	24.28	11.06		
Group 1 vs. group 2						2.23	.13
Group 1 vs. group 3						4.33	.053
Group 1 vs. group 4						22.2	<.001[a]
Group 2 vs. group 3						0.12	.88
Group 2 vs. group 4						21.29	<.001[a]
Group 3 vs. group 4						27.13	<.001[a]

[a] $P=.001$; $\chi 2 = 55.12$.

Badawy. Success of intrauterine insemination. Fertil Steril 2009.

Badawy. Fertil Steril 2009.

Predictive factors for pregnancy after intrauterine insemination



Ocmbelet W, RBM Online 2014

The effects of timing of intrauterine insemination in relation to ovulation and the number of inseminations on cycle pregnancy rate in common infertility etiologies

Single IUI timed post-ovulation gives a better CPR when compared with single pre-vulation IUI for non-male infertility, whereas for male factors, pre-ovulation, double IUI gives a better CPR when compared with single IUI.

Table II Unruptured follicle cycles at 36 ± 2 h randomized to single versus double IUI.

Parameter	All cycles	Male	Non-male		
Total unruptured	298		Total	Anovulation	Unexplained
Single IUI (*n*)[a]	192	70	122	50	72
Single IUI positive (*n*)[a]	10	2	8	4	4
Single IUI CPR[b] (%)	5.05	2.8	6.6	8	5.5
Double IUI (*n*)[a]	106	30	76	16	60
Double IU positive (*n*)	10	4	6	2	4
Double IUI CPR[b] (%)	9.4	13.3	7.8	12.5	6.6
OR (95% CI) of pregnancy in double versus single IUI	1.90 (0.76–4.70)	4.66 (0.90–24.13)	1.20 (0.43–3.33)	1.56 (0.31–7.75)	1.23 (0.29–5.08)
P	0.22[c]	0.064[c]	0.779[c]	0.626[c]	1[c]

[a]Number.
[b]Cycle pregnancy rate.
[c]χ^2 test.

Ghanem ME, Human Reproduction 2011