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'President's Medal' for best medical graduate 1970-75
Awareded by DMA on Dr. B.C Roy's birthday' for outstanding contribution towards medicine,1999
'Vikas Ratan Award' by Nations economic development & growth society 2002
'**Chitsa Ratan Award**' by International Study Circle in 2007
'Life time Medical excellence award' Obs & Gyne by Hippocrates foundation 2014
'Abdul Kalam gold medal' by Global Economic Prog & Research Association 2015
Rashtriya Gaurav Gold Medal award', October 2017 by GEPRA
'Distinguished teacher of excellence award' for PG medical education by national board of examinations and ANBAI in 2017
'Inspiring Gynecologist of India', by the Economic Times on doctors day 2018
Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE since 2007 and by FOGSI for basic & advanced infertility training since 2008.
Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** Member of advisory board for '**Journal of Fertility Science & Research'** and consultant advisor for queries to NDTV.com
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection. and ART.

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Optimizing IUI results

Prof. Abha Majumdar (GRIPMER)
Director and Head
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Introduction

What is Intra Uterine Insemination?

IUI is a relatively simple, low-tech, safe and inexpensive treatment modality compared to *IVF-ET*

Rationale behind IUI is to bypass cervical-mucous barrier to increase gamete density at site of fertilization.

(Practice Committee ASRM 2006)

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Who benefits most from IUI?

- Male factor infertility with mild OAT's
- First line management for couples with unexplained infertility as most popular treatment
- Couples requiring donor insemination can benefit from first line IUI treatment.

William Ombelet: Reproductive Biomedicine Online- vol 7. Comp1,66-72 1995

What does evidence say?

Unexplained Infertility: OS and IUI?

- IUI in a natural cycle *vs.* expectant management (n = 334) → no evidence of increased live birth (OR 1.60, 95% CI 0.92 – 2,8)
- *IUI vs. TI* ***(both in stimulated cycles)*** *→ increase chance of pregnancy after IUI*

  (6 RCTs, n = 517, OR 1.68, 95% CI 1.13 – 2.50)
- *OH vs natural cycle* ***(in both cycles IUI)*** *→ significant increase in live birth rate in OH cycles*

  (4 RCTs, n = 396, OR 2.07, 95% CI 1.22 – 3.50)
- IUI alone *vs.* TI + OH (one RCT, N = 342) → a marginal significant increase in live births for IUI

Veltman-Verhulst SM *et al*, *Cochrane Sys Rev* 2012, Issue 9, CD001838

NICE GUIDELINES 2013

The UK National Institute for Health and Care Excellence (NICE) recommended in 2013 that intrauterine insemination, with or without ovarian stimulation, should not be routinely offered to couples with unexplained infertility and that IVF could be considered after 2 years of EM.[10] However, a 2015 survey of UK fertility clinicians reported that 96% continued to offer IUI.[11]

At the annual meeting of ESHRE in Geneva, July 2017, the results of two randomized controlled trials (RCT) on IUI and unexplained infertility were presented.

Results of first RCT with 201 couples with 3-4 years unexplained infertility were randomised to receive three cycles of IUI or expectant management. ***Live birth rate of 31% with IUI and 9% with expectant management was observed,*** a three-fold difference in outcome. (Cindy Farquhar et al., (Auckland) 2017a, 2017b).

Second RCT performed in the Netherlands ***stimulated IUI with clomiphene citrate turned out to be first-line therapy compared to low dose FSH***. (Danhof et al., 2017)

Facts Views Vis Obgyn, 2017, 9 (3): 131-132

Editorial

The revival of intrauterine insemination: evidence-based data have changed the picture

W. Ombelet[1, 2, 3]

[1]Editor-in-Chief, [2]Genk Institute for Fertility Technology, ZOL Hospitals, Schiepse Bos 6, 3600 Genk, Belgium, [3]Hasselt University, Department of Physiology, Martelarenlaan 42, 3500 Hasselt, Belgium.

Abstract

According to a number of high quality studies intrauterine insemination (IUI) with homologous semen should be the first choice treatment in case of unexplained and moderate male factor subfertility. IVF and ICSI are clearly over-used in this selected group of infertile couples.

The limited value of IUI in infertility treatment as mentioned in the 2013 NICE guidelines was surely a premature statement and should be adapted to the actual literature.

More evidence-based data are becoming available on different variables influencing the success rates after IUI. It can be expected that these findings may lead to a better understanding and use of IUI in the near future.

Current concepts on factors determining success of IUI?

Unchangeable factors

Demographic factors

- Age of female
- Ovarian reserve
- Duration of infertility
- Underlying subtle tubo-peritoneal factors
- Unilateral tubal blocks

Changeable factors:

- Ovarian stimulation
- Use of GnRH agonist antagonist
- Timing of insemination
- Post wash total MSC
- Sperm wash techniques
- Single or double insemination?
- Bed rest ?

Questions to be addressed?

Current concepts on factors determining success of IUI

- Changeable factors:
  - Ovarian stimulation protocols
  - Use of GnRH agonist/ antagonist
  - Timing of insemination
  - Single or double insemination?
  - Sperm wash techniques and Post wash MSC
  - Sexual intercourse, bed rest & luteal support?

Ovarian Stimulation and IUI

The rationale behind the use of Ovarian stimulation in IUI is :

- Increase in number of available oocytes for tubal pickup and site of fertilization
- Correction of subtle endocrinological or ovulatory dysfunction

Common drugs used for OI in IUI

1. Clomiphene: Day 3 to 7 for 5 days 100 mg/day

2. Tamoxifen: Day 3 to 7 for 5 days 40 mg/day

3. Letrozole: Day 3 to 7 for 5 days 2.5 to 5mg/day

4. Gonadotropins: Daily dosing starting with 50 to 75 units/day from day 3 or 4 of cycle till dominant follicle is made

OS protocols : anti-oestrogens, gonadotrophins for IUI for subfertility

43RCTs, n=3957

- CC with letrozole: no significant difference (OR 1.2)
- Gonadotrophins with CC: Significant higher PR with gonadotrophins (**OR 1.8**)
- Different gonadotrophins: no significant difference
- No evidence of benefit in doubling the dose of gonadotrophins (OR 1.2), multiple pregnancy rates and OHSS rates increased.

Cochrane Jan 21 2009 (up to date: January 23, 2007)

Ovarian Stimulation Protocols

- Gonadotrophins *vs.* anti-estrogens (7 studies, $n = 556$) → significant higher pregnancy rates with gonadotrophins (OR 1.8, 95% CI 1.2 – 2.7)

Cantineau & Cohlen, Cochrane Sys Rev, 2011, Issue 2, CD005356)

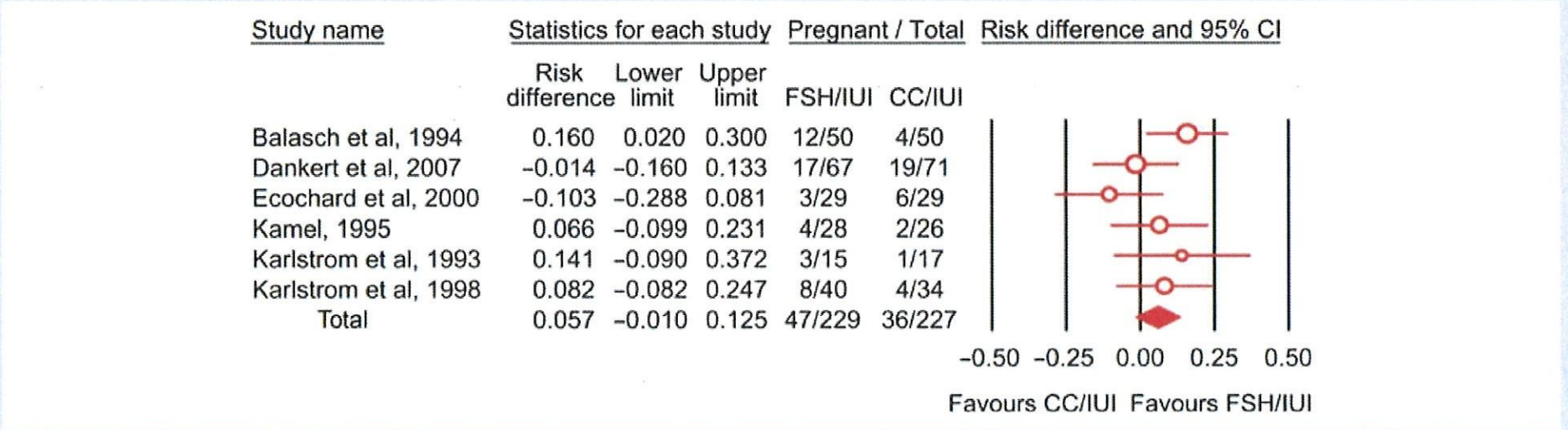


Figure 1 Pregnancy rates following IUI combined with ovarian stimulation using either anti-estrogens or FSH. Live birth rates could not be assessed (Cantineau *et al.*, 2007).

BMJ Open
2017

The SUPER study: protocol for a randomised controlled trial comparing follicle-stimulating hormone and clomiphene citrate for ovarian stimulation in intrauterine insemination

NA Danhof,[1] M van Wely,[1] CAM Koks,[2] J Gianotten,[3] JP de Bruin,[4] BJ Cohlen,[5] DP van der Ham,[6] NF Klijn,[7] MHA van Hooff,[8] FJM Broekmans,[9] K Fleischer,[10] CAH Janssen,[11] JM Rijn van Weert,[12] J van Disseldorp,[13] M Twisk,[14] M Traas,[15] MFG Verberg,[16] MJ Pelinck,[17] J Visser,[18] DAM Perquin,[19] DES Boks,[20] HR Verhoeve,[21] CF van Heteren,[22] BWJ Mol,[23] S Repping,[1] F van der Veen,[1] MH Mochtar[1]

The study, performed in 24 fertility centres in the Netherlands and including only couples with unexplained or mild male subfertility, randomised 369 women to IUI with FSH and 369 women to IUI with clomiphene. Results showed that 31% (113 women) had an ongoing pregnancy following IUI with FSH and 26% (97 women) had an ongoing pregnancy following IUI with clomiphene; there was no statistical difference between the two.

Which gonadotropin?

R- FSH versus U- gonadotrophins (HMG, P-FSH, HP- FSH) for ovarian stimulation in ART

- 42 RCTs, n=9606
- R-FSH with U- gonadotrophins: no difference in live birth rate, OHSS or any other outcomes.
- r-FSH with P-FSH or HP-FSH: No difference in live birth rate
- r-FSH with HMG/HP-HMG: Lower live birth rate in the rFSH group though differences were insignificant. (OR 0.84)

Conclusion: all gonadotrophins equally effective and safe, and further trials unwarranted. Choice of gonadotrophin should depend on availability, convenience and costs.

- Cochrane Feb 16, 2011(up to date: October 20, 2010)

Questions to be addressed?

Current concepts on factors determining success of IUI

- Changeable factors:
  - Ovarian stimulation protocols
  - Use of GnRH agonist/ antagonist
  - Timing of insemination
  - Single or double insemination?
  - Sperm wash techniques and Post wash MSC
  - Sexual intercourse, bed rest & luteal support?

Problems with OS in IUI cycles

- Unexpected rise or surge of LH
- Too early & too late for IUI
- Improper timing of IUI may lead to lower pregnancy rates

Benefits of agonist/ antagonist in IUI

- Controls LH surge and times ovulation better
- Proper synchronization with single IUI
- May be used to tide over a weekend

Gonadotrophins with and without GnRH analogues for IUI in women with sub-fertility

43 RCTs 3957

•Gonadotrophins alone more effective than with the addition of GnRH agonist (OR 1.8)

•Adding a GnRH antagonist to gonadotrophins: better pregnancy rates in antagonist cycles but not statistically significant (OR 1.5)

Cochrane Jan 21 2009 (up to date: January 23, 2007

GnRH antagonist or gonadotropin alone

Study name	Statistics for each study			Pregnant / Total		Risk difference and 95% CI
	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	

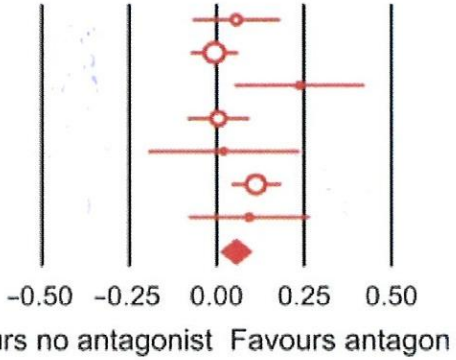


Figure 4 Ongoing pregnancy rate per couple with one cycle of FSH/IUI with and without GnRH antagonist treatment.

Cantineau & Cohlen, *Cochrane Sys Rev*, 2011, Issue 2, CD005356)

Original Article

Impact of gonadotropin-releasing hormone antagonist addition on pregnancy rates in gonadotropin-stimulated intrauterine insemination cycles

Shikha Jain,
Abha Majumdar
Centre of IVF and Human Reproduction, Sir Ganga Ram Hospital, New Delhi, India

level of 0.20. **RESULTS:** Clinical pregnancy rate in Groups I and II was 27.6% (n = 56) and 26.5% (n = 54), respectively (P=0.800). Ongoing pregnancy and multiple pregnancy rates were likewise similar between the groups. **CONCLUSIONS:** Addition of GnRH antagonist to gonadotropin-stimulated IUI cycles results in no significant difference in clinical pregnancy rate.

OUTCOME MEASURES	STUDY GROUP antagonist (n = 203)	CONTROL GROUP only FSH (n = 204)	*p* value
Clinical Pregnancy Rate (%)	27.6 (n=56)	26.5 (n=54)	0.824
Biochemical Pregnancy Rate (%)	2.5 (n=5)	2.4 (n=5)	1.000
Abortion Rate (%)	17.9 (n=10)	13.0 (n=7)	0.600
Ectopic Pregnancy (%)	0 (n=0)	1.9 (n=1)	0.491
Ongoing Pregnancy Rate (%)	22.7 (n=46)	22.5 (n=46)	1.000
Multiple Pregnancy Rate (%)	14.3 (n=8)	9.2 (n=5)	0.557
Ovarian Hyper Response Rate (%)	8.9 (n=18)	16.7 (n=34)	0.025 (S)

Questions to be addressed?

Current concepts on factors determining success of IUI

- Changeable factors:
  - Ovarian stimulation protocols
  - Use of GnRH agonist/ antagonist
  - Timing of insemination
  - Single or double insemination?
  - Sperm wash techniques and Post wash MSC
  - Sexual intercourse, bed rest & luteal support?

Why pregnancy rates are reported low with IUI

- Improper selection of case
- Too early or too late for IUI
- Improper timing may lead to lower pregnancy rates

Same precision needed as in IVF oocyte retrieval. Therefore ***the importance of `Timing of insemination in relation to ovulation and sperm collection?'***

Facts associated with semen collection, wash and insemination

- Removal of seminal plasma initiates sperm capacitation by changes in the ions in the acrosome
- Washed sperms fertilize oocyte only within 2 to 3 hours from preparation time
- No sperm reservoir in cervical mucous in IUI, only forms after coitus

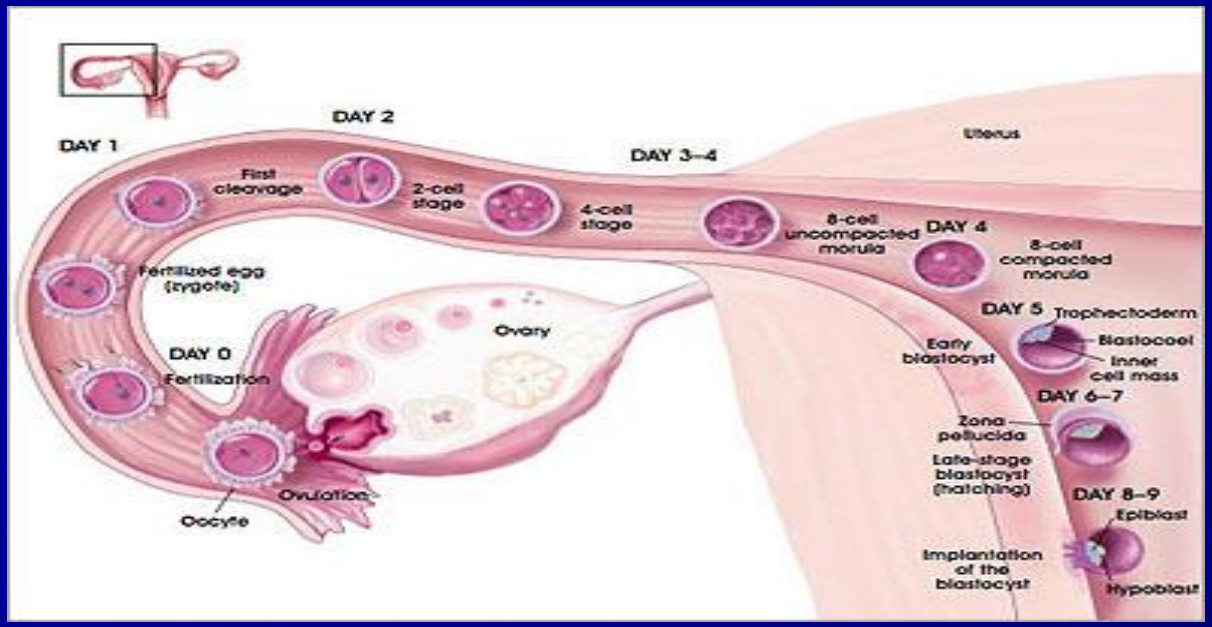
Editorial :J Obstet Gynecol India Vol. 59, No. 5 : September/October 2009 pg 407-409
Relationship between the time interval from semen collection to sperm wash and IUI outcome
Fertil Steril Vol 92, Issue 3, Supplement , Page S145, September 2009

Facts associated with timing of ovulation

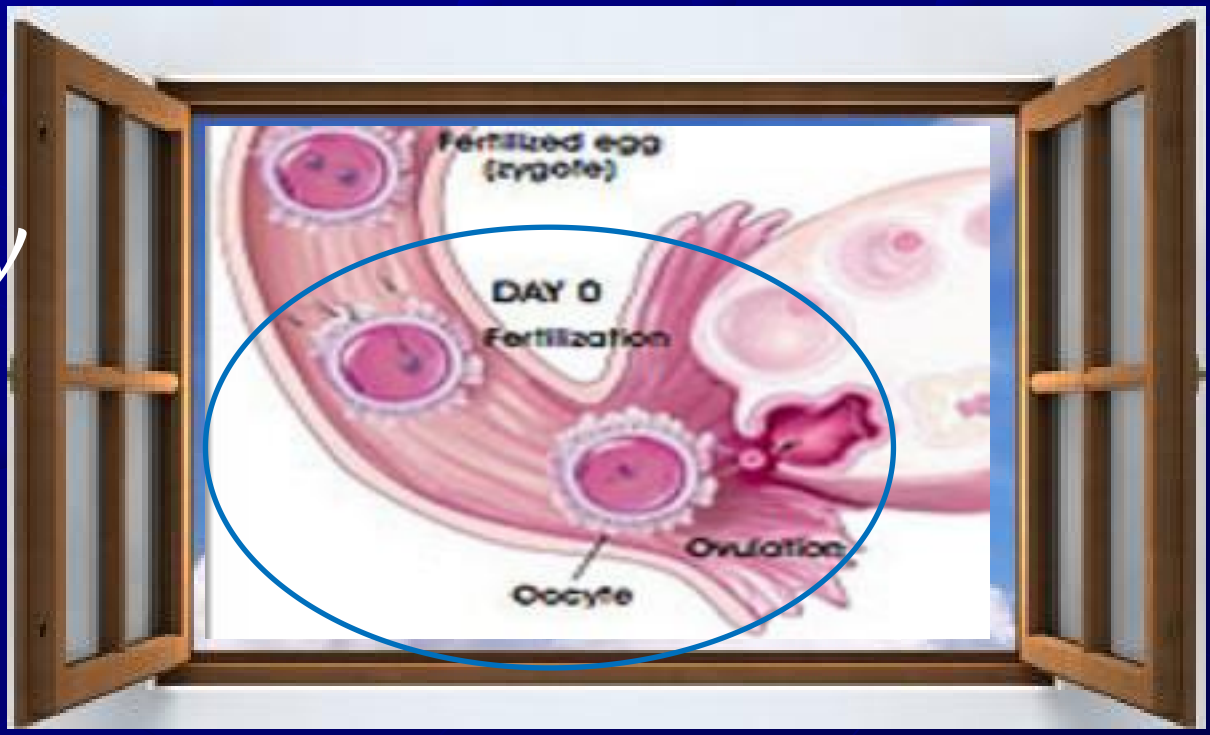
WHO probit analysis of natural cycles:

- Ovulation 24 to 56 hours after onset of ***LH surge***
- Ovulation after 36 hours & sequential over several hours up to 48 hours ***after hCG injection***

Oocytes after being released is fertilizable within 12 -16 hours only



Window of opportunity 12 to 16 hours post ovulation



Original Article

Impact of gonadotropin-releasing hormone antagonist addition on pregnancy rates in gonadotropin-stimulated intrauterine insemination cycles

https://www.semanticscholar.org/.../13d4a63f362d934d7830365d9e0730f338459999
Impact of gonadotropin-releasing hormone antagonist addition on pregnancy ...
Shikha Jain, **Abha Majumdar**; Journal of human reproductive sciences; 2016.

These results suggest that most important determinant of achieving optimal pregnancy rates in IUI cycles is perfect timing of insemination in relation to ovulatory trigger (44–48 h) and semen preparation (2–3 h). Other factors such as choice of stimulation regimen, prevention of premature luteinization with the use of GnRH antagonist can only marginally add on to the success.

Single or double insemination

- If the timing of insemination is within 12 to 16 hours post ovulation one insemination during the window of insemination should be enough.
- Double insemination is needed only when one is not sure of the time of ovulation (24 and 48 hours post trigger.
- If ovulation ensured by USG at first insemination then second insemination will only double complication and cost of IUI but no change in pregnancy rate

What is the optimal number of inseminations per cycle?

- Draft recommendations
  - Insufficient evidence that a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI. **Women undergoing IUI should be offered a single insemination per cycle.**
  - However, in male infertility, there might be a positive effect. **Double IUI may be used when more dominant follicles, which rupture with different time-intervals, are available**

IUI: review and systematic assessment of the evidence that supports global recommendations.
Human Reproduction Update, pp. 1–20, 2018

What is the ultimate number of consecutive IUI cycles per couple/woman in which pregnancy rates still increase significantly?

- 3 to 6 cycles of IUI has become common practice worldwide
- INeS-trial : six cycles of IUI–OS is still cost-effective compared to direct IVF in patients with unexplained & mild male infertility.

Bensdorp et al. (2015), Br Med J 2015.

Is there evidence to perform more cycles? Custers et al. (2008) Retrospective cohort study 3714 women 15303 cycles. Cumulative CPR after 3 cycles: 18%, which increases to 30 & 41% after 6 and 9 cycles

IUI: review and systematic assessment of the evidence that supports global recommendations. Human Reproduction Update, pp. 1–20, 2018

Questions to be addressed?

Current concepts on factors determining success of IUI

- Changeable factors:
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  - Sperm wash techniques and Post wash MSC
  - Sexual intercourse, bed rest & luteal support?

Semen analysis: poor predictor of male fertility

- Over time, reference values for normal semen parameters have changed

WHO Laboratory Manual	1999	2010
Sperm conc. (× 10^6/mL)	20	15 (12 -16)
Total sperm number (10^6/ejaculate)	40	39 (33 – 46)
Total motility (PR + NP %)	-	40 (38 – 42)
Progressive motility (PR %)	50 (a+b) or 25 (a)	32 (31 – 34)
Morphology (normal forms, %)	30	4 (3.0 – 4.0)

- Semen characteristics are highly variable among men, and are not the sole determinants of a man's fertility; (WHO Laboratory Manual 5th edition, 2010)

Inseminating Motile Count (IMC)

- < 1 million (7 studies): *Makkar G et al, 2003, Ombelet W et al, 2003, Saucedo de la Llata E et al, 2003, Lee VM et al, 2002, Ombelet W et al, 1997, Campana A et al, 1996, Horvath PM et al*
- 1 – 2 million (4 studies): *De La Cuesta Benjumea R et al, 2008, Kdous M et al, 2007, De La Cuesta R et al, 2004, Toner JP et al, 1995*
- > 5 million (4 studies): *Badawy A et al, 2009, Wainer R et al, 2004, Khalil MR et al, 2001, Huang HY et al, 1996*

Ombelet W et al, 2014

Semen preparation techniques

5 RCT's	Swim up vs gradient	Swim up vs wash and centrifugation	Gradient vs wash and centrifugation
Pregnancy rate	30.5% *vs.* 21.5%	22.2% *vs.* 38.1%	23.5% *vs.* 13.3%
Odds ratio	OR 1.57	OR 0.41	OR 1.76
Confidence interval	95% CI 0.74 – 3.32)	95% CI 0.15 – 1.10	95% CI 0.57 – 5.44

Five *RCT*s (Dodson 1998; Xu 2000; Grigoriou 2005; Posada 2005; Soliman 2005) *n* = 262

Boomsma CM et al, Cochrane Sys Rev 2007, Issue 4, CD004507

Questions to be addressed?

Current concepts on factors determining success of IUI

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  - Sexual intercourse, bed rest & luteal support?

Sexual intercourse

- A day before IUI?
- After IUI?

Is there a benefit of bed rest after IUI?

Hypothesis

- The spermatozoa may reach the fallopian tube within 5- 10 min.
- Immobilization in supine position after IUI could prevent direct loss of a large percentage of the spermatozoa and improve fertility outcomes.

Draft recommendations

Women undergoing IUI, should have 10–15 min of bed rest after insemination.

IUI: review and systematic assessment of the evidence that supports global recommendations. Human Reproduction Update, pp. 1–20, 2018

Is there a benefit of bed rest after IUI?

Recent RCT comparing immobilization for 15 min vs direct mobilization

498 patients with UI or Male factor; *No significant difference in cumulative ongoing PR.* ***Van Rijswijk et al.,2017***

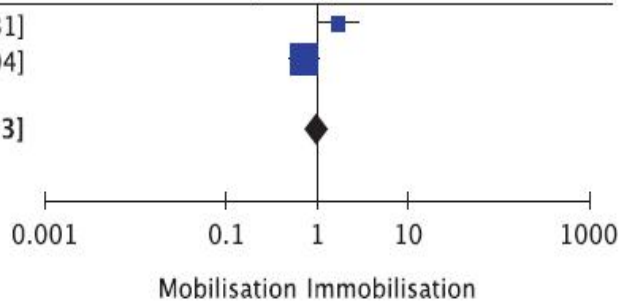
These data were not available at the time of the consensus meeting

Meta-analysis of immobilization vs direct mobilization after IUI

Study or Subgroup	immobilisation Events	Total	mobilisation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Custers 2009	54	199	34	192	27.9%	1.73 [1.07, 2.81]
van Rijswijk 2017	76	236	98	245	72.1%	0.71 [0.49, 1.04]
Total (95% CI)		**435**		**437**	**100.0%**	**1.00 [0.74, 1.33]**
Total events	130		132			

Heterogeneity: $Chi^2 = 8.07$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 0.02 (P = 0.98)



OR = 1.00, 95% CI: 0.74–1.33) Substantial statistical heterogeneity (I2 =88%) was found.

Human Reproduction Update, pp. 1–20, 2018

Luteal spport

- Good option in stimulated cycles with more than 1 to 2 dominant follicles
- To start progesterone vaginal softgel capsule 200 mg twice a day, vaginal gel 80mg 9% once a day one day after IUI for 14 days
-
- Dehydrogesterone 10 mg orally twice a day for 14 days

Take home message

- In IUI cycles for unexplained infertility OS appears to improve outcome in terms of PR
- Evidence suggests that IUI gives higher PR when combined with gonadotrophins than anti-estrogens
- Addition of antagonist may improve outcome marginally by possibly better timing of IUI
- We need to review timing of IUI to optimize PR
- 5-10 million post wash MSC appears minimal requirement.
- All methods of sperm wash equally effective in terms of PR
- Sexual intercourse before and after IUI good option
- Ne bed rest while treatment or after IUI
- Luteal support good option in stimulated cycles


Thank you
abhamajumdar
NATIONAL GEOGRAPHIC
Photograph by Jonathan Munshi, 2008 International Photography Contest
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BEDREST
DOES IT HELP?

Study Shows Bed Rest May Not Improve Pregnancy Rate Following IUI

October 25, 2016 Artificial insemination By Support

A European study has found that the practice of keeping women immobilized following intrauterine insemination has no bearing on pregnancy rates. Study results were presented at the annual meeting of the European Society of Human Reproduction and Embryology in June.

In fact, one researcher said keeping women on bed rest following the procedure may actually harm the chances of becoming pregnant. "Indeed, it even tends to the opposite, said researcher Dr. Joukje van Rijswijk from the VU University Medical Center Amsterdam.

Bed rest after IUI?

- Soon after IUI
- During follicular phase
- During luteal phase

Don’t put your patients to rest / bed rest!!

- Exercise improves metabolism and circulation, both of which contribute to better egg production.
- Regular activity also optimizes reproductive system by stimulating endocrine glands, which help eggs grow.
- Sweating out is a known stress reliever –a good thing, stress significantly decreases conception’s probability.
- Exercise increases heart rate and oxygenation - leading to better perfusion of all organs

Most favorable window of insemination

- Window of fertilization for an oocyte is 12 to 16 hours post release (age of unfertilized oocyte)
- Ovulation is sequential over several hours from 36 hours post hCG up to 48 hours
- Sperm capacitation sustains only for 2 hours after sperm wash but sperms live 48 to 72 in genital tract after coitus

Best time of insemination appears

Oocyte viability: *46 to 48 hours post hCG trigger and 12 to 16 hours post releasein absence of starting of LH surge*

Semen viability: *collection to insemination < 3 hours*