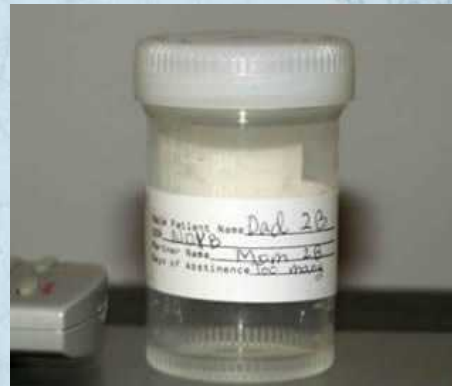
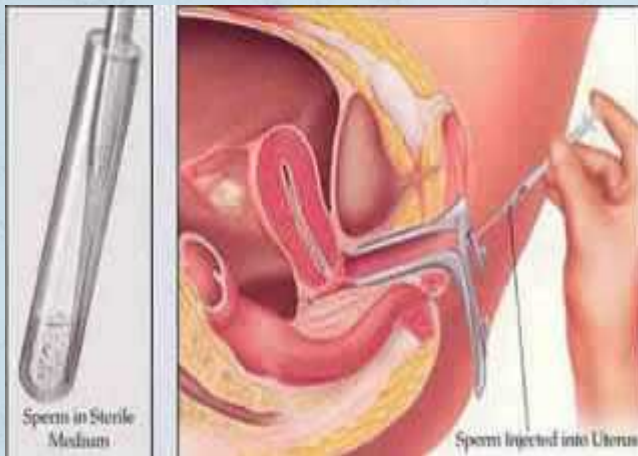


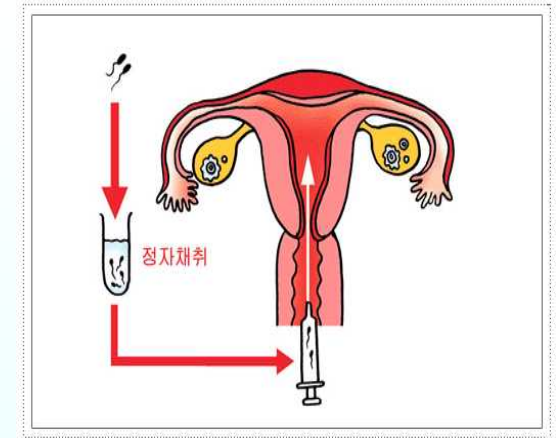
Improved pregnancy rate with
administration of
hCG after intrauterine insemination:
a pilot study

Järvelä et al. Reproductive Biology and
Endocrinology 2010, 8:18



家醫科 R2 侯欣好

Background



□ Intrauterine insemination (IUI)

□ 2001 -2004 in Europe

- ◆ Pregnancy rate in IUI cycles: 11.4% -12.6%
- ◆ Multiple birth rate :11.2% -13.1%

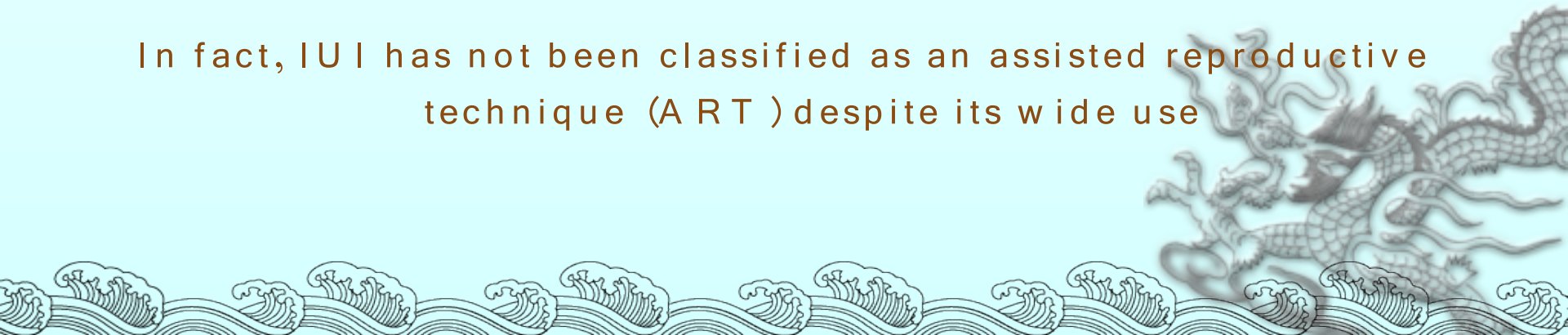


Background

ESHRE Capri Workshop Group on IUI

- Report: use of **clomiphene/gonadotrophins to induce multiovulation & preparation of men sample**
 - Pregnancy rates in IUI cycles are **not significantly better** than the results achieved after ordinary or timed intercourse
- Clarify the role of individual topics in the effectiveness of IUI treatment
 - ◆ One of the topics: **the timing of the insemination**

In fact, IUI has not been classified as an assisted reproductive technique (ART) despite its wide use



Background

Timing of the insemination



- Majority of the studies
 - Insemination was performed **hours after hCG administration**
- Among healthy women
 - Best chance to become pregnant is if **intercourse occurs up to six days before ovulation**
 - If this is applied to the IUI protocol, the HCG should be injected **after the insemination** rather than before it



Objective

- Evaluate the effect of postponing the hCG injection until after IUI



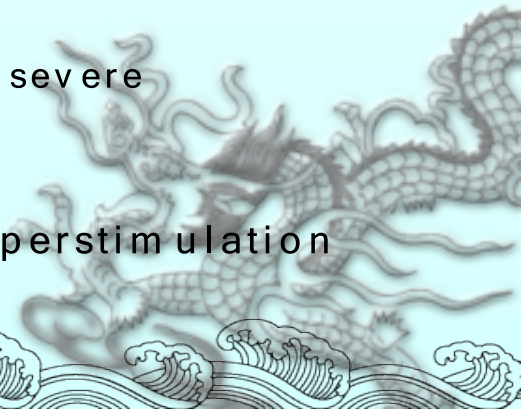
M e t h o d s

- ▣ January 2007 – September 2009
- ▣ Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland
- ▣ All of these cycles
 - ▣ Clomiphene citrate/FSH hCG stimulation protocol
 - ▣ Standard IUI technique with partner's sperm were used



Methods

- ▣ Study couples:
 - ▣ At least 1 year of infertility
 - ▣ Undergone a basic infertility evaluation
 - ▣ A n a m n e s i s , s e m e n a n a l y s i s u s i n g W H O g u i d e l i n e s a n d h y s t e r o s o n o s a l p i n g o g r a p h y
 - ▣ Age limit : 40 years
- ▣ If irregular menstrual period: assess prolactin and TSH concentrations
- ▣ Polycystic ovarian syndrome was not observed
- ▣ IUI:
 - ▣ First treatment offered
 - ▣ Performed up to two times in all the couples without severe oligospermia or bilateral tubal patency
- ▣ Unsuccessful: continued with controlled ovarian hyperstimulation and IVF/CSI

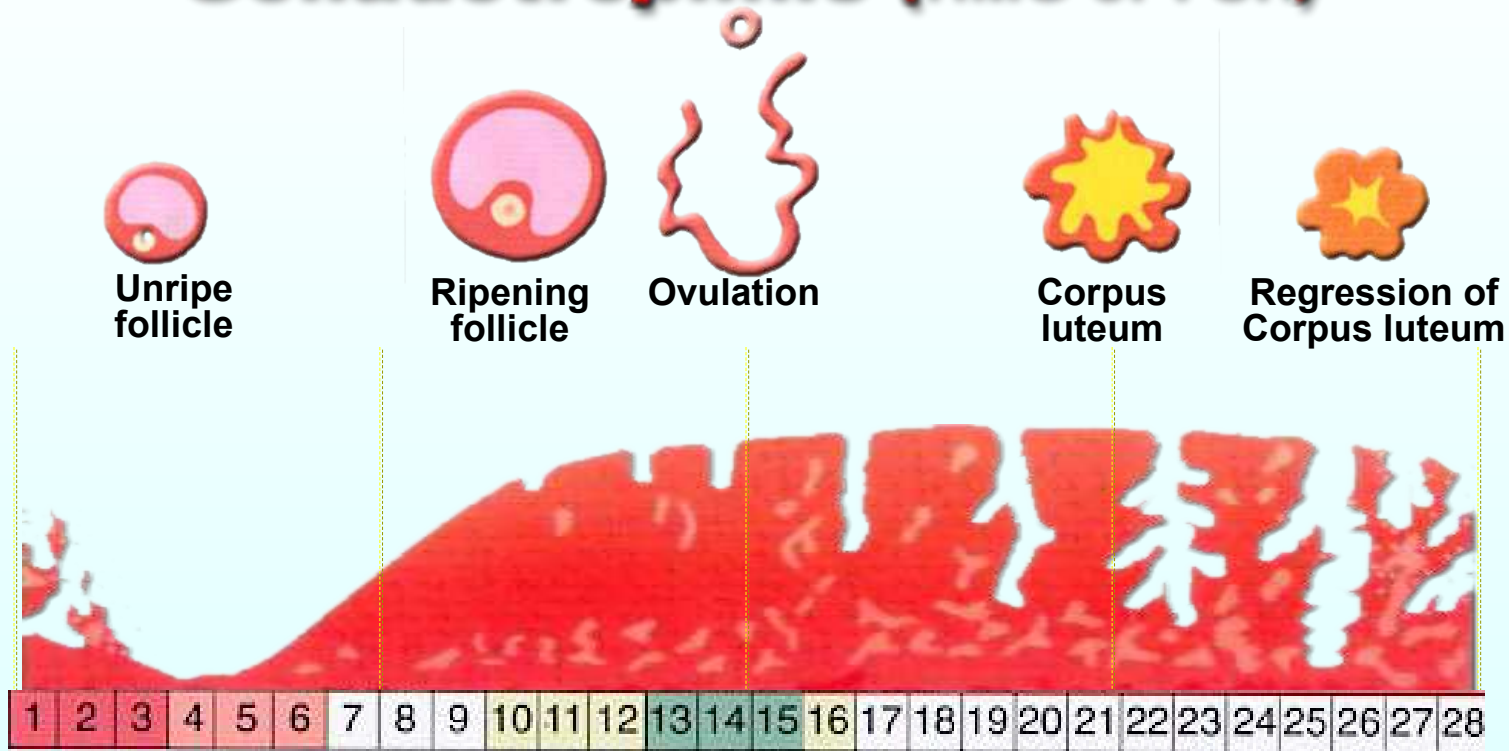


O v a r i a n s t i m u l a t i o n

- O v a r i a n s t i m u l a t i o n u s i n g c l o m i p h e n e c i t r a t e a n d F S H



Clomiphene Citrate plus Gonadotrophine (HMG or FSH)

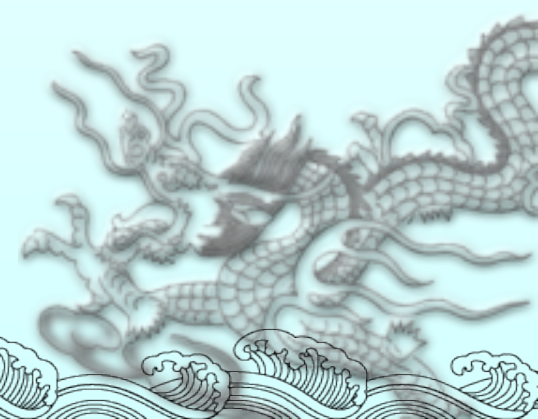


Clomiphene 50-
100 mg day3-7

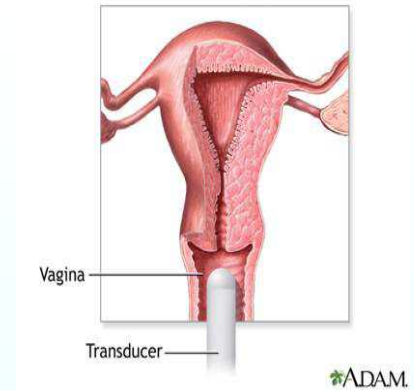
75-100 iu
FSH daily

IUI
24-32 hrs

D9-12 echo: HCG
follicle 17- 8mm



Ovarian stimulation



□ Cycle days 9-12:

□ Monitored by vaginal ultrasonography (ovarian and endometrial responses)

□ IUI was then scheduled

□ When the **largest follicles** (17-18 mm in diameter)

□ If time of IUI, >3 follicles (> 16 mm) existed

□ Excessive follicles were either emptied or abandoned cycle(not included in the analysis)

□ IUI was performed even when the follicles had already been ruptured by the time of IUI



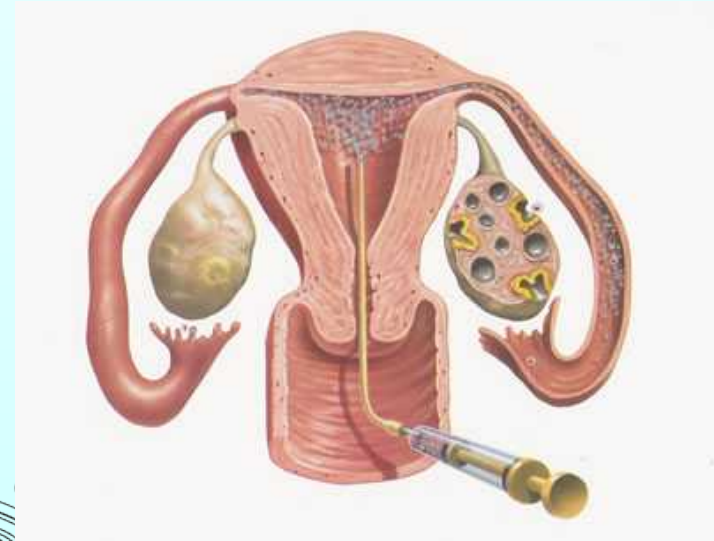
Sperm preparation and intrauterine insemination

- Sperm preparation
 - Semen samples were collected by masturbation after 2–4 days of sexual abstinence
 - After liquefaction and initial sperm analysis, the standard gradient centrifugation technique was used for preparation, employing Sperm-Grad™ gradient material in G-IVF™ Plus-medium (Vitro-life Ab, Gothenburg, Sweden)



Sperm preparation and intrauterine insemination

- Intrauterine insemination
 - Performed using an intrauterine catheter with a 1-ml syringe
 - Catheter was passed through the cervical canal and the sperm suspension expelled into the uterine cavity
 - Insemination volume was 0.5 ml
 - Women remained supine for 5-10 min after IUI



Timing of hCG injection

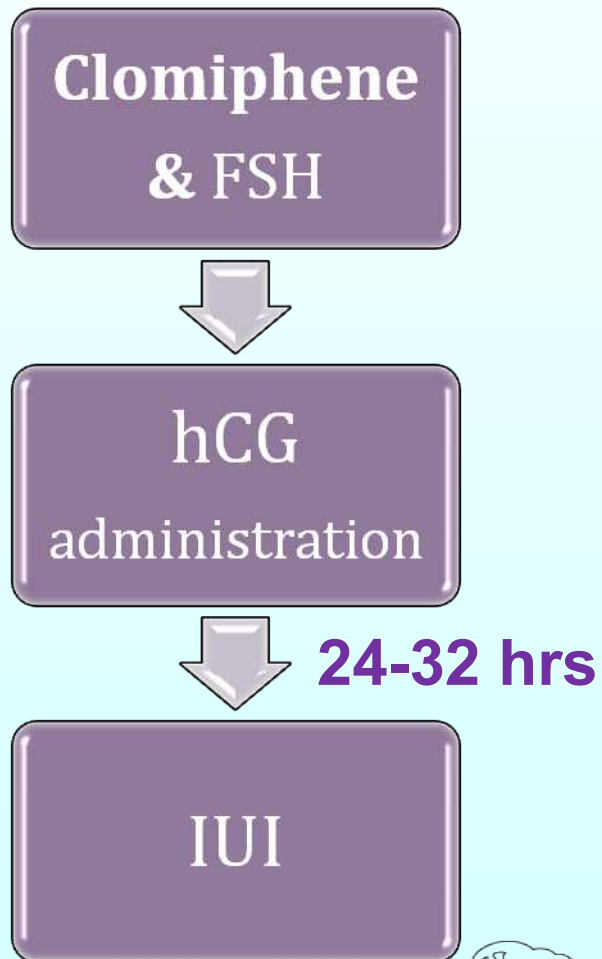
Standard protocol in our unit

- Inject hCG (5000 IU) when at least one follicle (17 mm in mean diameter)
 - The hCG was injected in the morning
 - IUI was performed next day, 24-32 hours after the administration of hCG

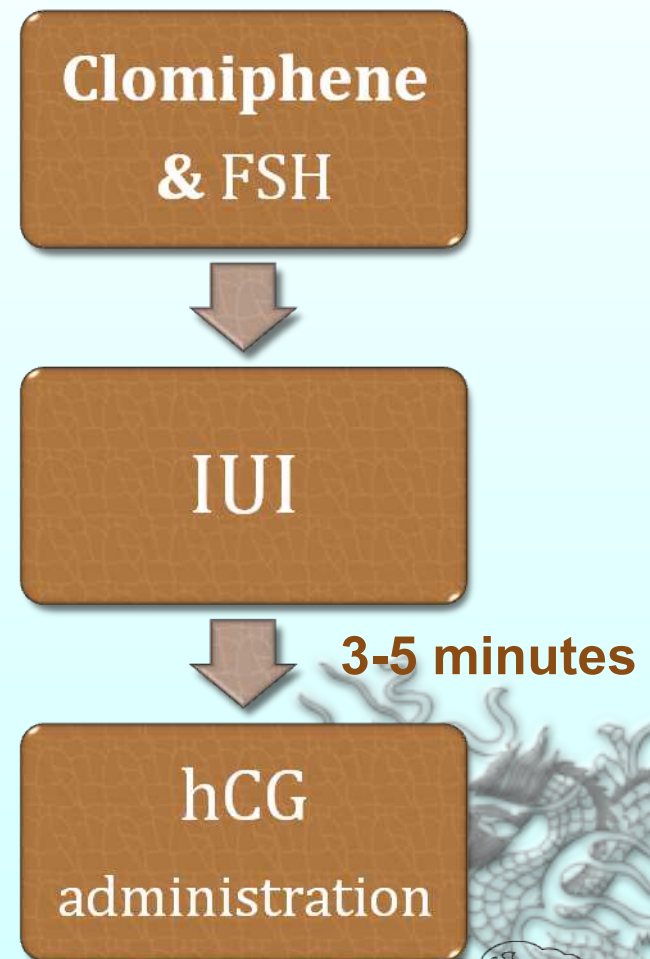


Timing of hCG injection

2007-2008

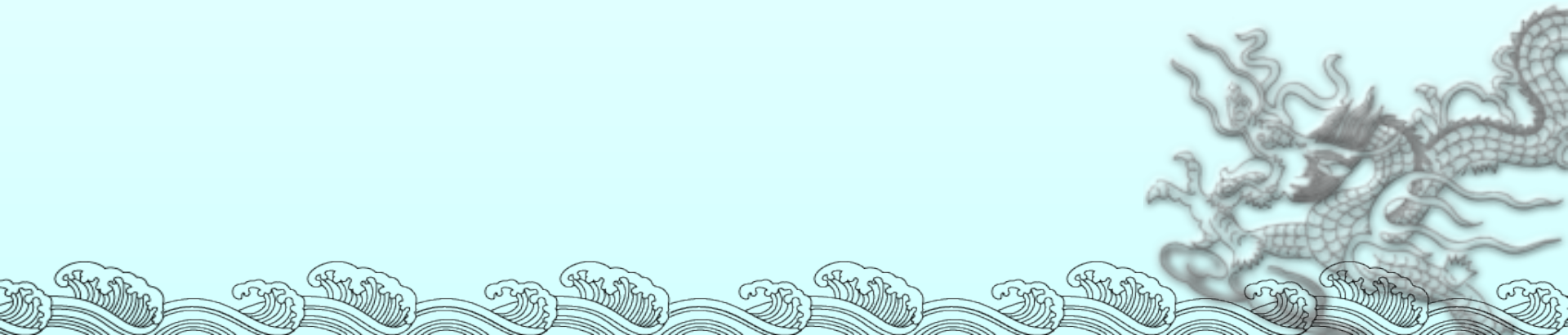


2008-2009



Performed pregnancy test

- ▣ If menstruation was delayed after IUI
 - ▣ Performed urinary pregnancy test
 - ▣ If pregnancy test: (+)
 - ◆ Preg week 7: transvaginal ultrasonographic examination
 - ◆ Confirmed: intrauterine gestational sac with heart beat



Statistical analysis

- ▣ Differences between groups:
 - ▣ Student's t test and the χ^2 test
- ▣ Used **Generalized Estimating Equations (GEE)** to identify independent factors contributing to the success (positive pregnancy test and clinical pregnancy rate) **of the IUI cycle**
 - ◆ GEE using the SPSS 16.0 for Mac (SPSS, Chicago, IL)



Statistical analysis

Factors selected for the analysis

□ Dichotomous variables

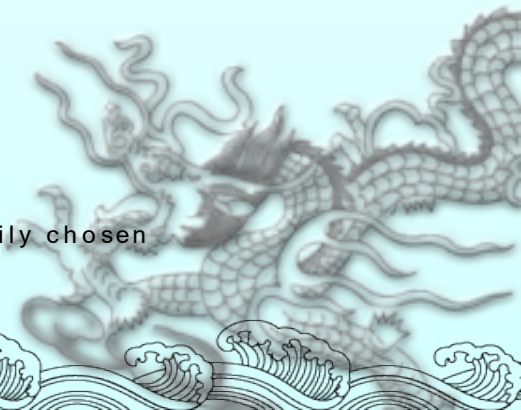
- sperm count after preparation ($\times 10^6/\text{ml}$), ($<$ or \geq)
- number of follicles > 16 mm at IUI, (0-1 or 2-3)
- time of hCG injection, either 24-32 h prior to IUI or just after IUI
- male-factor (either male or non-male)
- unexplained-infertility diagnosis (either unexplained or non-unexplained)

□ Continuous variable

- cycle day of insemination

□ The selected cut-off points for sperm count and number of follicles were arbitrarily chosen

□ level of significance: $P < 0.05$



Results

- 332 intrauterine inseminations
 - 99 : two inseminations
 - 134 : only one insemination
- Urinary pregnancy test(+), n = 45 cycles
(pregnancy rate of 13.6%)
- Clinical pregnancy rate: 12.3%
- 25 out of 332 cycles (7.5%) all the follicles were already ruptured at the time of insemination; the urinary pregnancy test became positive in 4 cycles



Results

Table 1 Comparison of characteristics between those who tested positive and negative in urinary pregnancy test.

	Preg. test + (n = 45)	Preg. test - (n = 287)	P
Age (SD) In years	29.8 (5.1)	30.1 (4.3)	NS
Main diagnosis			
Unexplained	65.9%	47.3%	0.024
Male factor	6.8%	18.8%	0.053
Endometriosis	4.5%	8.7%	NS
Hormonal	13.6%	17.7%	NS
Multiple	4.5%	6.5%	NS
Sperm count $\geq 20 \times 10^6$ /ml after preparation	80.0%	61.1%	0.019
Total FSH consumption (SD)	155 IU (58)	160 IU (91)	NS
2-3 follicles at insemination	64.4%	49.1%	0.076
Cycle day of insemination (SD)	13.7 (1.7)	13.8 (1.6)	NS
hCG injection after IUI	46.7%	28.9%	0.024



HCG administration before vs. after IUI

Table 2 Comparison of characteristics in patients with different timing in hCG injection

	hCG injection 24-32 h before IUI (n = 228)	hCG injection after IUI (n = 104)	P
Age (SD) in years	30.3 (4.4)	29.5 (4.5)	NS
Main diagnosis			
Unexplained	50.2%	50.0%	NS
Male factor	17.6%	16.7%	NS
Endometriosis	6.8%	10.2%	NS
Hormonal	16.7%	17.6%	NS
Multiple	7.2%	3.7%	NS
Sperm count $\geq 20 \times 10^6$ /ml after preparation (SD)	65.5%	62.2%	NS
Total FSH consumption (SD)	163 IU (98)	152 IU (58)	NS
Number of follicles >16 mm at insemination (SD)	1.5 (0.8)	1.6 (0.7)	NS
2-3 follicles at insemination	50.0%	53.2%	NS
Cycle day of insemination (SD)	13.9 (1.7)	13.5 (1.3)	0.014
Positive urinary pregnancy test	10.9%	19.6%	0.040
Clinical pregnancy rate	9.6%	18.3%	0.032

Aim of the GEE analysis

independent factors affecting the cycle outcome

Male factor, unexplained infertility or the insemination cycle day were NOT independent factors

Table 3 GEE (n = 322) for positive pregnancy test: three independent factors significantly contribute to positive pregnancy test.

Variable		OR (95% CI)	P value
1 Sperm count after preparation	≥ 20 × 10 ⁶ /ml vs. < 20 × 10 ⁶ /ml	2.65 (1.20-5.81)	0.015
2 Number of follicles at insemination	2-3 vs. 0-1	2.01 (1.07-3.81)	0.031
3 Time of hCG injection	after IUI vs. 24-32 h before IUI	2.21 (1.16-4.19)	0.016

OR, odds ratio; CI, confidence interval.

Table 4 GEE (n = 322) for clinical pregnancy revealed two independent factors, which significantly contributed to clinical pregnancy after IUI cycle.

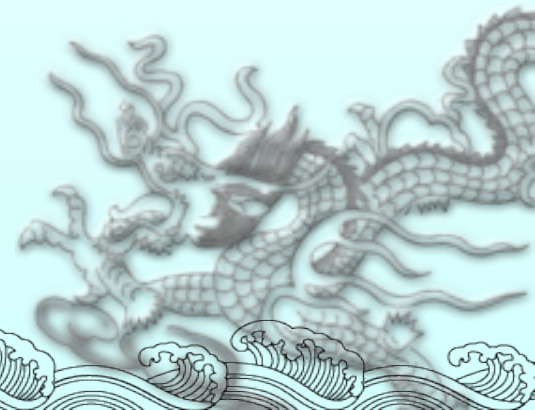
Variable		OR (95% CI)	P value
Sperm count after preparation	≥ 20 × 10 ⁶ /ml vs. < 20 × 10 ⁶ /ml	2.21 (1.02-4.82)	0.045
Number of follicles at insemination	2-3 vs. 0-1	1.88 (0.98-3.61)	0.057
Time of hCG injection	after IUI vs. 24-32 h before IUI	2.11 (1.11-4.05)	0.025

P > 0.05

OR, odds ratio; CI, confidence interval

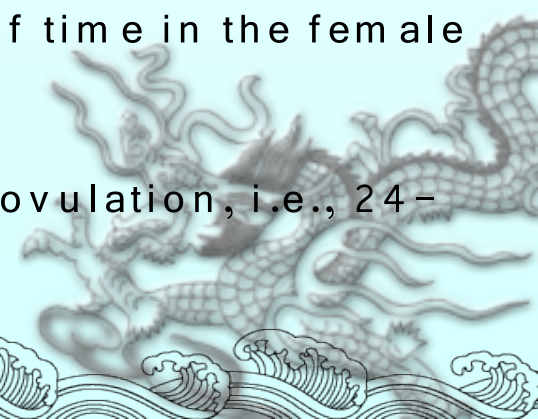
Discussion

- Postponing the hCG administration until after the IUI instead of injecting it 24-32 hours before IUI resulted in a **significantly increased pregnancy rate**
- Independent factors affecting the IUI cycle outcome in this study
 - Number of follicles > 16 mm
 - Sperm count



Discussion

- ▢ Reasons for insemination after 24-36 hours of hCG administration
 - ▢ Natural cycles: ovulation takes place 32 hours (range 24-56 hours) after the onset of the luteinizing hormone (LH) surge
 - ▢ Stimulated cycles: it takes place approximately 36-38 hours after the hCG injection
 - ▢ Oocytes are fertilisable for **only 12-16 hours**
 - ▢ Spermatozoa survive only for a limited period of time in the female reproductive tract
- ➔ Schedule the insemination to the time of expected ovulation, i.e., 24-36 hours after the administration of hCG



Discussion

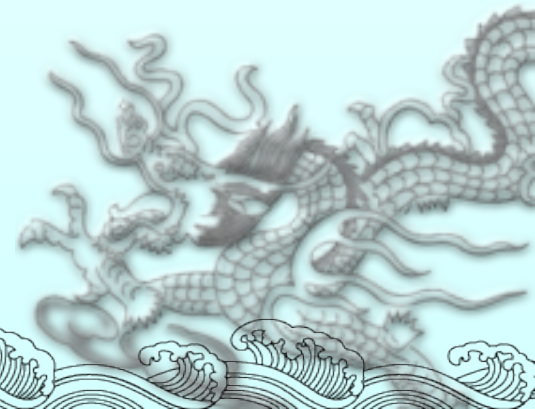
- ▣ Wilcox et al. published (1995)
 - ▣ 221 healthy women who were planning to become pregnant
 - ▣ After stopping birth-control methods, the women collected daily urine specimens and kept daily records of their sexual intercourses
 - ▣ Oestrogen and progesterone metabolites were measured from the urine samples to estimate the day of ovulation

→→ → **Conception** occurred only when intercourse took place during a **six-day period** that ended on the estimated day of **ovulation**



Discussion

- Wilcox et al. (1995) suggests
 - Chances to **conceive** in the natural cycle **diminish** considerably **after ovulation**
 - Preferably, the **spermatozoa** should be available in the reproductive tract **before** ovulation occurs
 - Spermatozoa may survive for several days after intercourse, as women whose last intercourse took place 5-6 days before ovulation did conceive



Discussion

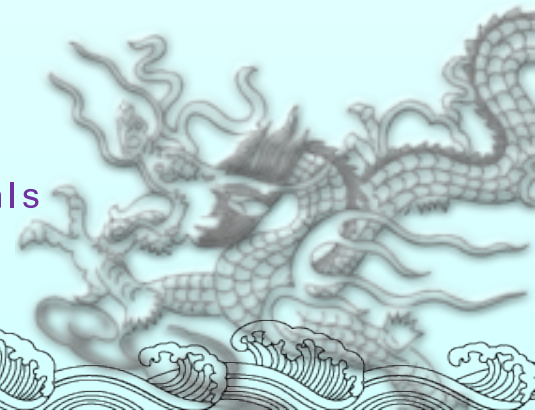
▣ Our study

- ▣ An increase of 80% in pregnancy rate by postponing the hCG injection after the IUI



Conclusion

- ▣ The finding of the study
 - ▣ Postponing the hCG administration until after the IUI seems to **increase** considerably the pregnancy rate in IUI cycles
- ▣ Significant of the study
 - ▣ If the finding is confirmed, it may eventually lead to avoidance of long-lasting, inconvenient and expensive ovarian hyperstimulation and IVF/CSI in some couples undergoing infertility treatment
- ▣ Limitation:
 - ▣ **Retrospective study**
 - ▣ Limited number of outcomes
 - ▣ Needs to be confirmed in randomized controlled trials



Thanks you~

