

# Relationship Of Follicle Number And Sperm Parameter To Pregnancy Rate In Different Ovulation Induction Protocol Induced Intrauterine Insemination Cycles

Ming Te Lin, Nan Hung Yeh, Long Yau Lin

The aim of the present study was to evaluate whether the induction of multiple ovulation can increase the pregnancy rates in couples treated with AIH. 624 couples underwent a total of 1242 cycles of IUI with husband's sperm after ovarian stimulation with clomiphene citrate (CC)-human gonadotropin combination or human gonadotropins alone. We compared the follicle numbers of induction by CC, CC/hMG, hMG with the pregnancy rates, and the outcome of three stimulation protocols with washed husband's sperm of different parameter. This figure was significantly higher pregnancy rates in ovulation stimulation groups (15.6%) than natural group (8.3%). On the other hand, we also get satisfied results of oligospermia group (10.8%) and asthenospermia group (11.5%) after ovarian stimulation. However, there was still low pregnancy rates in the oligospermia groups (3.0%). It is therefore suggested that a trial of induction of multiple follicular development may be performed in couples with male-related before their inclusion in protocols for advance procedures, such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

**key words:** Infertility, Intrauterine Insemination (IUI), Ovarian Stimulation.

## Introduction

Poor quality of semen is the major cause of male infertility, various trials have been made to improve it by means of pharmaceutical administrations, however, poor effican-

cious was expected.<sup>[1]</sup> New methods in sperm separation and preparation have been developed, it is generally accepted that insemination after superovulation should be attempted in couples with male-related or unexplained infertility before entering the advance procedures, such as IVF or gamete intrafallopian

transfer and intracytoplasmic sperm injection (ICSI).<sup>[2,3]</sup> Intrauterine insemination (IUI) has been used for treatment of infertility for over 100 years,<sup>[4]</sup> it with processed sperm is believed to superior to intracervical insemination in the treatment of infertility due to male factors.<sup>[5-7]</sup>

Ovulation stimulation is clearly useful in patients with irregular or absent ovulation by clomiphene citrate (CC) and human menopausal gonadotropin (hMG). Superovulation before IUI may simply provide more oocytes and spermatozoa in the distal oviduct, thereby increasing the opportunity for fertility.<sup>[2-3,5-12]</sup> Martinez et al. found no any improvement in pregnancy rate with superovulation and IUI in a prospective controlled trial,<sup>[13]</sup> but the lower dosage may not to be adequate to produce multiple ovarian follicles was thought to be the most reason.<sup>[6]</sup>

The purpose of this retrospective study was to determine the pregnancy rate of IUI after ovarian stimulation with hMG and/or clomiphene citrate, and the relationship of follicle number and different sperm parameter on pregnancy outcome.

## Materials and Methods

1242 cycles of IUI with husband's sperm were performed in 624 patients between Jan-

uary 1991 and December 1994. Three different protocols were used for ovulation induction before IUI treatment procedure. The induction protocol was randomised for the 352 patients, induction method was changed to another if results of previous cycle was unsatisfied.

A woman in the study demonstrated a cyclic menstrual history, a spontaneous midcycle LH surge, and a biphasic basal body temperature after ovarian stimulation. Infertility evaluation included a medical history, at least one semen analysis and postcoital testing. Evaluation of uterus and adnexa was done by transvaginal ultrasound, hysteroscopy, laparoscopy and hysterosalpingogram.

Normal semen analysis according to the following criteria: volume > 2cc, count >  $20 \times 10^6$  sperm/cc, morphology > 30% normal, and motility > 50%. Results of semen analysis was divided to normal (fitting to upper criteria), oligospermia (count <  $20 \times 10^6$  sperm/cc), athenospermia (motility < 50%), oligoatherospermia (count and motility < normal) and azoospermia five types, but azoospermia was excluded in our study.

Three treatment regimens were list as table 1.

1. Clomiphene citrate (CC) (Serophene, Sereno Laboratories, Randolph, MA) 100 mg daily from days 5 to 9 with patients monitoring follicle size by transvaginal ultrasound, and

Table 1. Three regimens of ovulation induction of IUI

Protocol	Drug	Treatment
Regimen 1.	Clomiphene Citrate (CC)	CC 100 mg/day D5-D9
Regimen 2.	CC + hMG	CC 100 mg/day D5-D9 hMG 2 amp./day since day 10 and on the alternate day
Regimen 3.	hMG only	hMG 2 amp./daily since day 3 booster dose depend on E2 level and follicle size

their urine for the endogenous LH surge. A single IUI was performed after the detection of the LH surge.

2. CC 100 mg was taken daily from days 5 to 9 followed by 2 amp. human menopausal gonadotropin (hMG) (Perganol, Sereno Laboratories, Randolph, MA) on the day 10 and thereafter on the alternate days with individualized dosages in accordance with follicle size, urine LH surge and serum estradiol (E2) measurement. When leading follicle size greater than 18 mm and E2 levels reached approximately 250-300 pg/ml/ per follicle for greater than 15 mm follicle, no further hMG was given and ovulation was triggered with 10,000 IU of human chorionic gonadotropin (hCG; Sereno Laboratories, Randolph, MA). A single IUI was made 32-36 hours later.
3. 2-3 AMP. hMG was given daily from days 3 with monitoring by ultrasound for follicle size and E2 levels. Leading follicle size greater than 18 mm and E2 levels reached 250-300 pg/ml/ per follicle for each follicle size over 15 mm, hCG and IUI was handled as in the regimen 2.

### Statistical analysis

The data were analysis using student t-test and  $X^2$ , when P value < 0.05, difference

was regarded as significant.

### Results

624 couples underwent a total of 1242 cycles of IUI in this study. The female patients' ages ranged from 24 to 46 years (mean ages:  $31.56 \pm 3.8$ ). Duration of infertility in this population was 1 to 17 years (mean years:  $4.50 \pm 3.03$ ). All of these IUI procedures was performed with husbands' sperm, azoospermia and insemination with donor's sperm were excluded in this study.

Three induction protocol, clomid (n=241), clomid + hMG (n=874) and hMG (n=55), and natural group (n=72) were in this study (Table 1). Table 2 show the follicle number of three induction groups and natural group. The hMG group has more follicles ( $6.30 \pm 2.80$ ) than the other groups (natural group =  $0.94 \pm 0.24$ , clomid =  $1.46 \pm 0.72$ , clomid + hMG =  $2.55 \pm 1.63$ ,  $P < 0.05$ ). The number of follicle was record as the follicle size large than 15 mm. The follicle number of pregnant cases was also more than non-pregnant cases in these four groups.

Table 3 reveal hMG group has significantly higher pregnancy rate (27.3%) than the remain three groups. ( $P < 0.05$ ) (natural group = 8.3%, clomid group = 12.9, clomid + hMG group = 15.6%) and the total pregnancy rate

Table 2. Follicle number in different protocol

Ovulation	Cycles	Pregnancy	Non-pregnancy	Mean
Spontaneous	72	$1.00 \pm 0.01$	$0.93 \pm 0.26$	$0.94 \pm 0.24$
Clomiphene Citrate	241	$1.65 \pm 0.87$	$1.59 \pm 1.02$	$1.46 \pm 0.72$
CC + hMG	874	$2.82 \pm 2.08$	$2.69 \pm 1.92$	$2.55 \pm 1.63$
hMG	55	$6.73 \pm 3.73^a$	$4.37 \pm 3.16^a$	$6.30 \pm 2.80$

Student t-test

<sup>a</sup> $P < 0.05$

was 15.1% (188/1242). The abortion rate was 16.7% (1/6) for natural group, 12.9% (4/31) for clomid group, 16.9% (23/136) for clomid + hMG group and 20.0% (3/15) for hMG group. 11 sets of twins (8.1%), 2 set of triplets (1.5%) and 5 ectopic cases were in the clomid + hMG group, 3 sets of twins and 1 set of quadruplet were in hMG group. In fact, the total delivered rate was 12.2% (152/1242), and the multiple pregnancy rate was 9.3% (17/183) in this study.

Table 4 show the pregnancy rate of different number of follicle in the clomid + hMG

and hMG groups. The more number follicles the higher pregnancy rate was achieved. More than 3 follicles has higher pregnancy rate than 1-2 follicles in both groups (23.6% vs 11.8%,  $P < 0.05$  in clomid + hMG group and 35.9% vs 13.5%,  $P < 0.05$  in hMG group) (table 5).

Four type of sperm parameter were in our study, table 6 reveal normal sperm group has the highest pregnancy rate after ovarian stimulation (18.8%), oligospermia group was 10.8%, asthenospermia group was 11.5%, the oligoasthnespermia group only has 3.0% pregnancy rate. ( $P < 0.05$ ) The pregnancy rate of

Table 3. Treatment and Monthly Probability of Pregnancy Occurrence (MPO) with intrauterine insemination (IUI) During Spontaneous Cycles, Clomiphene Citrate (CC) Cycles, CC-hMG Cycles, and hMG Cycles

Ovulation	Cycles	Pregnancy	(MPO)
Spontaneous LH <sup>a</sup>	72	6	(0.083)
Ovulation management <sup>a</sup>	1170	182	(0.156)
Clmiphene Citrate	241	31	0.129
CC-hMG	871	136	0.156
hMG	55	15	0.273

X<sup>2</sup> test

<sup>a</sup>p<0.05

Table 4. Relationship between Follicle Number and Cycle Fecundity in CC-hMG and hMG Groups

follicle no.	CC-hMG (N=874)			hMG (N=55)		
	P.	N.P.	Fecundity	P.	N.P.	Fecundity
1	27	272	9.0%	0	8	0%
2	30	210	12.5%	1	7	13.5%
3	25	99	20.0%	2	4	33.3%
4	22	80	21.6%	3	6	33.3%
5	12	35	25.5%	2	4	33.3%
>6	20	42	48.0%	7	11	38.9%

P: pregnant

N-P: non-pregnant

Table 5. Relationship between Follicle Number and cycle Fecundity in hMG Group (n=55) and hMG+CC (n=874)

Follicle	*hMG group			hMG + CC group		
	P	N-P	(Fecundity)	P	N-P	(Fecundity)
1-2	1	15	(13.5%) <sup>a</sup>	57	482	(11.8%) <sup>b</sup>
>3	14	25	(35.9%) <sup>a</sup>	79	256	(23.6%) <sup>b</sup>

X<sup>2</sup> test  
<sup>a,b</sup>P<0.05  
 P: pregnant  
 N-P: non-pregnant

Table 6. Cycle Fecundity of Different Sperm Parameter with Different Induction Protocol

Sperm parameter	CC (n=241)			CC-hMG (n=874)			hMG (n=55)			Total
	P	NP	PR	P	NP	PR	P	NP	PR	
Normal	21	116	15.0%	105	466	18.4%	13	20	39.4%	18.8%
Oligo	2	15	11.8%	5	40	11.1%	0	3	0.0%	10.8% <sup>a</sup>
Astheno	8	60	11.8%	24	192	11.1%	2	11	15.4%	11.5% <sup>b</sup>
Oligoasthno	0	19	0.0%	2	40	4.8%	0	6	0.0%	3.0% <sup>c</sup>
Total	31	210	12.9%	136	738	15.6%	15	40	27.3%	15.5%

Student t-test  
<sup>a,b,c</sup>P<0.05  
 P: pregnant  
 N-P: non-pregnant

normal sperm group with superovulation by hMG even reach 39.4%.

## Discussion

Intrauterine insemination (IUI) is not a new procedure. It appeared to have marginal value in the treatment of couples whose infertility was due to poor semen quality but has gained some acceptance in the treatment of infertility believed to be caused by the inability of apparently normal sperm to pass the cervical mucus. It is possible to deliver, in a timely fashion, large numbers of washed, active sperm into the uterine fundus with

minimal risks and adverse effects. However, the use of IUI for oligospermia was also questioned. IUI in natural cycles is not useful for treatment of oligoasthenospermia was also described by Ho et al.<sup>[14]</sup> The purpose of this study was to treat infertile couple due to subnormal semen with IUI after ovarian stimulation. Cruz et al., showed that in couples with subfertility because of oligoasthenospermia receiving hMG with or without clomiphene citrate (CC) for ovarian stimulation, the pregnancy rate of IUI was significantly better than intracervical insemination.<sup>[5]</sup> We found IUI after ovulation induction with each protocol, the pregnancy rate was higher than after sponta-

neous LH without ovarian stimulation. However, a control group having natural intercourse without ovarian stimulation was not included in this study. In the ovarian stimulation with hMG only group, there were significantly higher pregnancy rate than the another two protocols. ( $P < 0.05$ ) Ovarian stimulation proceeded a larger number of oocytes available for fertilization and ovarian stimulation may also correct subtle defects in ovulation that may not be detected with the usual mid-luteal serum P assays.<sup>[6]</sup> The number of follicles in the pregnant cycles was also higher than the nonpregnant cycles of each protocols. These findings suggest that the increase in the number of oocytes may be an important factor. Considerable increase in ovarian size bring the ovary in close proximity to the fimbria. Multiple ovulation increases the chance of ovum pickup, and superstimulation may have an effect on tubal vascularity and motility that may enhance ovum pickup mechanism.<sup>[11]</sup> We found the highest pregnant rate was noted in more than six follicles of groups with ovulation induction with hMG and/or clomiphene citrate respectively. (38.9% and 48%) More than three follicles has significantly higher pregnancy rate than 1-2 follicles in both groups.

Intrauterine insemination with ovarian stimulation improve the pregnancy rate of subnormal semen in our study. The patients treated with urinary LH-timed IUIs in spontaneous cycles with pregnancy rate of 0.083. When superovulation was utilized, the pregnancy rate increased to 0.156. One reason was it provides a high number of hyperactive sperm that can be introduced into the uterine cavity in a small volume. A second advantage was to facilitate scheduling, by insemination at a specific time after hCG administration. Control over the time sequence is obviously critical for success. The third possible cause of ovar-

ian stimulation is the potential presence of perhaps more than one oocytes, or oocytes of overlapping windows of capacity for fertilization. Fourth, hMG improved ovarian follicular and corpus luteum function and there was improvement in the quality and quantity of cervical mucus.

In conclusion, IUI after ovarian stimulation achieve higher monthly conception rates in the treatment for infertility because of subnormal semen. These results suggest that a trial of induction of multiple follicle follicular development and AIH should be performed in couples with male-related infertility before advanced treatment.

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