# The Influence of Women Age and Successfulness of Intrauterine Insemination (IUI) Cycles

Patsama Vichinsartvichai MD*, Supatchaya Siriphadung MD*,
Khanitta Traipak MN*, Pornprom Promrungrueng BSc*,
Chirawattana Manolertthewan MSc*, Sarwinee Ratchanon MD*

** Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand*

***Objective:*** *To evaluate the association between success and the benefit of repeated intrauterine insemination (IUI) cycles among women of different age groups.*

***Material and Method:*** *A retrospective analysis of 466 IUI cycles from 221 patients treated in a fertility center of a university hospital between 2005 and 2013. The female age was stratified as younger than 35 years, 35 to 40 years, and older than 40 years old. The outcomes were the biochemical pregnancy rate, clinical pregnancy rate, live birth rate, and miscarriage rate. Kaplan-Meier analysis of the suitability cycle in each age group was also performed.*

***Results:*** *The average age of patients was 35.2±4.6 years (range 21 to 49 years). The overall biochemical pregnancy rate was 18.6%. The biochemical pregnancy rate significantly decreased with advancing female age groups (27.6%, 12.8%, and 7.1% in female age group younger than 35 years, 35 to 40 years, and older than 40 years respectively, p = 0.008). The other pregnancy outcomes were not different among female age groups. In all age groups, the increment of the cumulative biochemical pregnancy rate was observed up to four cycles.*

***Conclusion:*** *The biochemical pregnancy rate of IUI cycle decreased with advancing female age; however, clinical pregnancy rate, live birth rate, and miscarriage rate were not different among female age groups. We recommend performing up to four insemination cycles before proceeding to IVF/ICSI cycle.*

***Keywords:*** *Artificial insemination, IUI, Age groups, Pregnancy rate*

***J Med Assoc Thai 2015; 98 (9): 833-8***
***Full text. e-Journal:*** *http://www.jmatonline.com*

Generally, intrauterine insemination (IUI) is the first line of assisted conception method, which has been widely used for the treatment of subfertility couples. It is a technique in which the semen is processed into highly concentrated motile sperm and inseminated into the uterus through the cervix using a fine catheter. It is often suggested to infertile couples of which the woman has at least one patent fallopian tube[1].

Many prognostic factors are associated with successful pregnancy in IUI cycles e.g., younger female age[2], higher total motile sperm per ejaculate[1,3], better ovarian reserve[4], and more number of dominant follicles[1]. However, only some prognostic factors are applicable to low resource settings.

Unlike some developed countries where government subsidizes the cost of infertility treatment, all infertile couples in Thailand have to cover their own expenses. The IUI can appeal to them by being more affordable and accessible than the other assisted reproductive technology (ART), as well as being repeatable at short intervals. However, the major disadvantage is that the success rates per cycle are much lower than that of ART cycle[4] with overall pregnancy rate ranging from 5% to 20%. The information about how many repeated IUI cycles still have benefit for each couple would guide clinicians and patient's judgment for selection of the optimum modalities of treatment.

The aim of this retrospective study was to evaluate the pregnancy outcomes of IUI cycles in women of different ages and determine the benefit of repeated insemination cycles in women of different age ranges.

***Correspondence to:***
*Vichinsartvichai P, Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Samsen Road, Dusit, Bangkok 10300, Thailand.*
*Phone: +66-2-2443405*
*E-mail: patsi109@gmail.com*

## Material and Method

### *Patients*

Data were retrospectively collected from IUI cycles performed in infertile couples between 2005 and 2013 at a fertility center in tertiary-care university

hospital, after excluding the couples that were diagnosed with severe male factor infertility and tubal factor infertility.

***Ovarian stimulation and ovulation triggering***

In each IUI cycle, ovarian stimulation was performed either by clomiphene citrate (CC) alone, gonadotrophin alone, or combination of CC and gonadotrophin, based on physician discretion. The growth of follicles was monitored by transvaginal ultrasonography. When at least one follicle reached the size of at least 18 mm, human chorionic gonadotrophin (hCG) was administered to the patient for ovulation induction. The IUI was performed 36 to 40 hours after hCG administration.

***Sperm preparation and IUI procedure***

The semen samples were collected by masturbation following an abstinence of three to five days and then were left to liquefy in a 37°C incubator for 30 minutes. A droplet of undiluted semen was analyzed according to WHO criteria[5]. After the semen analysis, the samples were centrifuged at 350 g for 15 minutes in a 45% and 90% Sil-Select-STOCK sperm preparation medium (FertiPro, Beernem, Belgium). The supernatant was discarded and the pellet was washed twice in FertiCult sperm washing medium (Beernem, Belgium) in 250 g for five minutes in each washing process. The prepared sperm was kept in the 37°C incubator until used.

The prepared sperm was inseminated into the uterus through the cervix using an in-house compile soft IUI catheter. Two weeks after the IUI procedure, the urine pregnancy test (UPT) was done. In case of positive UPT, a serum level of β-hCG was used for the confirmation of pregnancy. A vaginal sonography was performed two weeks after the positive pregnancy result to observe the gestational sac and every two weeks until gestational age of 12 weeks.

***Statistical analysis***

The Statistical Package for the Social Sciences (SPSS 22.0) (SPSS Inc., Chicago, IL, USA) was used. Results were expressed as mean ± SD, frequency, or percentage as appropriate. Categorical variables were compared using a Chi-square test, and continuous variables were analyzed using independent sample t-test. Kaplan-Meier analysis with log rank test was used to determine the cumulative pregnancy rate between age group. The $p<0.05$ was considered statistically significant. The office of the Institutional Review Board, Navamindhradhiraj University approved the study protocol.

**Results**

Four hundred forty six IUI cycles in 221 patients were included in the final analysis. The average women age was 35.2 years (range from 21 to 49 years). Mean duration of infertility in each cycle was 3.8 years. The three most common causes of infertility were unexplained infertility (53.0%), endometriosis (31.3%), and anovulation (7.9%). Most of the ovarian stimulation protocol was CC alone (92.1%) and the average total motile sperm count was 57.1 million/mL (Table 1).

The pregnancy outcomes were described in Table 2. The 466 IUI cycles gave rise to 42 pregnancies (i.e., 9% per cycle). The biochemical pregnancy rate (BPR) per patient was 18.6% (95% CI 10.0-20.0) and clinical pregnancy rate (CPR) per patient was 14.0% (95% CI 8.0-17.0). The outcomes of pregnancies were 21 live births (18 singletons, 2 sets of twins, and 1 triplets), 10 miscarriages, and 3 ectopic pregnancies (8 biochemical pregnancies were lost to follow-up). When compared between patients with and without

**Table 1.** Demographics and cycle characteristics

| | Total (n = 221) mean (SD) or n (%) |
|---|---|
| Female age (years), mean (SD) | 35.2 (4.6) |
| <35 | 94 (42.5) |
| 35-40 | 96 (43.6) |
| >40 | 31 (13.9) |
| Duration of infertility (years), mean (SD) | 3.8 (2.7) |
| Cause of infertility | |
| Unexplained infertility | 117 (53.0) |
| Endometriosis | 69 (31.3) |
| Anovulation | 17 (7.9) |
| Leiomyoma of uterus | 6 (2.8) |
| Number of IUI cycle, mean (SD) | 2.2 (1.7) |
| Stimulation protocol (n = 466) | |
| CC alone | 429 (92.0) |
| CC + FSH | 19 (4.1) |
| FSH alone | 18 (3.9) |
| Number of DF, mean (SD) | 1.5 (0.7) |
| Size of DF (mm), mean (SD) | 20.6 (3.4) |
| ET (mm), mean (SD) | 8.1 (2.3) |
| TMSC ($x10^6$), mean (SD) | 57.1 (47.1) |

IUI = intrauterine insemination; CC = clomiphene citrate; FSH = follicle-stimulating hormone; DF = dominant follicles; ET = endometrial thickness; TMSC = total motile sperm count

pregnancy, patients with pregnancy were younger at initial treatment (32.8±4.6 vs. 35.5±4.5 years, $p$<0.001), and had shorter duration of infertility (2.7±1.9 vs. 4.0±2.8 years, $p$ = 0.006). The others ovarian response or semen parameters were not statistically different (data not shown).

The women age had a significant impact on pregnancy rates. The biochemical pregnancy rate decreased when the woman's age became more advanced (27.6% in younger than 35 years, 12.8% in 35 to 40 years and 7.1% in older than 40 years, $p$ = 0.008). While the CPR and live birth rate (LBR) demonstrated the same trend, these rates were not significantly different between age groups (Table 3).

The log rank test was run to confirm if there were discrepancies in cumulative pregnancy rates among different age groups. The cumulative BPR was significantly better in the age group of younger than 35 years while group 35 to 40 years and older than 40 years were not different (overall comparison; $p$ = 0.002). The cumulative CPR and LBR were not different between age groups (data not shown).

The cumulative BPR from age group younger than 35 years and older than 40 years demonstrated that the maximum cycle that achieved the cumulative pregnancy rate was four cycles, while maximum cycle that achieves the cumulative pregnancy rate in the age group 35 to 40 years was six cycles (Fig. 1).

**Table 2.** Pregnancy outcomes per patient (n = 221)

| | n (%) | 95% CI |
|---|---|---|
| Biochemical pregnancy rate | 41 (18.6) | 10.0-20.0 |
| Clinical pregnancy rate | 31 (14.0) | 8.0-17.0 |
| Live birth rate | 22 (10.0) | 6.0-14.0 |
| Miscarriage rate | 11 (4.8) | 2.0-8.0 |
| Ectopic pregnancy rate | 3 (1.4) | 0.0-3.0 |

**Table 3.** Pregnancy outcomes per patient stratified by female age group

| | Age group (years) | | | |
|---|---|---|---|---|
| | <35 | 35-40 | >40 | $p$-value[a] |
| Biochemical pregnancy rate | 27.6 | 12.8 | 7.1 | 0.008 |
| Clinical pregnancy rate | 18.5 | 12.8 | 3.6 | 0.124 |
| Live birth rate | 13.5 | 8.6 | 3.6 | 0.261 |
| Miscarriage rate | 6.7 | 3.2 | 3.6 | 0.512 |
| Ectopic pregnancy rate | 3.1 | 0.0 | 0.0 | 0.151 |

[a] Chi-square test

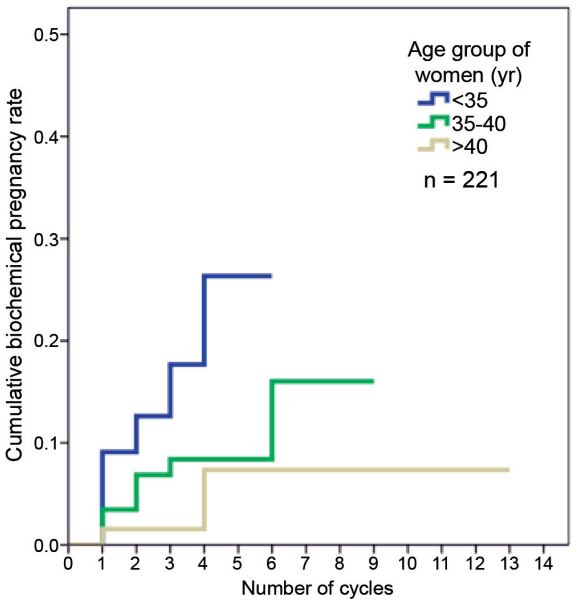


**Fig. 1** Cumulative biochemical pregnancy rates stratified by female age group (Kaplan-Meier analysis with log rang test; $p$ = 0.002).

## Discussion

The increased women age significantly decreases fecundity in an IUI cycle. Our data suggested that the pregnancy rate per patient in women aged younger than 35 years was significantly higher compared to women aged 35 to 40 years and older than 40 years group. Our results were consistent with other previous studies that the successful pregnancy with IUI was lower in the more advanced female age[1-4,6]. There was evidence to support these results that oocyte quality[7] and endometrial receptivity[8] declined with age.

In women older than 40 years, all studies found that the pregnancy rate was the lowest, especially when compared Asian to Caucasian women. We found very small BPR per patient in women age older than 40 years (7.1% per patient). However, the pregnancy rate in Caucasian women seems to be higher (7.4 to 20% per patient)[2,9]. This finding was supported by Lamb et al[10] that Asian women got the lower pregnancy likelihood compared to white women (adjusted OR 0.68; 95% CI 0.47-0.98, $p$ = 0.039). The reasons for poorer pregnancy outcomes are not well understood and appear to be a complex issue. Many investigators proposed that Asian women might have premature ovarian aging[11], discrepancies in follicle-stimulating hormone (FSH) receptor polymorphism (more NN variant in exon 10)[12], and differences in

steroid hormone synthetic enzyme polymorphism such as *CYP19*, *CYP17 MspAI*[13].

Before stopping IUI cycle and proceed to more costly intracytoplasmic sperm injection/in vitro fertilization (IVF/ICSI) cycle, multiple aspects should be taken into serious consideration. For a couple with repeated failed IUI attempts, continuing IUI can become an emotional distress. Psychological stress can occur in a failed ART couple. Since a patient's opinion is partially dependent on the way she is counseled, it is crucial for a reproductive care team to discuss the benefits of repeating IUI cycles and emphasize the cumulative pregnancy rate instead of pregnancy rate per cycle.

Financial burden should also be considered. It is important not to proceed with IVF/ICSI too soon at a much higher cost before the maximum likelihood of pregnancy with IUI has been achieved. On the other hand, it is important not to waste time or money on ineffective treatments for many IUI cycles if the chances of success are low. Most previous studies recommended that IUI is more cost-effective than IVF/ICSI[14,15]. In our center, the cost of four IUI cycles is only 10% of the cost of one IVF/ICSI cycle. The lower cost of IUI makes it more attractive and cost-effective for the infertile couple. However, starting from the fifth cycle onward, the present study showed that the pregnancy rate was low and IVF/ICSI seems to be more cost-effective.

The optimum number of repeated IUI cycles is an adamant issue, especially when counseling the couple. Many publications suggested various answers and limitation since some centers had their policy to limit IUI cycle attempted. Several literatures recommended the maximum of three[16], four[17], six[18], or even nine[19] treatment cycles. From our data analysis, we recommended four repeated IUI cycles for the maximum chance of pregnancy.

In summary, the biochemical pregnancy rate of IUI cycle decreases with advancing female age. However, CPR, LBR, and miscarriage rate is not different among female age groups. We recommend performing up to four insemination cycles before proceeding to IVF/ICSI cycle.

**What is already known on this topic?**

Many prognostic factors are associated with successful pregnancy in IUI cycles e.g., younger female age, higher total motile sperm per ejaculate, better ovarian reserve, and more number of dominant follicles.

The optimum number of repeated IUI cycles is also an important issue, especially when counseling the infertile couple. Many studies suggest various answers and limitation. Some centers have a policy to limit IUI cycle attempted. Several studies recommended a maximum of three, four, six, or even nine treatment cycles.

To the best of our knowledge, there is sparse information about woman age as a prognostic factor for IUI in Asian people and how many cycles should be performed.

**What this study adds?**

In our institution, which no limitation of repetitive IUI cycles, the biochemical pregnancy rate of IUI cycle decreases with advancing female age. We recommend performing up to four insemination cycles before proceeding to IVF/ICSI cycle.

**Acknowledgement**

The present study was supported by the grant from the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University.

**Potential conflicts of interest**

None.

**References**

1. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril 2010; 93: 79-88.
2. Schorsch M, Gomez R, Hahn T, Hoelscher-Obermaier J, Seufert R, Skala C. Success rate of inseminations dependent on maternal age? An analysis of 4246 insemination cycles. Geburtshilfe Frauenheilkd 2013; 73: 808-11.
3. Azantee YW, Murad ZA, Roszaman R, Hayati MY, Norsina MA. Associated factors affecting the successful pregnancy rate of intrauterine insemination at International Islamic University Malaysia (IIUM) Fertility Centre. Med J Malaysia 2011; 66: 195-8.
4. Speyer BE, Abramov B, Saab W, Doshi A, Sarna U, Harper JC, et al. Factors influencing the outcome of intrauterine insemination (IUI): age, clinical variables and significant thresholds. J Obstet Gynaecol 2013; 33: 697-700.
5. World Health Organization. WHO laboratory manual for the examination and processing of

human semen. 5th ed. Geneva: WHO; 2010.
6. Sahakyan M, Harlow BL, Hornstein MD. Influence of age, diagnosis, and cycle number on pregnancy rates with gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril 1999; 72: 500-4.
7. Ge ZJ, Schatten H, Zhang CL, Sun QY. Oocyte ageing and epigenetics. Reproduction 2015; 149: R103-14.
8. Yaron Y, Botchan A, Amit A, Kogosowski A, Yovel I, Lessing JB. Endometrial receptivity: the age-related decline in pregnancy rates and the effect of ovarian function. Fertil Steril 1993; 60: 314-8.
9. Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles. Fertil Steril 2008; 90: 2281-6.
10. Lamb JD, Huddleston HG, Purcell KJ, Modan A, Farsani TT, Dingeldein MA, et al. Asian ethnicity is associated with decreased pregnancy rates following intrauterine insemination. Reprod Biomed Online 2009; 19: 252-6.
11. Bhide P, Gudi A, Shah A, Homburg R. Serum anti-Mullerian hormone levels across different ethnic groups: a cross-sectional study. BJOG 2014 Oct 7. doi: 10.1111/1471-0528.13103.
12. Simoni M, Nieschlag E, Gromoll J. Isoforms and single nucleotide polymorphisms of the FSH receptor gene: implications for human reproduction. Hum Reprod Update 2002; 8: 413-21.
13. Miyoshi Y, Noguchi S. Polymorphisms of estrogen synthesizing and metabolizing genes and breast cancer risk in Japanese women. Biomed Pharmacother 2003; 57: 471-81.
14. Chambers GM, Adamson GD, Eijkemans MJ. Acceptable cost for the patient and society. Fertil Steril 2013; 100: 319-27.
15. Connolly MP, Hoorens S, Chambers GM. The costs and consequences of assisted reproductive technology: an economic perspective. Hum Reprod Update 2010; 16: 603-13.
16. Aboulghar M, Mansour R, Serour G, Abdrazek A, Amin Y, Rhodes C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. Fertil Steril 2001; 75: 88-91.
17. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 1999; 14: 698-703.
18. Campana A, Sakkas D, Stalberg A, Bianchi PG, Comte I, Pache T, et al. Intrauterine insemination: evaluation of the results according to the woman's age, sperm quality, total sperm count per insemination and life table analysis. Hum Reprod 1996; 11: 732-6.
19. Custers IM, Steures P, Hompes P, Flierman P, van Kasteren Y, van Dop PA, et al. Intrauterine insemination: how many cycles should we perform? Hum Reprod 2008; 23: 885-8.

## ผลของอายุของสตรีกับโอกาสสำเร็จของการฉีดเชื้อผสมเทียมในโพรงมดลูก

**พัฒน์ศมา วิจินศาสตร์วิจัย, ศุภัชญา สิริผดุง, ขนิษฐา ไตรปักษ์, พรพรหม พรหมรุ่งเรือง, จิรวัฒนา มโนเลิศเทวัญ, สาวินี รัชชานนท์**

***วัตถุประสงค์:*** *เพื่อศึกษาอัตราการตั้งครรภ์และประโยชน์จากการฉีดเชื้อผสมเทียมในโพรงมดลูกหลาย ๆ รอบ ในสตรีที่มีช่วงอายุต่าง ๆ ที่เข้ารับการรักษาภาวะมีบุตรยากด้วยวิธีฉีดเชื้อผสมเทียมในโพรงมดลูก*

***รูปแบบการศึกษา:*** *การศึกษาแบบย้อนหลัง*

***วัสดุและวิธีการ:*** *ผู้นิพนธ์ได้ย้อนดูข้อมูลของสตรีที่เข้ารับการรักษาภาวะมีบุตรยากด้วยการฉีดเชื้อผสมเทียมในโพรงมดลูกระหว่าง พ.ศ. 2548 ถึง พ.ศ. 2556 จากเวชระเบียนผู้ป่วยนอกและแฟ้มประวัติประกอบการรักษา 466 รอบ ฉีดเชื้อผสมเทียม ซึ่งมาจากสตรีที่เข้ารับการฉีดเชื้อผสมเทียมในโพรงมดลูกทั้งหมด 221 คน อายุของสตรีที่ทำการศึกษาทั้งหมดสามารถแบ่งออกเป็น 3 กลุ่มตามช่วงอายุ ดังนี้ กลุ่มอายุน้อยกว่า 35 ปี กลุ่มอายุระหว่าง 35-40 ปี และกลุ่มอายุมากกว่า 40 ปี ตัวแปรที่ใช้ประเมินความสำเร็จของการฉีดเชื้อผสมเทียม ได้แก่ อัตราการตั้งครรภ์ทางเคมี อัตราการตั้งครรภ์ทางคลินิก อัตราการเกิดมีชีพ และอัตราการแท้ง อีกทั้งจำนวนรอบฉีดเชื้อผสมเทียมที่เหมาะสมและก่อให้เกิดประโยชน์สูงสุดสำหรับในแต่ละช่วงอายุสตรีได้ถูกวิเคราะห์จากการคำนวณทางสถิติแบบ Kaplan-Meir analysis*

***ผลการศึกษา:*** *อายุเฉลี่ยของสตรีอยู่ที่ 35.2±4.6 ปี (มีค่าระหว่าง 21 ถึง 49 ปี) อัตราการตั้งครรภ์ทางเคมีลดลงอย่างมีนัยสำคัญทางสถิติเมื่ออายุสตรีมากขึ้น (27.6%, 12.8% และ 7.1% ในกลุ่มอายุน้อยกว่า 35 ปี, 35-40 ปี และมากกว่า 40 ปี ตามลำดับ, $p = 0.008$) อัตราการตั้งครรภ์อื่น ๆ เช่น อัตราการตั้งครรภ์ทางคลินิก อัตราการเกิดมีชีพ และอัตราการแท้ง พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มอายุของสตรี สำหรับทุกกลุ่มอายุสตรีพบว่า รอบฉีดเชื้อผสมเทียมที่ทำให้ยังมีการเพิ่มของอัตราการตั้งครรภ์สะสม คือ รอบการฉีดเชื้อรอบที่ 4*

***สรุป:*** *อัตราการตั้งครรภ์ทางเคมีจากการฉีดเชื้อผสมเทียมในโพรงมดลูกมีค่าลดลงเมื่ออายุสตรีเพิ่มขึ้น อย่างไรก็ตามสำหรับอัตราการตั้งครรภ์ทางคลินิก อัตราการเกิดมีชีพ และอัตราการแท้ง ไม่พบว่ามีความแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่มอายุของสตรี การศึกษานี้ได้แนะนำจำนวนรอบการฉีดเชื้อผสมเทียมที่ควรทำ คือ จำนวน 4 รอบ ก่อนที่จะเริ่มการรักษาด้วยเทคโนโลยีช่วยการเจริญพันธุ์ เช่น การทำเด็กหลอดแก้ว*