



Association between ICSI cycle outcome and response in women with infertility

Sara Samir Sadoon^{1*}, Amal Abdulwahid Mohammed², Ali Ibrahim Rahim³

^{1*}Kirkuk Health Directorate, Iraq

²Lecturer at higher institute for diagnosis of infertility and assisted reproduction techniques, Iraq

³Al-Ameed University, College of Medicine; Al-Kafeel Specialized Hospital, IVF Center; Karbala, Iraq

*Corresponding Author: sara.samir@ierit.nahrainuniv.edu.iq

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Keyword

ISCI, Infertility, AMH, Pregnancy Rate, Ovarian Response.

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Abstract:

Background: Infertility is the inability to achieve a clinical pregnancy after 12 months of regular and unprotected sexual activity. Increases in child-bearing delay and maternal age at first pregnancy significantly impact the rise of age-related infertility and the demand for treatment using assisted reproduction techniques (ART). As a result, many women with a low ovarian reserve and a poor ovarian response (POR) to conventional stimulation seek medical assistance at infertility clinics. Aim: The study aimed to evaluate the quality of oocytes and embryos, as well as the rates of conception, in infertile women who were candidates for fresh intracytoplasmic sperm injection between good and poor-responder women (ICSI). Patients and methods: The study was conducted on 45 infertile women undergoing ICSI at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University/ Baghdad/ Iraq from October 2021 to April 2022, regardless of whether they had previously undergone ICSI. The morphology of the oocytes and the quality of the resulting embryos were assessed. The patients' ages ranged from 20 to 42 years old. There was primary and secondary infertility ranging from one to 20 years. Every couple had a basic reproductive assessment. The

antagonist protocol was used for all infertile females. All females had their serum levels of AMH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and oestradiol (E2) measured on the second or third day of their cycle. The serum oestradiol (E2) level was re-measured on the day of the hCG injection. Results: The participants in the study were 32.6 ± 5.3 years old. The findings showed that 57.8% of the patients had a well response, and 24.4% of the women were pregnant. In those who became pregnant, anti-müllerian hormone (AMH) levels were significantly higher, and follicle-stimulating hormone (FSH) levels were noticeably lower ($p > 0.05$). The E2, LH, prolactin, and progesterone levels were not statistically different ($P > 0.05$). Conclusion: In conclusion, the findings revealed a positive relationship between response and ICSI outcomes in infertile women.

Keywords: ISCI, Infertility, AMH, Pregnancy Rate, Ovarian Response.

العلاقة بين نتائج دورة الحقن المجهري والاستجابة عند النساء المصابات بالعمق

ساره سمير سعدون^١، آمال عبد الواحد محمد^٢، علي إبراهيم رحيم^٣

^١مديرية صحة كركوك، العراق

^٢المعهد العالي لتشخيص العمق وتقنيات الإنجاب، العراق

^٣جامعة العميد، كلية الطب، مستشفى الكفيل التخصصي، مركز أطفال الأنابيب، كربلاء، العراق

*sara.samir@ierit.nahrainuniv.edu.iq

الخلاصة:

يُعرف العمق بأنه عدم القدرة على تحقيق الحمل السريري بعد ١٢ شهرًا من النشاط الجنسي المنتظم وغير المحمي. تؤثر الزيادة في تأخر الإنجاب وعمر الأم عند الحمل الأول بشكل كبير على زيادة العمق المرتبط بالعمر والطلب على العلاج باستخدام تقنيات الإنجاب المساعدة (ART). يتسبب هذا في وجود عدد كبير من النساء ذوات احتياطي المبيض المنخفض واستجابة المبيض الضعيفة (POR) للتحفيز التقليدي يطلبن المساعدة الطبية في عيادات العمق. كان الهدف من الدراسة هو تقييم جودة البويضات والأجنة وكذلك معدلات الحمل لدى النساء المصابات بالعمق والمرشحات لحقن الحيوانات المنوية الجديدة داخل الهيولى في كل من النساء المستجيبات الطبيعيات والضعيفات (الحقن المجهري). المرضى والأساليب: أجريت الدراسة على ٤٥ امرأة مصابة بالعمق يخضعن للحقن المجهري في المعهد العالي لتشخيص العمق والتقنيات الإنجابية المساعدة / جامعة النهدين / بغداد / العراق من أكتوبر ٢٠٢١ إلى أبريل ٢٠٢٢، بغض النظر عما إذا كانوا قد خضعوا سابقًا للحقن المجهري. تم تقييم مورفولوجيا البويضات ونوعية الأجنة الناتجة. تراوحت أعمار المرضى من ٢٠ إلى ٤٢ عامًا. كان هناك عمق أولي وثانوي يتراوح من عام إلى ٢٠ عامًا، خضع جميع الأزواج لتقييم الإنجاب الأساسي. كان بروتوكول جميع الإناث المصابات بالعمق هو البروتوكول المضاد. تم قياس مستويات مصل الدم من AMH، وهرمون (LH) LUTEINIZING، وهرمون تحفيز الجريب

(FSH) ، والإستراديول (E2) في اليوم الثاني أو الثالث من الدورة. تم إعادة قياس مستوى مصلى الأوستراديول (E2) في يوم حقن (HCG). النتائج: تراوحت أعمار المشاركين في الدراسة بمتوسط عمر $32,6 \pm 5,3$ سنة. وأظهرت النتائج أن $57,8\%$ من المرضى لديهم استجابة طبيعية، وأن $24,4\%$ من النساء كن حوامل. كان الهرمون المضاد للمولر (AMH) أعلى بشكل ملحوظ وكان الهرمون المنبه للجريب (FSH) أقل بشكل ملحوظ ($P > 0.05$) في النساء الحوامل. لم تكن مستويات LH و E2 والبرولاكتين والبروجسترون مختلفة إحصائياً ($P > 0.05$) بينهما. الخلاصة: في الختام أوضحت النتائج وجود علاقة إيجابية بين الاستجابة ونتائج الحقن المجهرى في النساء المصابات بالعقم.

الكلمات المفتاحية: ISCIK، العقم، AMH، معدل الحمل استجابة المبيض.

1. INTRODUCTION:

Infertility is a worldwide medical and financial issue that can cause stress and psychological distress. Infertility is the inability to obtain a clinical pregnancy following at least one year of regular unprotected sexual intercourse. Lifestyle has had a significant impact on the decline of fertility and the rise of assisted reproductive technologies in recent years [1]. Infertile patients undergoing in vitro fertilization (IVF) programs have a poor ovarian response in 9 to 24 % of cases [2]. Follicles that respond to FSH are fewer in women with a poor ovarian response, resulting in poor IVF outcomes and presenting a significant challenge to clinicians worldwide [3]. Several standards for determining POR have been proposed. However, none had been accepted as the international standard for defining POR until the development of Bologna standards in 2011[4]. Treatment of poor-responder patients during Assisted Reproductive Technologies (ART) is still a controversial topic [3]. The main goal is to determine the optimum treatment strategy for them depending on their ovarian capacity to enhance pregnancy potential while remaining clinically safe. It is most likely to reduce the risk of treatment failure, improve IVF outcomes, raise the chances of conception, provide proper counseling to patients, and set realistic expectations for ovarian stimulation outcomes. Increasing the gonadotropins or decreasing the GnRH agonist (GnRH-a) doses, as well as the use of adjunctive growth hormone, clomiphene citrate, aromatase inhibitors, or the use of a micro dose flare regimen with or without oral contraceptive pretreatment, or the use of a GnRH antagonist regimen, have all been suggested for the management of the poor-responder patient to improve the ovarian responses as well as the IVF outcomes [5]. The study's goal was to assess oocyte and embryo quality as well as conception rates in women with infertility who were candidates for fresh intracytoplasmic sperm injection in both well and poor responder women (ICSI).

2. Patients and Methods:

The study included 45 infertile women who underwent ICSI who underwent ICSI at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/Al-Nahrain University/Baghdad, Iraq, from October 2021 to April 2021, regardless of whether they had previously undergone ICSI. The morphology of the oocytes and the quality of the generated embryos were assessed in the same institute's laboratory. The age of patients was between 20 and 42. Primary and secondary infertility were also present, with a period of 1 to 20 years. All couples underwent a basic reproductive assessment, which included a history, physical examination, hormone measurement, and the exclusion of uncontrolled endocrine problems, as well as sperm analysis for their partner. The protocol for all infertile females was the antagonist protocol. All patients had their serum levels of AMH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), as well as oestradiol (E2) tested on the second or third day of their periods. The serum oestradiol (E2) level was re-measured the day after the hCG injection. The average age of the females included in this study was 20 to 42, had normal BMI, or weighed less than 30 kg, and had a partner with adequate normal sperm. Females with uncontrolled endocrine and systemic diseases, as well as those who had a partner with severe oligospermia or azoospermia, were excluded from the study.

Methods: To discover the reason for infertility, each infertile couple who participated in this study had a thorough medical history and physical examination. Questions about medical history include medical history (thyroid illness symptoms, diabetes, hirsutism, weight gain or loss, nipple discharge, lower abdomen or pelvic pain, mumps history, medication allergies, oral contraceptive pill use, steroids, chemotherapy, radiation, and non-steroidal anti-inflammatory medications, etc.). Past surgical history includes (cesarean section, appendectomy, diagnostic or therapeutic curettage, thyroid surgery, abdominal surgery, etc). Menstrual history includes (age of menarche, length of cycle, character of menstrual cycle, and presence of dysmenorrhea). Past gynecological history includes a history of vaginal discharge, pelvic pain, previous exposure to pelvic inflammatory disease, and history of PAP smears, a history of marriage, date of marriage, coital timing and frequency, methods of contraception if present, etc. Fertility history includes the type, duration, causes, previous investigations, and treatments, including IVF-ICSI trials and their outcomes. Past obstetrical conditions include the following: a history of gravidity and parity; a history of pregnancy-induced hypertension, gestational diabetes, a miscarriage; vaginal bleeding; a previous history of cervical cerclage; the birth of an abnormal

child; and post-partum hemorrhage). Family history; includes a history of infertility, premature ovarian failure, diabetes mellitus, thyroid diseases, or congenital abnormalities, etc.). Social history includes occupation, smoking, alcohol, address, and animal contacts. Both partners underwent physical examinations, including body mass index (BMI), general, cardiovascular, abdominal, central nervous system, thyroid, and breast examinations. Gynecological examination, including vaginal and cervical abnormalities, discharge, and uterine size. The Hormonal Assay was used to assess ovarian reserve, whereas serum prolactin, progesterone, and 17 estradiol (E2) were all used to evaluate hypothalamic-pituitary-ovarian (HPO) axis function. Based on their ovarian response, women were divided into two groups. Women with a poor ovarian response to stimulation had a reduced follicular response and low levels of oestradiol (E2) to stimulation according to the "Bologna criteria" developed by the European Society of Human Reproduction and Embryology (ESHRE).

3-Result

Figure 1 depicts the distribution of study patients based on general characteristics. Patients in the study ranged in age from 23 to 42 years old, with a mean of 32.6 ± 5.3 years old. However, the majority of participants (57.8%) were under the age of 35.

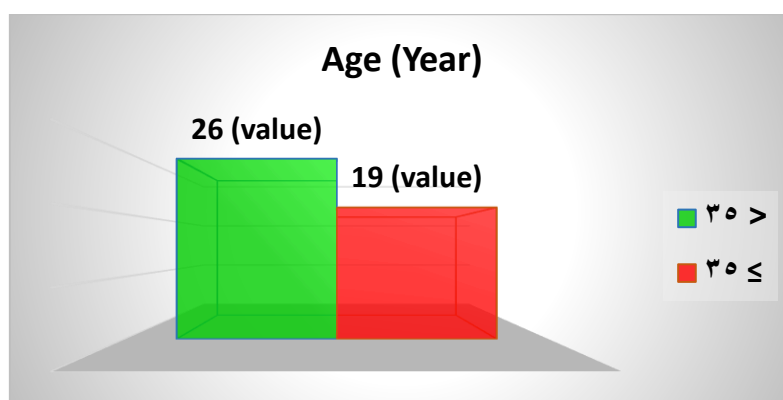


Fig 1. Distribution of participants by age

According to the findings, (57.8%) of patients had well responses, as shown in **Table 2**.

Table 1. Distribution of study patients by response

Response	No. (n= 45)	Percentage (%)
Poor responder	19	42.2
Well responder	26	57.8

Figure 2 shows the distribution of study patients by ICSI cycle outcome. The prevalence of pregnancy was (24.4 %).

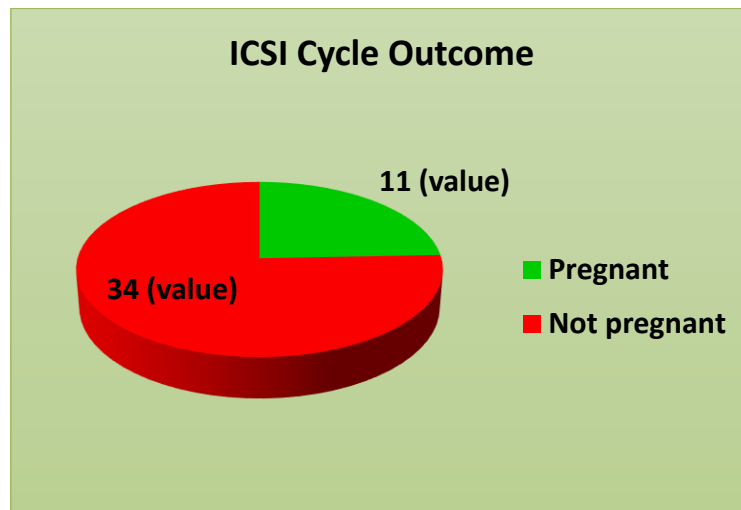


Figure 2: Distribution of study patients by ICSI outcome

Furthermore, pregnant women have considerably increased AMH and significantly lower FSH, as seen in **Table 2** ($p < 0.05$). There were no statistically significant differences ($p > 0.05$) between E2, LH, prolactin, and progesterone.

Table 2: Comparison of hormonal parameters based on ICSI cycle outcome

Hormonal Parameter	ICSI cycle outcome		P - Value
	Pregnant Mean \pm SD	Not pregnant Mean \pm SD	
Estradiol (pg/ml)	1590.01 \pm 631.1	1261.13 \pm 929.7	0.209
AMH (ng/ml)	2.85 \pm 1.6	1.51 \pm 1.1	0.032
FSH (IU/L)	6.97 \pm 1.8	9.02 \pm 2.6	0.01
LH (IU/L)	7.62 \pm 2.4	7.22 \pm 2.4	0.651
Prolactin (ng/ml)	13.21 \pm 4.2	14.11 \pm 5.1	0.321
Progesterone (ng/ml)	1.69 \pm 1.1	1.71 \pm 1.2	0.833

As shown in **Table3**, there was no statistically significant difference in response between pregnant and non-pregnant women ($P = 0.063$).

Table 3: Association between ICSI cycle outcome and response

Response	ICSI cycle outcome		Total (%) n= 45	P - Value
	Pregnant (%) n= 11	Not pregnant (%) n= 34		
Poor responder	1 (9.09%)	18 (52.9%)	19 (42.2%)	0.027
Well responder	10 (90.91%)	16 (47.1%)	26 (57.8%)	

Table 4 compares clinical indicators based on the outcome of an ICSI cycle. Those who got pregnant had a considerably larger mean number of grades I embryos ($p = 0.03$) than those who did not. All other clinical measures' means did not show statistically significant changes ($P > 0.05$).

Table 4: Comparison in clinical parameters by ICSI cycle outcome

Clinical Parameter	ICSI cycle outcome		P - Value
	Pregnant Mean \pm SD	Not pregnant Mean \pm SD	
Endometrial Thickness (mm)	9.36 \pm 1.2	8.89 \pm 1.3	0.306
No. of oocyte retrieved	12.9 \pm 5.5	8.91 \pm 6.5	0.07
No. of ruptured follicle	0.8 \pm 1.31	0.54 \pm 0.85	0.571
No. of GV stage oocyte	2.0 \pm 1.9	0.82 \pm 1.8	0.101
No. of M1 stage oocyte	2.4 \pm 1.7	1.65 \pm 1.8	0.25
No. of M2 stage oocyte	7.0 \pm 4.1	5.34 \pm 4.8	0.292
No. of embryos	5.9 \pm 3.4	4.31 \pm 3.5	0.217
No. of grade I embryo	4.1 \pm 2.9	2.25 \pm 2.1	0.03
No. of grade II embryo	1.3 \pm 1.1	0.97 \pm 0.92	0.39
No. of grade III embryo	0 \pm 0	0.25 \pm 0.78	0.059

4. Discussion

Despite advances in reproductive technology, significant proportions of patients remain poor responders (PORs) to aspects of oocyte retrieval and pregnancy rates [6]. According to the current findings, 57.8% of patients responded well to ART treatment programs, whereas 42.2% responded poorly. Furthermore, the prevalence of pregnancy was 24.4%. A previous study estimated that the pregnancy rate was about 26%, which is highly approximate to the result of the present study [7].

In contrast to the results of Hassan et al.'s 2020 study, better results were published, with an overall prevalence of pregnancy after ICSI of 32.3% [8]. In other studies, 33 patients out of 90 in Kamkar et al.'s study in 2018 got pregnant (36%), only 27 of which were clinical pregnancies, giving a 30% clinical pregnancy rate [9]. In the Ashrafi et al. study from 2013, 1492 infertile women were enrolled and underwent ICSI, and the overall clinical pregnancy rate was 33.9% [10].

As shown in **Table 3**, there was no statistically significant difference in response between women who became pregnant and those who did not, as shown in **Table 3** ($P = 0.063$). Similarly, there was a non-significant response difference between those who became pregnant and those who did not [8]. Another study found a significant difference in ovarian response between the two groups, with clinical pregnancy rates of 14.8 percent in poor-responder women and 36.7 percent in normal-responder women [11].

In addition, in the current study, AMH, FSH, LH, prolactin, and E2 were measured for females' ovarian reserve assessment, which is critical before any ICSI trial [12]. Furthermore, this information can be used to analyze and advise couples before ICSI stimulation, as well as optimize stimulation techniques. The current study found that AMH levels differed significantly between pregnant and non-pregnant women ($P < 0.05$), with pregnant women having higher levels. Other studies have supported the current study's findings. [13, 14, and 15].

According to Gomez et al. (2016), women with low serum AMH levels can become pregnant. However, the findings revealed significant differences in FSH levels between pregnant and non-pregnant women, with the mean FSH being significantly lower in pregnant women than in non-pregnant women ($P < 0.05$). Tulic also confirmed that lower basal FSH levels are associated with a positive assisted reproduction outcome [16]. According to Salama et al. [17], lower basal FSH levels are associated with chemical and clinical pregnancies.

Moreover, the current study showed no significant differences with E2, LH, prolactin, and progesterone ($P \geq 0.05$). In contrast, Al-Ghazali et al. found that E2 levels were higher in pregnant women than in non-pregnant women in 2013, indicating significant ovarian response [18]. Jiang et al. found that, despite having normal FSH, women with elevated basal E2 had poor pregnancy outcomes [19].

In a 2020 study, Pizarro et al. discovered that FSH, LH, and serum estradiol were higher, while serum progesterone was lower on the day of hCG in those who got pregnant versus those who couldn't after ICSI, with no significant relationship observed among these

parameters ($P > 0.05$). [11]. According to a different conclusion from a 2013 study by Ashrafi and other co-authors, the mean LH serum concentration in the pregnant group was significantly higher than that in the non-pregnant group ($p = 0.04$). Despite this, the serum concentrations of FSH and prolactin measured on day three did not differ significantly between the two groups ($P > 0.05$) [10]. However, basal LH and E2 levels are not assumed to be appropriate markers for differentiating infertile patients who respond differentially to ovarian stimulation [19]. The ability to assess embryos quality is critical for decreasing the chance of multiple pregnancies and rising pregnancy rates by transferring the best embryos [21].

In the current study, there was no significant difference in oocyte quality, MII, or MI germinal vesicles between pregnant and non-pregnant women. However, pregnant women had a higher GI embryo count than non-pregnant women, which was statistically significant ($P = 0.03$). The overall number of embryos, the number of GII embryos, and the number of GIII embryos were not significantly different ($P \geq 0.05$). On the other hand, Sivrikoz discovered that high-quality embryos improve pregnancy rates [20]. According to a study published in 2020 by Hassan et al., there is no difference in total oocytes, aberrant oocytes, germinal vesicle oocytes, MII, or MI oocytes between pregnant and non-pregnant women ($p > 0.05$). Furthermore, there was no discernible difference in the percentage of grade I, II, III, IV, as well as selected embryos between pregnant and non-pregnant women after ICSI ($p > 0.05$) [8].

5- Conclusions

In conclusion, the study showed that oocyte quality affects the pregnancy rate. Furthermore, the results of ICSI have strong associations with AMH and FSH levels.

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