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Predictive percent decrease in the expected metaphase II oocytes with increasing age among infertile women undergoing intracytoplasmic sperm injection.

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Disminución porcentual predictiva del número esperado de ovocitos en metafase II con el aumento de la edad en mujeres infértiles sometidas a inyección intracitoplasmática de espermatozoides.

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ABSTRACT

Objective: This study aimed to determine which variables primarily influence the number of expected mature oocytes (MII) and to establish the expected percent decrease in the number of MII oocytes retrieved in infertile patients undergoing ICSI.

Materials and Methods: In this retrospective cross-sectional study, we included infertile women aged 23 to 44 years who underwent intracytoplasmic sperm injection between January 2013 and November 2017 at an assisted reproduction center in Guayaquil, Ecuador. The study variables included patient age, infertility diagnosis, ovarian stimulation protocol, number of aspirated follicles, number of recovered oocytes, and number of MII-stage oocytes. Ethical approval was obtained from the director of the reproductive medicine clinic for handling patient medical records, and inclusion and exclusion criteria were rigorously applied. A Poisson regression model was utilized to predict the decrease in the proportion of expected MII oocytes retrieved annually with increasing age.

Results: The medical records of 244 infertile women were analyzed. There were marked differences in the number of oocytes retrieved and MII oocytes retrieved, particularly in women with ovarian insufficiency and those aged >40 years. The Poisson regression model predicted that the proportion of expected MII oocytes would decrease by 3.99% each year as the patient's age increased. Other variables in the model did not significantly predict the decrease in MII oocyte proportions.

Conclusion: This study's findings suggest a 3.99% annual decrease in the proportion of expected MII oocytes with increasing age among infertile women undergoing ICSI. These results underscore the importance of age-specific strategies in infertility treatment to optimize outcomes, particularly for women of advanced maternal age.

Keywords: Age, infertile women, intracytoplasmic sperm injection, MII oocytes retrieved, ovarian stimulation.

INTRODUCTION

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have revolutionized infertility treatment, with the retrieval of an adequate number of mature metaphase II (MII) oocytes being a critical factor for successful outcomes (1). The maturation and availability of these oocytes are influenced by various factors, including patient age, ovarian reserve, hormonal profiles, and specific infertility diagnoses such as polycystic ovary syndrome (PCOS) (2, 3). However, the decline in oocyte quantity and quality with advancing maternal age remains a significant challenge in reproductive medicine (4-7).

Despite the well-documented decline in oocyte retrieval with age, the specific impact of age on the proportion of MII oocytes retrieved remains unclear, with contradictory findings reported in the literature (8-12). Some studies suggest no significant correlation between age and oocyte maturity, while others indicate a negative correlation, further complicating treatment strategies for older women (13).

This study aims to clarify this issue by retrospectively analyzing data from infertile women who underwent ICSI. It focuses on identifying the primary variables influencing MII oocyte retrieval and quantifying the expected annual decrease in MII oocytes as age increases. The hypothesis guiding this research posits that age significantly predicts MII oocyte retrieval, with a measurable yearly decline as women age.

MATERIALS AND METHODS

Funding:

Espíritu Santo University, School of Medicine, and the Assisted Reproduction Center INNAIFEST have funded this research.

Ethical Considerations:

This study was conducted under the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, revised in 2000. Informed consent was obtained from all participants, ensuring confidentiality and anonymity when handling personal health data. As this is a retrospective study and the information handled is given directly from the patient to the doctor, signed consent from the medical directors of the reproductive clinic was given to handle patient medical records.

This retrospective cross-sectional study analyzed the medical records of 296 infertile women who underwent ICSI between January 2013 and November 2017 at a single assisted reproduction center in Guayaquil, Ecuador. Following stringent inclusion and exclusion criteria, 244 patients were selected for the study.

Inclusion Criteria:

- Cases of oocyte donors and patients diagnosed with male factor, female factor, or unexplained infertility were included, in which at least three follicles were aspirated and at least one oocyte recovered.

Exclusion Criteria:

- Women with fewer than two follicles suitable for puncture/aspiration.
- Women over 44 years old.
- Patients in whom no oocytes were recovered from follicular aspirations.

Data collection focused on the following variables: age, infertility diagnosis (anatomic female factors, endocrine factors, endometriosis, ovarian insufficiency, unexplained infertility, and male factor), ovarian stimulation protocol (rFSH + agonist GnRH, rFSH + antagonist GnRH, uFSH + hMG + agonist GnRH), number of aspirated follicles, number of recovered oocytes, and number of MII-stage oocytes.

Statistical analysis was performed using SPSS software, applying chi-square tests for categorical variables and Poisson regression to predict the relationship between age and MII oocyte retrieval. A P-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study analyzed records from 244 infertile women, with an average age of 34.83 ± 0.26 years (range: 23-44 years). The mean number of follicles aspirated per patient was 16.98 ± 0.63, with an average of 10.31 ± 0.41 oocytes recovered and 8.20 ± 0.35 MII oocytes retrieved. The majority of patients were diagnosed with either unexplained infertility (n=50) or male factor infertility (n=100), followed by anatomic factors (n=49), endocrine factors (n=7), endometriosis (n=23), and ovarian insufficiency (n=15).

Table 1: presents the total number of oocytes and MII oocytes retrieved according to the stimulation protocol and age group. Patients aged over 40 years exhibited a significantly lower proportion of MII oocytes retrieved compared to younger age groups ($P < 0.05$).

Three ovarian stimulation protocols were used, with no significant differences observed in the number of oocytes or MII oocytes retrieved across protocols. However, age had a pronounced effect, with women aged >40 showing a significant decline in the total number of oocytes and the proportion of MII oocytes retrieved ($P < 0.05$).

Figure 1. Box plot of the number of MII oocytes retrieved and age according to infertility diagnosis.

Figure 2. Decrease in expected MII oocytes retrieved with increasing age.

The Poisson regression model indicated that the proportion of expected MII oocytes decreased by 3.99% with each additional year of age. Other variables, such as stimulation protocol, number of aspirated follicles, and infertility diagnosis, did not significantly predict changes in MII oocyte retrieval.

DISCUSSION

In IVF and ICSI, retrieving an adequate number of high-quality MII oocytes is crucial for successful fertilization (13); however, in these treatments, approximately 15% of the retrieved oocytes are in prophase I or metaphase I (14-16). MII oocyte retrieval after

ovarian stimulation and follicular aspiration is influenced by different factors, such as patient age, ovarian reserve, hormonal profile, and infertility diagnosis (3, 17).

In this study, a reduced number of MII oocytes was evident in women with ovarian insufficiency. This result is in line with the findings of infertile patients with premature ovarian insufficiency who underwent IVF and presented a high number of empty follicles, limited oocyte recovery, and atretic oocytes (18, 19). Another diagnosis of infertility associated with a reduce number of MII oocytes recovered is polycystic ovary syndrome (5). In this study, patients with this disease are included in the group with endocrine diagnosis and did not present a lower number of MII oocytes compared to the other diagnoses.

Controlled ovarian stimulation has been described as an essential step for recovering oocytes for fertilization. The gonadotropin dosage influences the final number of retrieved oocytes (2, 20, 21) and is associated with the number of MII oocytes retrieved during IVF (17, 22); however, the ovarian stimulation used in this study, whether an agonist or antagonist protocol, did not affect the number of MII oocytes retrieved. Similarly, follicular aspiration of three or more follicles measuring 17, 18, 19, or 20 mm, 36 hours before aspiration did not affect the number of MII oocytes retrieved. This last result agrees with other work showing that nondominant follicles also produce many MII oocytes (23, 24).

On the other hand, we found that age impacts the number of MII oocytes retrieved in infertile patients aged >40 years. These results are consistent with some of the literature, where age has a negative correlation with oocyte maturity (10), and increasing age has been associated with a decrease in ovarian reserve and oocyte competition (8, 9) and has a negative correlation with oocyte maturity (10). However, it has also been described that women’s age was not associated with oocyte maturity ratios (4).

The results led us to question the percentage of MII oocytes retrieved lost as the patient's age increased, which was not found in the literature, at least for Ecuador. Therefore, a Poisson regression analysis was carried out to test this prediction, and the results revealed that the proportion of expected MII oocytes retrieved decreased by 3.99% each year among infertile patients undergoing IVF as the woman's age increased. In an article in

which Poisson regression was used to predict this value, the statistical model could not be adjusted to relate age to MII oocyte retrieval (17).

The limitations of this study include its retrospective design, single-center nature, and lack of data on the pregnancy rate and development. Likewise, the variability in the number of cases per diagnosis did not allow for a differentiated analysis based on age, considering the infertility diagnosis. In the same way, there was a difference in the number of cases based on the stimulus protocol, and the hormone dosage and its relationship with oocytes were not evaluated. Within the Poisson model, the patient's recurrence of treatments was not considered, nor was it whether this treatment consisted of the first or more cycles performed.

Despite all limitations of this work, the findings could have significant implications for infertility treatment, particularly for women of advanced maternal age who need more MII oocytes in IVF treatment to have a likelihood of having at least one live birth (25), being able to conclude that according to the Poisson statistical model, the proportion of expected MII oocytes retrieved decreased by 3.99% each year as the woman's age increased, among infertile patients undergoing ICSI. More exhaustive investigations with a more significant number of cases are necessary, including other vital variables of infertile patients, to determine what other variables, individually or together, influence the number of expected oocytes.

CONCLUSION

Among infertile patients undergoing ICSI, the proportion of expected MII oocytes retrieved is predicted to decrease by 3.99% each year as female age increases. These findings highlight the critical need for tailored infertility treatment protocols that consider the patient's age to optimize outcomes. Further research is essential to explore other factors that may influence MII oocyte retrieval and to refine age-specific treatment strategies such as lifestyle modification goals, the predictive quality of oocytes retrieved based on BMI, and nutritional standards.

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Tables & Figures

Table 1. Total number of oocytes and MII oocytes retrieved according to the stimulation protocol and age.

	Total oocytes retrieved (n)	Total MII oocytes (n)	Proportion total MII/total oocytes retrieved
Stimulation protocol			
• rFSH + Agonist GnRH	1897	1511	0.79

● rFSH + Antagonist GnRH	1172	965	0.82
● uFSH + hMG + Agonist GnRH	153	965	0.83
Age Groups (years)			
● ≤25	36	30	0.83
● 26 - 30	320	250	0.78
● 31 - 35	1060	826	0.78
● 36 - 40	985	814	0.83
● > 40	116	82	0.71*

*: $P < 0.05$ between patients >40 years with other age groups.

Figure 1. Box plot of number of MII oocytes retrieved and age according to infertility diagnostic.

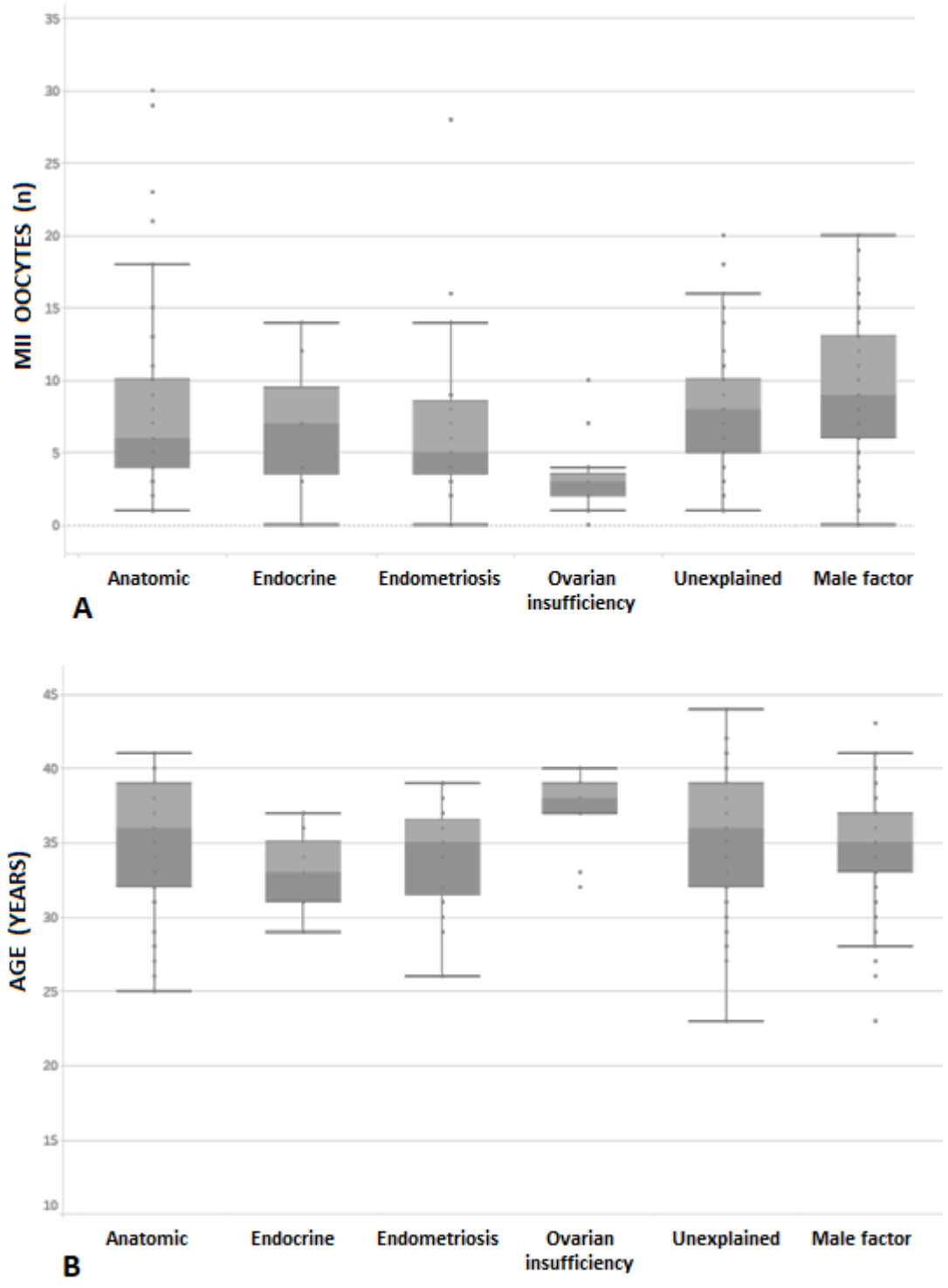

Figure 2. Decrease in expected MII oocytes retrieved with increasing age.

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