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Original Article

Prediction of ovarian response in IVF/ICSI cycles

Alfredo Cortés-Vazquez[1], Guillermo A. Goitia-Landeros[1], Miguel A. Regalado[1], Saúl R. León-Hernández[2], Alfredo L. Cortés-Algara[1], Cindy Bandala[3,4], Jesús D. Moreno-García[1], Panagiotis Drakopoulos[5,6]

[1]Instituto de Seguridad Y Servicios Sociales de Los Trabajadores del Estado, Mexico City, Mexico
[2]Investigation Support Unit, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
[3]Neuroscience Laboratory, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
[4]Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City, Mexico
[5]Center for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium
[6]Faculty of Medicine and Pharmacy, Department of Surgical and Clinical Science, Vrije Universiteit Brussel, Belgium

ABSTRACT

Objective: Our study aims to evaluate the various correlations between demographic, biochemical, ultrasound, and ovarian stimulation parameters with the percentage of mature oocytes in conventional stimulation for IVF/ICSI cycles in order to develop a predictive model to improve our understanding of the oocyte maturation process.

Methods: This is a retrospective cohort study; patients underwent conventional antagonist ovarian stimulation protocols for fresh IVF/ICSI cycles. A total of 256 IVF/ICSI cycles were included. Age, antral follicle count (AFC), baseline serum follicle-stimulating hormone (FSH) levels, baseline serum luteinizing hormone (LH) levels, baseline serum estradiol (E2) levels, peak estradiol, P4 on hCG day, the body mass index (BMI), and stimulation length were measured. The variables were tested for correlations with the number of retrieved oocytes (#RO) and the number of mature oocytes (#MO). A backward stepwise regression was performed to identify the variables that correlated more strongly with percentage of mature oocytes (%MO).

Results: A predictive equation was obtained with the variables that were not excluded in the model. % MO = 72.700 – 0.910 (Age) + 0.979 (BMI) + 1.209 (Baseline serum LH) – 0.647 (Progesterone on human Chorionic Gonadotropin day).

Conclusions: We concluded that age, the BMI, baseline serum LH, and progesterone level on hCG day may predict %MO. Prospective studies are required to validate this predictive equation.

Keywords: Oocyte, Mature, Age, body mass index, progesterone, LH

INTRODUCTION

The world entered a new era in 1978, with the birth of Louise Brown. Since then, more than five million babies have been born worldwide through *in vitro* fertilization (IVF) techniques (van Loendersloot *et al*., 2014). This global trend was not caused by a recent infertility pandemic, but by increased access to IVF treatments. Differently from common belief, IVF does not guarantee success; between 38% and 49% of the couples have unsuccessful IVF cycles even after undergoing six IVF cycles (Malizia *et al*., 2009).

One of the strategies commonly used to increase pregnancy rate is to induce multiple follicles, to produce several mature oocytes and embryos subsequently. Oocyte maturation is essential because only metaphase II (MII) oocytes are injected in intracytoplasmic sperm injection (ICSI) cycles. MI oocytes that complete maturation *in vitro* exhibit lower fertilization rates. Only sporadic pregnancies were obtained following the transfer of embryos developed from MI oocytes that had matured *in vitro* (Strassburger *et al*., 2004; Nagy *et al*., 1996). The goal of oocyte cryopreservation is generally to freeze mature oocytes for later thawing and fertilization with IVF (Lee *et al*., 2013). However, 8.6% to 20% of the oocytes retrieved after controlled ovarian stimulation are metaphase I (MI) or immature at the germinal vesicle (GV) (Beall *et al*., 2010; Parrella *et al*., 2019), with total failure in oocyte maturation occurring occasionally, leading to no mature oocytes being produced (Beall *et al*., 2010). Successful fertilization depends on synchronic cytoplasmic and nuclear maturation (Pereira *et al*., 2016). There is evidence that an increased proportion of immature oocytes (GV and MI) diminish the ability of the MII sibling oocytes to be normally fertilized, resulting in a diminished number of good-quality embryos (Parrella *et al*., 2019).

Adverse effects from obesity on natural fecundity have been reported since the 1980s, with authors looking into the isolated impact of obesity on ICSI cycles. Statistically significant differences have been observed among women with different BMI. Women with a normal BMI had more MII oocytes than women with higher BMI (Esinler *et al*., 2008). Prospective observational cohort studies have reported a significant effect of the BMI on the number of mature oocytes. Women with a body mass index (BMI) greater than 25 kg/m^2 and final oocyte maturation with 0.2mg triptorelin had a significantly lower number of mature oocytes compared to women with a BMI below 25 kg/m^2 (Lainas *et al*., 2020).

This study evaluated the various associations between demographic, biochemical, ultrasound, and ovarian stimulation parameters with ovarian response, reflected in the number of mature oocytes obtained after conventional ovarian stimulation for IVF/ICSI.

MATERIALS AND METHODS

Study Design

After attaining approval from the institution's ethics committee, we performed a retrospective cohort analysis of 256 fresh IVF/ICSI cycles. The study included patients treated at the Reproductive Endocrinology Department of the Centro Médico Nacional 20 de Noviembre of Mexico City in 2018. Patient data sets were anonymized for analysis. The individuals included in this study underwent conventional ovarian stimulation protocol without adjuvant therapy.

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Patients

All patients underwent fresh IVF/ICSI cycles. Mild stimulation and social/medical freezing cycles were excluded.

Protocol for Ovarian Stimulation

Patients underwent conventional ovarian stimulation as described in the literature (Chalumeau *et al*., 2018). Ovarian stimulation was initiated with recombinant FSH (rFSH) (Gonal F, Merck-Serono, Switzerland) at a starting dose of 150-450 IU daily depending on the age, body mass index (BMI), and ovarian reserve (OR). Physicians subjectively chose the daily rFSH starting dose. A GnRH flexible antagonist protocol was used to achieve pituitary suppression (Cetrotide, cetrorelix 0.250mg, Pierre Fabre, France) and recombinant human chorionic gonadotropin (rhCG) (Ovidrel, 250 mg, Merck-Serono, Italy) was administered to trigger ovulation when at least three leading follicles had reached a mean diameter of 18 mm. Whenever necessary, dose adjustments of rFSH were performed according to the results of ovulation monitoring (ultrasound evaluation and estradiol). Data analysis revealed that 28 patients had late follicular phase progesterone elevation, and ten had ovarian hyperstimulation syndrome.

Hormonal assays and evaluation of ovarian reserve

Tests using the same method were performed in the same laboratory (Laboratorio Clínico, CMN 20 de Noviembre) for serum basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) between cycle days 2 or 3. Serum progesterone (P4) and E2 concentration on the day of the trigger were measured. The samples were defined using an enzyme immunoassay (Axsym System, Advia Centaur; Siemens). To limit diurnal variations of hormone levels, all measurements were taken between 8 and 9 a.m.

Evaluation of ovarian reserve included antral follicle count (AFC) (2-9mm using a 2D 7.5 MHz probe, ClearVue 350, Philips, USA), baseline FSH, LH, and E2 concentrations.

Oocyte retrieval and fertilization

Oocytes were retrieved transvaginally 34-36 hours after rhCG administration. Oocytes were graded for maturity based on the morphological characteristics of the cumulus mass, corona radiata ooplasm and detached granulose membrane cells, presence or absence of a GV or the first polar body (PB) seen with a stereomicroscope, as described in the literature (Lin *et al*., 2003). Conventional IVF was performed to fertilize mature and immature oocytes. The reasons for ICSI were male infertility and fertilization failure in conventional IVF. ICSI fertilized only MII oocytes. Only in the case of ICSI or unclear maturity, the oocytes were denuded using 85 IU/ml hyaluronidase and mechanical pipetting. The embryos were cultured to the blastocyst stage in sequential media.

Endpoints

Baseline demographic characteristics analyzed included age and BMI. Baseline IVF and ICSI cycle characteristics were FSH (mIU/ml), LH (mIU/ml), and E2 (pg/ml) levels at the start of the menstrual cycle. Conventional ovarian stimulation parameters included stimulation length (days), E2 and P4 concentration (ng/ml) on the day of trigger, total and mature oocytes retrieved, and percentage of mature oocytes.

Statistical analysis

Correlations between data extracted from the Reproductive Endocrinology Department database and the selected parameters were analyzed with Pearson's coefficient. A backward stepwise regression was performed to exclude parameters without statistical significance. Data analysis was performed on SPSS version 13.0 (SPSS Inc., USA).

RESULTS

A total of 256 IVF and ICSI cycles were included; baseline demographic characteristics are shown in Table 1. Mean age was 35.5±3.1 years (24-44 years) and mean BMI was 26.8±4.0 kg/m^2 (18.6-34 kg/m^2).

Table 1 shows the biochemical parameters, which effects are shown in Table 2. On average, seven oocytes were retrieved, five of which mature, meaning that 70% were MII oocytes. The number of retrieved oocytes was significantly correlated with age, AFC, FSH, and estradiol (E2) levels on trigger day, as seen in Table 3. It is essential to note that FSH and age were significantly correlated, while higher FSH levels and older age adversely affected the number of retrieved oocytes. Higher AFC and E2 levels on trigger day had a positive significant correlation with the number of retrieved oocytes. On step 2 of the backward stepwise regression, the number of mature oocytes had a significant positive correlation (r=0.92, p=0.0001) with the total number of retrieved oocytes, in such a way that a higher number of retrieved oocytes corresponded to a greater number of mature oocytes as seen in Figure 1. After step 3, the percentage of mature oocytes was significantly correlated with the number of retrieved oocytes, BMI, AFC,

Table 1. Baseline patient demographic and IVF/ICS cycle characteristics

	(n=256)
Stimulation length (days)	9.80±1.34
BMI (Kg/m^2)	26.80±4.0
Age (years)	35.50±3.10
AFC	13.87±8.37
Baseline serum FSH (mIU/ml)	6.82±3.21
Baseline serum LH (mIU/ml)	3.97±2.16
Peak E2 (pg/ml)	3181.69±6017.52
P4 on hCG day (ng/ml)	1.60±6.12
Baseline serum E2(pg/ml)	65.9077±106.98

Data are expressed as mean ± standard deviation. AFC= antral follicle count, BMI=body mass index, FSH= follicle stimulating hormone, LH= luteinizing hormone, E2= estradiol, P4=progesterone, hCG= human chorionic gonadotropin.

Table 2. Ovarian stimulation cycle outcomes	
	(n=256)
Oocytes retrieved (n)	7.01±4.44
Mature oocytes (n)	5.0±3.59
Mature oocytes (n)	70.31±21.08

Data are expressed as mean ± SD

Table 3. Correlations between oocytes retrieved		
Parameter	Coefficient r	*p*
Age	-0.19	0.002
AFC	0.42	0.0001
Baseline serum FSH (mIU/ml)	-0.25	0.0001
Peak E2	0.38	0.0001
BMI	-0.004	0.94
Stimulation length	0.04	0.50
Baseline serum LH (MIU/ml)	-0.06	0.32
P4 on hCG day	-0.03	0.58
Baseline serum E2	0.00	0.99

AFC= antral follicle count, FSH= follicle stimulating hormone, LH= luteinizing hormone, E2= estradiol, P4=progesterone, hCG= human chorionic gonadotropin.

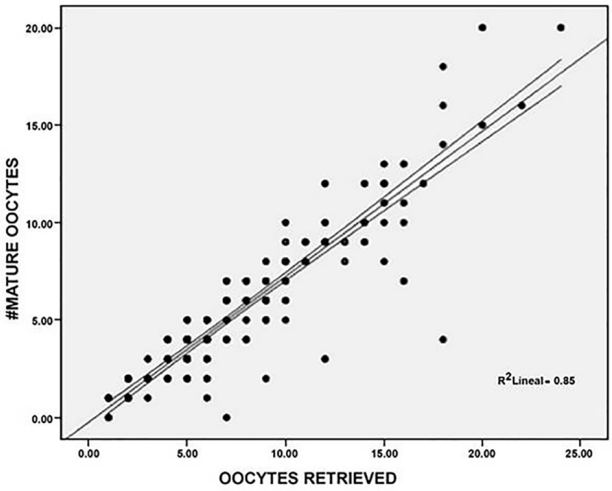

Figure 1. Correlation between number of retrieved oocyte and number of mature oocytes. #Mature oocyte= number of mature oocytes

and progesterone (P4) levels on trigger day. The process was carried out until all variables were excluded in the 6th step, at which time an equation to predict % MO was developed.

It is essential to consider the fact that the constant 72.700 was also significant (*p*=0001), in it a condition required for the model to be valid. Our model was potent to predict the number of retrieved oocytes, the number of mature oocytes, and %OM.

Table 4 shows the variables excluded with the backward stepwise regression. It is crucial to understand that when patients were categorized according to age (<36 years old or >36 years old), there were relevant differences in AFC, FSH levels, baseline LH level and, above all, in the number of retrieved oocytes, number of mature oocytes, and %MO (Table 4). When patients were categorized according to the BMI, differences were seen in FSH levels and AFC, but mainly on the number of mature oocytes and even more on %MO. However, they did not differ in the number of retrieved oocytes.

DISCUSSION

Around 2% of women have primary infertility, and approximately 10% of women have secondary infertility, according to a World Health Organization survey (Nisal *et al*., 2020). Personalized assisted reproductive treatments help to reduce the financial burden that these treatments involve. Some studies have shown that dosages derived from predictive models are nearly 40% lower (Nisal *et al*., 2020) than the dosages prescribed in IVF clinics, with greater numbers of mature follicles. Patient-tailored care decreases the number of daily tests and increases patient satisfaction.

Patients with low oocyte maturity or an inability to retrieve mature oocytes have overwhelming prognoses on account of having fewer embryos for transfer. In our study, we found that baseline LH levels had a significant impact on the percentage of MII oocytes. There is evidence in cattle that LH regulates the expression of cell cycle-related transcripts such as STMN1, BCAR3, ESCO2, PTTG1, or NCAPG, which are associated with DNA stabilization, oogenesis, folliculogenesis and, most notably, with the acquisition of competence (Sirard, 2016). Cell cycle regulation and function is a complex process, regulated by numerous genes, such as cyclin B1 or STMN1, which exhibit lower levels of mRNA in cetrorelix-treated cattle (Sirard, 2016). Therefore, the suppression of baseline LH during that period might reduce the quality of the oocytes.

We found that age negatively affected the percentage of mature oocytes, more specifically in individuals older than 36 years with a normal BMI. Below that threshold, age did not have an impact on healthy women irrespective of ovarian reserve. Other authors have reached the same conclusions and found no correlation between AFC and oocyte competence in women younger than 35 years (López

Table 4. Excluded Variables[f]

Model	Beta	t	Sig.	Partial Correlation	Collinearity statistic	
					Tolerance	
2	Baseline serum FSH	-.010[a]	-.134	.893	-.009	.713
3	Baseline serum FSH	-.011[b]	-.144	.885	-.009	.714
	Stimulation duration	-.024[b]	-.377	.707	-.025	.974
4	Baseline serum FSH	-.017[c]	-.230	.818	-.015	.721
	Stimulation duration	-.020[c]	-.321	.749	-.021	.978
	Peak E_2	-.055[c]	.844	.400	.055	.910
5	Baseline serum FSH	-.006[d]	-.083	.934	-.005	.741
	Stimulation duration	-.021[d]	-.334	.739	-.022	.978
	Peak E_2	-.055[d]	.852	.395	.056	.910
6	Baseline serum FSH	-.023[e]	-.330	.742	-.022	.776
	Stimulation duration	-.022[e]	-.355	.723	-.023	.978
	Peak E_2	-.071[e]	1.141	.255	.074	.983
	Baseline serum E_2	-.058[e]	.927	.355	.060	.981
	AFC	-.075[e]	1.179	.240	.077	.943

[a.] Predictive variables in the model: (Constant), Baseline serum E2, P4 on hCG day, peak E2, BMI, Stimulation duration, Age, AFC, baseline serum LH
[b.] Predictive variables in the model: (Constant), Baseline serum E2, P4 on hCG day, peak E2, BMI, Age, AFC, baseline serum LH
[c.] Predictive variables in the model: (Constant), Baseline serum E2, P4 on hCG day, BMI, Age, AFC, baseline serum LH
[d.] Predictive variables in the model: (Constant), P4 on hCG day, BMI, Age, AFC, baseline serum LH
[e.] Predictive variables in the model: (Constant), P4 on hCG day, BMI, Age, baseline serum LH
[f.] Dependent variables: % mature oocytes

Martín *et al*., 2018). However, not all populations seem to behave in the same way, and some authors observed that the rate of immature oocyte was not proportional to female patient age. Indeed, the highest rates of immature oocytes were seen in women older than 41 years, followed women younger than 30 years old (Lee *et al*., 2012).

It is essential to discuss and encourage future research on the effects of stimulation on %MO. We observed that stimulation length did not correlate with %MO, as described by other authors, who found that delaying oocyte maturation trigger by 24 hours did not affect the number of MII oocytes (Davar *et al*., 2017), although other clinicians have different opinions and some concluded that delaying the administration of hCG by 24 hours with progesterone levels of less than 1ng/ml might yield a higher number of MII oocytes (Vandekerckhove *et al*., 2014). Unquestionably, the ovarian reserve plays a pivotal role in the outcome of stimulation. At the same time, normal responders had significantly lower maturation rates with less than six stimulation days and low responders had similar stimulation days with similar maturation rates with either short or long stimulation length, as observed by other authors (Yang *et al*., 2019).

The role of progesterone in ovarian stimulation cycles and its effect on the maturation process must be further recognized. Our study found a negative effect of progesterone on hCG day and %MO. Tanada *et al.* (2017) observed the same effect and found that premature late follicular phase progesterone increases above 1.3 ng/ml might adversely affect the oocyte maturation process.

Recently, Simon *et al*. (2019) evaluated the progesterone to mature oocytes index (PMOI) and found that lower PMOI was associated with increased live births and a statistically significant increased number of mature oocytes. They also found that the PMOI was increased mainly in low ovarian response, which was evaluated through the Ovarian Sensitivity Index (OSI). Likewise, it should be noted that high blood progesterone levels on the day of ovulation trigger may reflect either many follicles with proper follicular fluid progesterone levels or a few follicles with high follicular fluid progesterone levels (Grin *et al*., 2018).

Huang *et al*. (2016) published a retrospective study with 4236 fresh IVF cycles, in which progesterone levels higher than 2.0ng/ml were associated with a reduction on the rate of top quality embryos. It might be worth encouraging research to establish a progesterone threshold in humans in which %MO is maximal. Also, it is essential to address the highly important role of cumulus cells in oocyte health; increased cumulus cell apoptosis is followed by impaired oocyte maturation and lower fertilization rates (Dumesic *et al*., 2015). Thus, ovarian stimulation protocols that apparently improve cumulus cells activity might have a remarkable effect on oocyte health, consequently increasing the proportion of oocytes that develop into healthy embryos and eventually yield live births. This is particularly relevant, since approximately less than 7% of the oocytes retrieved by IVF generate a healthy embryo (Dumesic *et al*., 2015).

We found a positive correlation between the BMI and %MO. However, other authors have not observed this positive correlation. They found that overweight and obese women had altered oocyte morphology and lower fertilization rates, particularly when aged less than 35 years (Dumesic *et al*., 2015). Some studies demonstrated that hyperglycemia and high lipid concentrations disrupt somatic cell-oocyte signaling, leading to impaired growth and delayed maturation (Dumesic *et al*., 2015; Varghese *et al*., 2011). Primarily high lipid concentrations were associated with germinal vesicle breakdown inhibition, which prevents the oocyte from proceeding beyond the arrested prophase 1 stage (Varghese *et al*., 2011). In addition to obesity, it is crucial to keep in mind some infertility-associated pathologies, such as polycystic ovary syndrome (PCOS), in which higher androgen levels such as androstenedione are observed, a steroid hormone linked to oocyte maturation inhibition and spindle assembly prevention, which alters chromosomal alignment in oocytes (Tarumi *et al*., 2012),

best known as maturation failure type 2 (Beal *et al*., 2010). Lainas *et al*. (2020) conducted a prospective observational cohort study, in which the BMI significantly affected the number of mature oocytes. Women with a BMI higher than 25 kg/m^2 had significantly fewer mature oocytes when compared to women with a BMI below 25kg/m^2 (Esinler *et al*., 2008; Lainas *et al*., 2020). Above all, it is crucial to note that although there is no consensus about the optimal dose for GnRHa in trigger protocols, the most popular dose of GnRH agonist to trigger final oocyte maturation is 0.2mg triptorelin (Engmann *et al*., 2016). Consequently, a dose adjustment in the oocyte maturation trigger protocol for obese women is suggested, mainly when a GnRH agonist trigger is indicated (Lainas *et al*., 2020). We hypothesize that obesity increases the distribution volume and attenuates the effects of the continuously elevated FSH levels during ovarian stimulation, therefore reducing the quantity of precursor steroids generated and the ability of the ovary to convert them into estrogen.

To our knowledge, this is the first model to predict %OM. It is valuable to know in advance whether a patient might have low %OM, so that further procedures such as rescue IVM or dual trigger might be applied to increase the number of oocytes that eventually develop into viable embryos. There are several and very promising approaches to enhance ovarian stimulation protocols and lower serum progesterone levels, including the administration of corticosteroids in the follicular phase, reduction of FSH stimulation intensity towards the end of stimulation, use of coriofollitropin alpha, and stimulation length reduction (Lawrenz *et al*., 2018). The weaknesses of our study include the way oocyte maturity was assessed, the fact that it is a retrospective study, and the limited number of patients. Additional prospective studies are required to validate the results published herein.

CONCLUSIONS

The percentage of mature oocytes retrieved after conventional ovarian stimulation was strongly correlated with baseline serum LH and P4 on hCG day levels, age, and the BMI. Further prospective studies must be performed to confirm and validate these findings.

CONFLICT OF INTEREST

None.

Corresponding author
Alfredo Cortés-Vazquez
Instituto de Seguridad Y Servicios Sociales de Los Trabajadores del Estado
Mexico City, Mexico
Email: alfredo.cortes.vazquez@gmail.com

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