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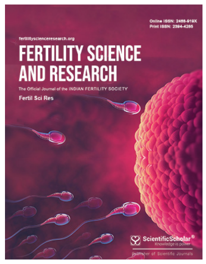

Original Article

From Oocyte to Blastocyst: A Comparison of IVF Embryo Attrition Rates Based on Ovarian Reserve

Valerie Chen[1], Lauren Kendall Rauchfuss[2], Yan Li[3], Alessandra J. Ainsworth[2], Samir N. Babayev[4], Chandra Camilla Paff Shenoy[2]

[1]Department of Obstetrics and Gynaecology, [2]Division of Reproductive Endocrinology and Infertility, [3]Department of Quantitative Health Science, Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA, [4]Department of Obstetrics and Gynaecology, Karabakh University Clinic, Khankendi, Azerbaijan.

***Corresponding author:**
Valerie Chen,
Department of Obstetrics and Gynaecology, Mayo Clinic, Rochester, MN, USA.

vchen812@gmail.com

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ABSTRACT

Objectives: The effect of ovarian reserve on expected in vitro fertilisation (IVF) attrition remains controversial. This study analyses IVF attrition rates based on ovarian reserve and stimulation protocol to create customised pre-treatment counselling tools for assisting clinicians in setting accurate patient expectations.

Material and Methods: We completed a retrospective chart review of 18–44-year-old patients who underwent IVF treatment at a single academic institution between January 1, 2013, and March 23, 2023. Cycle outcomes, number of retrieved oocytes, mature oocytes, fertilised embryos, and blastocysts were analysed for patients with polycystic ovary syndrome (PCOS), unexplained infertility, and diminished ovarian reserve (DOR). A Poisson regression model was used to compare oocyte maturation, fertilisation, and blastulation rates among groups, adjusted for age, body mass index, race, and insemination method.

Results: Three hundred and thirteen couples underwent a total of 385 IVF cycles analysed in this study. There were 109 patients who underwent 120 cycles in the unexplained infertility group (31% cycles), 133 patients with 143 cycles in the PCOS group (37% cycles), 40 patients with 45 cycles in the DOR antagonist stimulation group (12% cycles), and 39 patients with 77 cycles in the DOR minimal stimulation group (20% cycles). No differences in oocyte maturation, fertilisation, or blastulation rate were seen among PCOS or DOR antagonist cycle groups when compared to unexplained infertility. After adjusting for confounders, blastulation rate was higher for the DOR minimal stimulation group compared to unexplained infertility (1.37-fold change, p = 0.04).

Conclusion: Rates of oocyte maturation, fertilisation, and blastulation were similar among all antagonist protocol cycles regardless of ovarian reserve. However, patients with DOR who undergo minimal stimulation may have modestly higher blastulation rates compared to DOR patients who undergo the antagonist protocol.

Keywords: Diminished ovarian reserve, In vitro fertilisation, Infertility, Polycystic ovary syndrome

INTRODUCTION

In vitro fertilisation (IVF) treatment demands considerable time, emotion, and financial investment from the patient, making it imperative that clinicians set hopeful but realistic expectations prior to treatment start. Effective counselling is particularly important regarding the attrition that occurs with each step of the retrieval and fertilisation process. Attention to the number of oocytes and embryos becomes a crucial objective milestone for patients throughout this journey, and effective provider communication is critical for setting realistic expectations and defining relative success.[1] Most patient-facing models that explain attrition show average numbers irrespective of fertility diagnosis. While this is helpful for patients with average ovarian reserve, it is often not relevant for patients with robust or diminished ovarian reserve (DOR).

The impact of ovarian reserve on IVF attrition rate remains controversial. Some studies suggest that both high and low ovarian reserve, such as with polycystic ovarian syndrome (PCOS) and DOR, result in inferior oocyte quality that may lead to worse oocyte maturity or blastulation rates.[2–4] Therefore, it might not be reasonable to expect patients with extremes of ovarian reserve to have the same attrition rates as those with normal ovarian reserve.

There are many variations in oocyte stimulation protocol, often driven by patient medical history, indication for IVF, or previous IVF outcomes. For patients with DOR, clinicians commonly compare high-dose gonadotropin stimulation against stimulation with oral medications and concurrent low-dose gonadotropins (sometimes referred to as minimal stimulation). Existing literature has shown minimal stimulation to be non-inferior to high-dose protocols when considering pregnancy rates.[5] Advantages of minimal stimulation may include reduced costs, lower medication exposure, decreased risk of hyperstimulation, and increased patient satisfaction.[6–9] Lower medication exposure with minimal stimulation may better replicate the physiologic environment during folliculogenesis, which has been theorised to benefit oocyte quality.

In this study, we sought to compare fertilisation and blastulation rates for high, normal, and low oocyte stimulation responders. Additionally, we compared attrition rates for patients with DOR who underwent high-dose gonadotropin versus minimal stimulation.

MATERIAL AND METHODS

This retrospective chart review was determined to be IRB-exempt by the Mayo Clinic Institutional Review Board. We included patients aged 18–44 years who underwent IVF treatment for PCOS, unexplained infertility, or DOR between January 1, 2013, and March 23, 2023, at the Mayo Clinic in Rochester, MN. Exclusions included patients under 18 years of age at the time of stimulation start; those who underwent oocyte cryopreservation; those who utilised donor oocytes or gametes; those who had a cleavage stage embryo transfer; those who utilised surgically extracted sperm; those who had a diagnosis of tubal factor, uterine factor, male factor, or genetic causes of infertility; and those who underwent protocols other than antagonist or minimal stimulation.

Patients were stratified into three categories of ovarian reserve: normal ovarian reserve (unexplained infertility), PCOS, and DOR. PCOS was diagnosed based on the 2003 Rotterdam Criteria, with patients meeting at least two of the following: clinical or laboratory evidence of hyperandrogenism, anovulation or oligo-ovulation, and polycystic ovaries on ultrasound.[10] The diagnosis of DOR was assigned by the treating provider, and all patients in this cohort had an anti-Mullerian Hormone (AMH) level of <1.1 ng/ml, a cutoff for poor responders to IVF previously described by the Bologna criteria.[11] The DOR cycles were further stratified by antagonist protocol and minimal stimulation protocol.

All patients with PCOS and unexplained infertility underwent the antagonist protocol for ovarian stimulation. A subset of DOR cycles also used the antagonist protocol at the provider's discretion. In our institute's antagonist protocol, gonadotropins are started on cycle day three using recombinant Follitropin alpha/beta and menotropins (Menopur®, Ferring Pharmaceuticals, USA), administered together in the evening. Ganirelix acetate 250 mcg (Fyremadel®, Ferring Pharmaceuticals, India) is added once daily once E2 reaches or exceeds 300 pg/ml. Ovulation is triggered with either chorionic gonadotropin (Pregynl®, Organon USA Inc., USA) or leuprolide acetate (Lupron®, AbbVie Pharmaceuticals, Japan) when at least two follicles meet or exceed 18 mm in size and half of the cohort of follicles measure greater than 15 mm.

The remaining subset of DOR patients underwent the minimal stimulation protocol. In this protocol, stimulation is started on cycle day three with daily generic clomiphene citrate 100 mg. Daily cetrorelix acetate 125 mcg (Cetrotide®, ASTA Medica, Germany) and every other day menotropins 150 IU (Menopur®, Ferring Pharmaceuticals, USA) are started when oestradiol levels meet or exceed 300 pg/ml. Chorionic gonadotropin (Pregynl®, Organon USA Inc., USA) trigger is administered when at least one follicle reaches 18 mm.

Statistical Analysis

The outcome variables were the number of oocytes retrieved, mature oocyte count, fertilised embryo count, blastocyst count, oocyte maturation rate, fertilisation rate, and blastulation rate. To adjust for population imbalance, patients' age, race (White, Non-White, and Unknown), body mass index (BMI), AMH, and insemination type (conventional or intracytoplasmic sperm injection [ICSI]) were included as covariates in the fitted models. A Poisson regression model was utilised for the dependent variables to calculate attrition rates.

RESULTS

Population

This study included 313 patients/couples who underwent 385 IVF cycles. There were 109 patients who underwent 120 cycles in the unexplained infertility group (31% cycles), 133 patients with 143 cycles in the PCOS group (37% cycles), 40 patients with 45 cycles in the DOR antagonist stimulation group (12% cycles), and 39 patients with 77 cycles in the DOR minimal stimulation group (20% cycles).

Unsurprisingly, the age differed among groups, with the highest mean age of 36.5 years in the DOR minimal stimulation group and the youngest mean age of 31.0 years in the PCOS group ($p < 0.0001$) [Table 1]. Most participants from the four groups identified as White, which is consistent with our clinic's demographics. The mean BMI in all four groups reflected national averages in the United States. As expected, based on the study design, there were marked differences in mean AMH levels in the different infertility groups. Insemination type, determined by our embryology team, also varied between groups ($p = 0.04$). Baseline differences between the groups were adjusted for during further statistical analysis.

Outcome Comparison Between Four Groups

Oocyte maturation and fertilisation rates were similar across all groups regardless of ovarian reserve or stimulation protocol [Table 2]. In addition, blastulation rates did not differ between any groups that underwent the antagonist protocol, irrespective of ovarian reserve. However, stratifying by stimulation protocol yielded a statistically significant difference in blastulation rate between DOR groups when compared to controls, with a 45% blastulation rate in the antagonist protocol group and 58% in the minimal stimulation group ($p = 0.04$).

Counselling Diagram

Using the data in Table 3, a graphic depiction was created for use in clinical counselling [Figure 1]. For simplicity, the number of eggs retrieved, mature eggs, embryos, and blastocysts was rounded to the nearest whole number. Oocyte maturation, fertilisation, and blastulation rates were rounded to the nearest 5%.

DISCUSSION

In our study, no differences in IVF attrition rates were found based on infertility diagnosis for patients who underwent the antagonist protocol. Based on these results, it is reasonable to counsel patients that their blastocyst yield should correlate with oocytes retrieved, regardless of ovarian reserve. Despite similarities in attrition percentages between these groups, a pictorial counselling tool that more accurately portrays both estimates of absolute numbers and percentages will be helpful for personalised patient counselling.

One exception was among DOR patients who underwent minimal stimulation. This group had lower overall attrition compared to the antagonist groups (average numbers: 3.0 oocytes, 2.5 mature, 2.0 fertilised 2PN embryos, and 1.5 blastocysts). Statistically, this was demonstrated by a difference in blastulation rate between DOR-minimal stimulation cycles compared to controls (1.37-fold change, $p = 0.04$), whereas no difference was noted in blastulation rates between DOR-antagonist cycles and controls (1.0-fold change, $p = 0.97$). Current literature suggests that minimal stimulation is at least non-inferior to conventional stimulation protocols for DOR patients,[5] and may have benefits such as reduced risk for ovarian hyperstimulation, thromboembolism, lower medication cost, and improved patient satisfaction.[6,7] Our study found a higher blastulation rate in minimal stimulation cycles for DOR patients compared to controls, contributing to a growing body of literature favouring this stimulation method for the DOR population. One reason for this may be that lower-dose medications more closely mimic the natural physiology of follicular development, with the potential to create higher-quality oocytes and embryos. Although the absolute mean number of blastocysts was slightly lower in minimal stimulation (1.5) compared to antagonist protocol (2.0) among DOR patients, it is important to consider that minimal stimulation has a significantly lower cost per cycle, and most patients start treatment with the intent of multiple cycles.

The question of whether PCOS patients have lower oocyte quality remains controversial. Several studies show that more oocytes retrieved in PCOS patients do not always translate to more blastocysts or live births compared to non-PCOS patients [3,4,12] though studies vary in which step contributes to the greatest attrition. Conversely, other studies have found no difference in fertilisation rates among PCOS patients.[13] Our study did not find a significant difference in attrition rates among PCOS patients compared to unexplained infertility controls at any step. The variations between studies may be explained by discrepancies in stimulation protocols as well as in the control group among studies. Our study chose a control group of unexplained infertility patients with a normal mean AMH (3.5) compared to PCOS (8.6) to better elicit differences in oocyte potential caused by high response to stimulation. Additionally, our study contained more PCOS patients compared to many prior studies. Of note, in our study, PCOS was diagnosed based on the 2003 Rotterdam Criteria, which has since been updated with the 2023 International Evidence-based Guideline.[14] In the new guidelines, patients with both irregular cycles and clinical hyperandrogenism meet the diagnosis of PCOS regardless of imaging findings. Furthermore, the updated guidelines state that AMH may be used instead of ultrasound in equivocal cases, but neither imaging nor AMH should be applied to adolescent patients due to poor specificity. In our study, differences in PCOS diagnosis guidelines are unlikely to result in a significant difference since adolescents, who may experience the greatest difference in PCOS diagnosis based on the new guidelines, are excluded as a patient population. Nonetheless, in the future, it will be worthwhile to see how these changes to PCOS diagnosis affect fertility care outcomes.

Table 1: Demographic characteristics based on infertility diagnosis.

	Unexplained (n = 120)	PCOS (n = 143)	DOR, conv stim (n = 45)	DOR, minimal stimulation (n = 77)	p-value
Age	33.2 (4.0)	31.0 (4.3)	35.6 (4.7)	36.5(3.7)	<0.0001[a]
BMI	26.3 (5.3)	29.4 (6.7)	27.8 (5.8)	29.0 (7.2)	0.01
AMH	3.5 (2.7)[3]	8.6 (6.4)	0.7 (0.2)	0.6 (0.3)	<0.0001
Race n (%)					0.01[c]
White	97 (80.8)	128 (89.5)	31 (68.9)	67 (87.0)	
Non-White	13 (10.8)	7 (4.9)	12 (26.7)	8 (10.4)	
Unknown	10 (8.3)	8 (5.6)	2 (4.4)	2 (2.6)	
Insemination n (%)					0.04[b]
Conventional	27 (22.5)	51 (35.7)	9 (20.0)	27 (35.1)[1]	
ICSI	93 (77.5)	92 (64.3)	36 (80.0)	50 (64.9)	

Data represents the mean (SD) or number (percentage) unless otherwise specified. Superscripts indicate the counts of undocumented/unreported values, which are excluded from the percentage calculation.
[a]t-test used for continuous variables. [b]χ^2 test used for categorical variables as appropriate. [c]Fisher exact test used for categorical variables as appropriate.
BMI: Body mass index, AMH: Anti-Müllerian hormone, ICSI: Intracytoplasmic sperm injection, PCOS: Polycystic ovarian syndrome, DOR: Diminished ovarian reserve.

Table 2: Comparison of oocyte maturation, fertilization, and blastulation rates based on infertility diagnosis.

Oocyte maturation rate			
	Fold change	95% CI	p-value[a]
PCOS	1.04	0.97, 1.12	0.24
DOR, conv stim	0.93	0.81, 1.06	0.28
DOR, minimal stimulation	1.07	0.92, 1.25	0.36
Fertilisation rate			
	Fold change	95% CI	p-value[a]
PCOS	0.94	0.86, 1.03	0.16
DOR, conv stim	0.92	0.78, 1.08	0.32
DOR, minimal stimulation	1.03	0.86, 1.23	0.71
Blastulation rate			
	Fold change	95% CI	p-value[a]
PCOS	1.04	0.93, 1.17	0.48
DOR, conv stim	1.00	0.78, 1.25	0.97
DOR, minimal stimulation	1.37	1.09, 1.69	0.0049

[a]p-value is calculated from either a negative binomial or Poisson regression model.
Fold change is calculated by comparing the corresponding outcome variable to the unexplained infertility (control) group.
The covariates included in the regression models are age, BMI, AMH, race (White, Non-White) and insemination type. PCOS: Polycystic ovarian syndrome, DOR: Diminished ovarian reserve, CI: Confidence interval.

Whether DOR patients have poorer fertilisation outcomes is similarly controversial, though the literature available to investigate this question is less robust compared to PCOS. Some studies show lower oocyte maturation rates compared to normal ovarian reserve controls,[15] suggesting that the number and quality of oocytes diminish concurrently. However, our study found no difference in oocyte maturation or fertilisation rate in DOR patients compared to controls. An incremental increase in blastulation rate was noted among DOR patients who underwent minimal stimulation. Because the minimal stimulation protocol relies on a selective oestrogen receptor modulator and a gonadotropin-releasing hormone (GnRH) antagonist to stimulate pituitary production of gonadotropins, it may better replicate physiologic ovarian stimulation, leading to higher-quality oocytes.

This study takes a unique approach to post-retrieval patient counselling and has several strengths. It was performed at a single academic centre over 10 years and focuses on the practical translation of the results findings into a patient counselling tool. We also present a novel finding regarding the potential benefit, rather than simply non-inferiority, of minimal stimulation in patients with DOR.

Limitations to this study include a lack of patient diversity, a retrospective nature, and the use of blastulation, rather than live birth, as the end metric. In addition, this is a single-centre study where doses and protocols may be unique to the institution and limit generalisability. Lastly, limited sample size prevented direct comparisons between DOR cycles that used different protocols, and fold-change calculations were based on comparisons to unexplained

Table 3: Summary statistics based on infertility diagnosis.

	Unexplained (n = 120)	PCOS (n = 143)	DOR, antag stim (n = 45)	DOR, minimal stimulation (n = 77)
Retrieved oocytes (n)	17.7 (11, 21)	24.4 (16, 31)	8.0 (5, 10)	3.0 (2, 4)
Matured oocytes (n)	13.2 (8, 16)	18.8 (12, 24)	5.7 (3, 8)	2.5 (2, 3)
2PN embryos (n)	9.5 (6, 12)	12.5 (8, 16)	3.9 (2, 5)	2.0 (1, 3)
Blastocysts (n)	4.9 (2, 6)	7.4 (4, 9)	2.0 (1, 3)	1.5 (0, 2)
Oocyte maturation rate (%)	77 (68, 87)	78 (68, 92)	72 (52, 88)	85 (75, 100)
Fertilisation rate (%)	73 (62, 87)	68 (59, 82)	69 (53, 86)	74 (50, 100)
Blastulation rate (%)	50 (33, 70)	59 (44, 78)	45 (25, 67)	65 (0, 100)

Data represents mean (25% quantile, median, 75% quantile). PCOS: Polycystic ovarian syndrome, DOR: Diminished ovarian reserve.

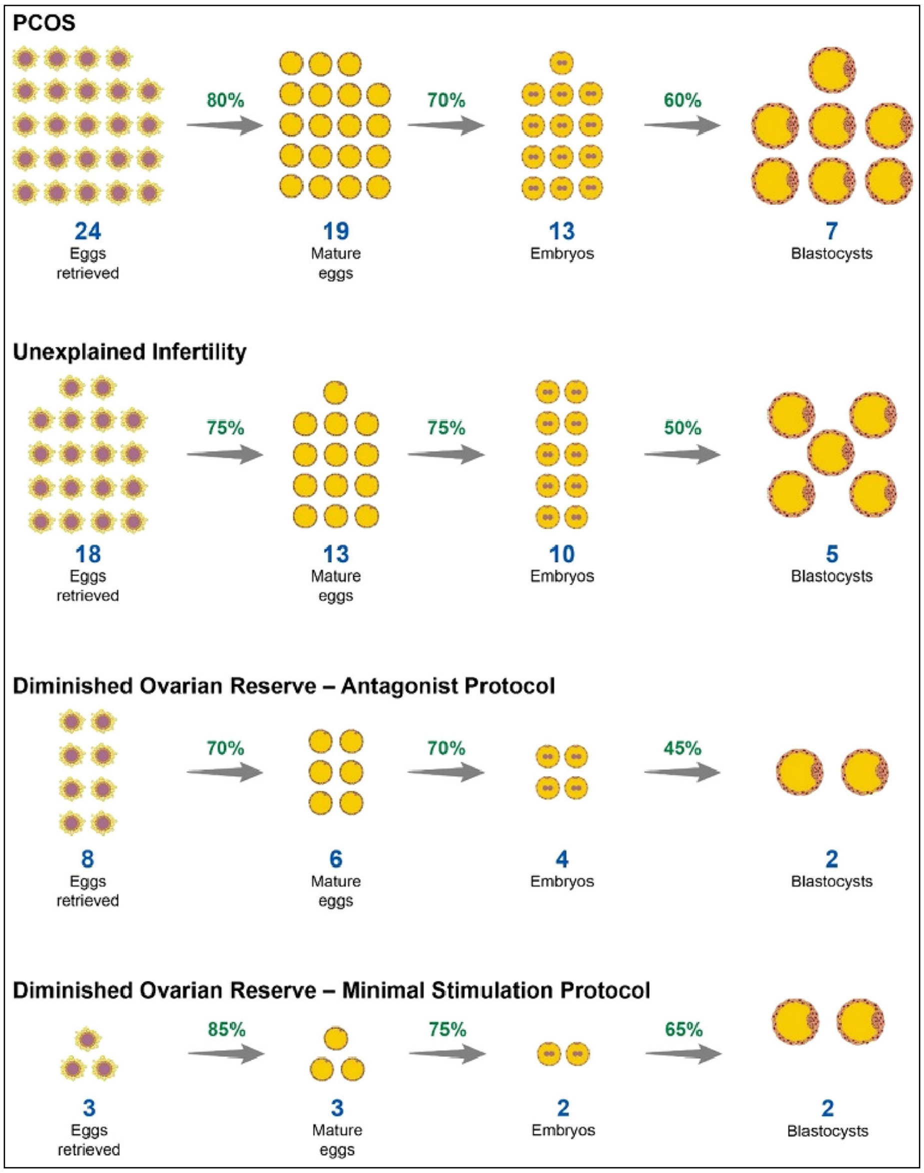

Figure 1: IVF attrition counseling diagram based on ovarian reserve. IVF: In vitro fertilisation, PCOS: Polycystic ovarian syndrome.

infertility rather than direct comparisons between DOR patients, which may be more clinically relevant.

Our results suggest that patients may be counselled that, regardless of ovarian reserve, oocytes can be expected to follow a similar pattern of attrition into the final blastocyst count. Minimal stimulation can be considered for DOR patients with the potential for a higher blastulation rate and lower medication costs.

CONCLUSION

For patients undergoing antagonist protocol IVF cycles, ovarian reserve does not appear to impact embryo attrition rates. However, minimal stimulation protocols utilised for those with DOR had a distinct advantage of a higher blastulation rate compared to a similar patient population undergoing stimulation with high-dose gonadotropins.

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These data were presented as a poster presentation at the Pacific Coast Reproductive Society Conference in Indian Wells, CA, in March 2024. It has not been published and is not up for consideration elsewhere.

Author's contributions

VC, LKR, YL, AJA, SNB: Study design and interpretation of data; LMKR, VC, YL and CCS: Data collection and analysis; VC and CCS: Wrote the first draft of the manuscript. All authors commented on previous versions and read and approved the final manuscript.

Ethical approval: The research/study was approved by the Institutional Review Board at Mayo Clinic IRB, number 23-001693, dated 3rd October 2023.

Declaration of patient's consent: Patient's consent is not required as the patient's identity is not disclosed or compromised.

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