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Immature oocyte proportion in a cohort led to poor embryo development but did not reduce clinical pregnancy rate

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Abstract

Purpose This study aimed to evaluate the effects of immature oocyte proportion in a cohort on both IVF laboratory and clinical outcomes.

Materials and methods This retrospective cohort study took place at Morula IVF Jakarta Clinic from January 2016 to July 2020. A total of 1.826 couples undergoing IVF-ICSI/IMSI were included and classified into four groups according to the proportion of immature oocytes retrieved during OPU as follows: (1) immature ≤ 15% ($n = 1.064$), (2) immature 16–25% ($n = 369$), (3) immature 26–50% ($n = 331$), and (4) immature > 50% ($n = 62$). Primary outcomes were clinical pregnancy and miscarriage. Embryology laboratory results were assessed as the secondary outcomes. Statistical analyses were carried out utilizing Kruskal–Wallis or chi-square tests. p-value < 0.05 was considered statistically significant.

Results Increased proportion of immature oocytes in a cohort was significantly associated with body mass index, tubal factors, and estradiol level on trigger day ($p < 0.05$). Neither clinical pregnancy nor miscarriage was associated with the immature oocyte proportion (adjusted p-value = 0.872 and $p = 0.345$, respectively). However, a higher proportion of immature oocytes significantly reduced the total number of fertilized oocytes, number of top-quality cleavages, and blastocysts ($p < 0.001$). Furthermore, embryo transfer cancelation rates due to poor embryo quality were elevated significantly.

Conclusion Despite overall poor embryo development in the laboratory, our study seems to suggest that the proportion of immature oocytes in a cohort has no impact on clinical pregnancy and miscarriage rate in IVF program.

Keywords Immature oocytes, In vitro fertilization, Oocytes, Embryo development

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Introduction

Controlled ovarian stimulation (COS) is a common procedure in IVF that is intended to yield multiple oocytes. Increased number of retrieved oocytes would elevate the probability of obtaining good quality embryos, thus increasing the likelihood of pregnancy [1, 2]. Various stimulation protocols are now available to attain individualized and desirable outcomes [3]. However, regardless of the COS protocols, up to 30% of retrieved oocytes during ovum pickup (OPU) are immature, at either the germinal vesicle (GV) or metaphase I (MI) stage [4]. Some of these oocytes eventually extrude the first polar body

and mature following an overnight culture, while others remain immature and are discarded [5].

Dyssynchronous follicular development is considered an underlying factor for the loss of oocyte resources [6]. Physiologically, LH surge triggers a germinal vesicle breakdown followed by a meiotic spindle assembly, releasing the first polar body to reduce the genetic material by half. Subsequent arrest of meiosis occurs when it reaches the metaphase of the second meiotic division (MII), also known as the nuclear maturation stage. Concurrently, to ultimately produce fertilizable oocytes, cytoplasmic maturation is characterized by structural changes in endoplasmic reticulum and mitochondria, which facilitates the completion of nuclear maturation, fertilization, and early embryo development, thus a contributary element for implantation, pregnancy, and normal fetal development [7–9]. Principally, reaching the MII stage in synchrony with cytoplasmic maturation is vital for successful oocyte fertilization following sperm microinjection [10].

A previous study reported a significantly higher percentage of poor-quality day-3 embryos in the group with a higher proportion of immature oocytes [11]. Correspondingly, it was found that subjects with high GV during OPU exhibited a significantly lower implantation and clinical pregnancy rate [12]. A high degree of DNA damage, confirmed through immunostaining assay, was postulated as one of the underlying causes [12]. Likewise, previous research suggested that an increased proportion of immature oocytes (GV and MI) in a cohort could reduce the fertilization ability of sibling MII oocytes, resulting in a lower number of good-quality embryos and a lower implantation rate [13]. Contrarily, other studies have demonstrated that the number of immature oocytes in a cohort does not influence early embryo development, implantation rate, and clinical pregnancy [14, 15]. Considering the current evidence is conflicting and inconclusive, this study aimed to elucidate the effects of immature oocyte proportion in a cohort on both the IVF laboratory and clinical outcomes.

Materials and methods

Study population

A total of 1.826 IVF cycles at Morula IVF Jakarta Clinic from January 2016 to July 2020 were retrospectively extracted from medical records and analyzed. The data included a complete patient medical history that was relevant to the IVF treatment. Patients who had fewer than five retrieved oocytes, were diagnosed with a poor prognosis, and underwent either freeze-all or natural cycle procedures were not included in the study. These exclusion criteria were established to minimize biases stemming from variations in patients' backgrounds, thereby enabling a more precise evaluation of the impact of the number of immature oocytes on both laboratory and clinical outcomes of IVF within a cohort. The data obtained were then classified into four groups according to the proportion of immature oocytes: (1) immature ≤ 15% ($n = 1.064$), (2) immature 16–25% ($n = 369$), (3) immature 26–50% ($n = 331$), and (4) immature > 50% ($n = 62$). Of all studied subjects, 1.631 couples managed to perform embryo transfer, of which 950 couples succeeded in performing embryo transfer on day 5/6, while the remaining ($n = 681$) were processed with embryo transfer on day 2/3. Patient characteristics including age, body mass index, duration of infertility, and other parameters were analyzed.

Ovum pickup and maturity assessment

All enrolled participants underwent controlled ovarian stimulation with an antagonist protocol. Briefly, recombinant follicle-stimulating hormone (rFSH, Gonal-f, Merck Serono) or rFSH plus recombinant luteinizing hormone (rFSH + rLH) (Pergoveris, Merck Serono) or highly purified human menopausal gonadotropin (HP-hMG, Menophur, Ferring) was injected daily, starting from day 2/3 of the menstrual cycle. Gonadotropin-releasing hormone (GnRH) antagonists (0.25 mg Cetrotide, Merck, KGaA) were administered daily on day 4/5 of stimulation. A maturation trigger injection (6,500 IU Ovidrel, Merck, Serono) was then given when at least three follicles had reached 18 mm and OPU was performed 36 h later. After retrieval, cumulus-oocyte complexes (COCs) were rinsed with a buffer medium (G-MOPS, Vitrolife, Sweden) and then incubated in a culture medium (G-IVF, Vitrolife, Sweden) at 37 °C in the presence of 6% CO_2 and 5% 0_2 for 3 h. Subsequently, COCs were denudated to remove cumulus cells after undergoing immersion in hyaluronidase (<30 seconds). Maturity assessment was performed immediately using an inverted microscope with 200× magnification. The distinct presence of the first polar body denoted a mature oocyte which was subsequently inseminated through intracytoplasmic sperm injection (ICSI) or intracytoplasmic morphologically selected sperm injection (IMSI). Infertile patients selected for IMSI displayed suboptimal sperm morphology, as evaluated through semen analysis and also those with a track record of repeated unsuccessful attempts to produce high-quality blastocysts. Meanwhile, immature oocytes at either prophase I (displayed as GV) or MI (characterized by GV breakdown without the first polar body extrusion) stage were recorded.

Fertilization, embryo grading, and outcome assessment

Eighteen hours after insemination, fertilization was assessed by observing for the presence of two pronuclei and a second polar body. The embryos were cultured up to day 2/3 or day 5 depending on the number

of available good cleavage-stage embryos. Extended culture was encouraged for patients with at least three good cleavage-stage embryos for transfer at the blastocyst stage. Embryos were graded as good, fair, or poor according to the Society for Assisted Reproductive Technology (SART) grading system [16]. Parameters to assess cleavage-stage embryos include cell/blastomere number, fragmentation level, blastomere size, and shape regularity. Blastocysts were graded on the density of inner cell mass and trophectoderm and blastocoel cavity expansion [17]. Embryo transfer was eventually performed on either day 2/3 or 5. Primary outcomes that were subsequently evaluated were clinical pregnancy, ultrasound confirmation of a gestational sac or fetal heartbeat, and miscarriage defined by pregnancy loss before the first 22 weeks of gestation.

Statistical analysis

Data were tested for normality using the Kolmogorov–Smirnov normality test and were presented as median (Q1, Q3) due to non-normal data distribution. The Kruskal–Wallis test was then used to analyze all numerical variables, while the chi-square test was used to analyze all categorical variables. Multivariate analysis was subsequently performed to adjust for potential confounding variables. The analyses were done using Statistical Package for Social Studies (SPSS) at a 95% confidence level.

Results

A total of 1.826 cycles were sorted into four groups based on the immature oocyte proportion. As shown in Table 1, subjects across all groups were broadly similar in female

Table 1 Baseline and clinical characteristics of studied subjects

Baseline and clinical characteristics	Overall ($n=1.826$)	Group 1 ($n=1064$)	Group ($n=369$)	Group 3 ($n=331$)	Group 4 ($n=62$)	*p*-value
Baseline characteristics						
Female age (year)	32 (29, 35)	32 (30, 35)	32 (30, 35)	32 (29, 34)	31 (29, 33)	0.153
Body mass index (kg/m^2)	23.05 (20.90, 25.78)	23.05 (20.90, 25.64)[a]	22.70 (20.74, 25.30)[a,b]	23.23 (21.15, 26.26)	23.84 (21.78, 27.06)	*0.031*
Duration of infertility (year)	4 (3, 7)	4 (3, 7)	5 (3, 7)	4 (3, 7)	4 (3, 7)	0.820
Type of infertility						
Primary infertility	1630 (89.4%)	947 (89.3%)	325 (88.1%)	300 (90.6%)	58 (93.5%)	0.500
Secondary infertility	193 (10.6%)	114 (10.7%)	44 (11.9%)	31 (9.4%)	4 (6.5%)	
Clinical characteristics						
Etiology of infertility						
Tubal factor	323 (17.7%)	200 (18.8%)[a]	66 (17.9%)	54 (6.3%)	3 (4.8%)	*0.039*
Endometrial factor	157 (8.6%)	94 (8.8%)	31 (8.4%)	28 (8.5%)	4 (6.5%)	0.926
Sperm factor	638 (34.9%)	372 (35%)	128 (34.7%)	117 (35.3%)	21 (33.9%)	0.996
Unexplained factor	603 (33.0%)	349 (32.8%)	126 (34.1%)	99 (29.9%)	29 (46.8%)	0.072
PCO	111 (6.1%)	69 (6.5%)	17 (4.6%)	18 (5.4%)	7 (11.3%)	0.180
Others factor	249 (13.6%)	140 (13.2%)	51 (13.8%)	47 (14.2%)	11 (17.7%)	0.754
Antral follicle count	12 (10, 16)	12 (10, 16)	12 (10, 16)	12 (10, 16)	13 (10, 18)	0.221
Anti-Mullerian hormone (ng/ml)	3.61 (2.47, 5.51)	3.58 (2.47, 5.42)	3.47 (2.28, 5.42)	3.93 (2.69, 6.08)	3.75 (2.74, 5.62)	0.057
Basal FSH (mIU/mL)	6.86 (5.85, 8.02)	6.89 (5.88, 8.11)	6.81 (5.84, 7.95)	6.97 (5.74, 7.98)	6.17 (5.52, 7.76)	0.308
Basal estradiol (pg/mL)	34.25 (26.45, 45)	34.18 (26.83, 45)	34 (26.52, 44)	35 (26.2, 45)	31.5 (23.47, 45)	0.494
Basal progesteron (ng/mL)	0.23 (1.13, 0.36)	0.24 (0.13, 0.36)	0.21 (0.11, 0.35)	0.25 (0.15, 0.38)	0.22 (0.09, 0.36)	0.165
Estradiol level on trigger day (pg/mL)	2467 (1884, 3201)	2509 (1914,3273)[b]	2497 (1882, 3183)	2373 (1835, 2942)	2370 (1867, 3126)	*0.039*
Total gonadotropin dosage (IU)	2025 (1650, 2700)	2100 (1914, 2700)	2025 (1800, 2550)	2025 (1650, 2700)	2081 (1500, 2700)	0.921
Stimulation duration (day)	9 (8, 9)	9 (8, 10)	9 (8, 9)	9 (8, 9)	9 (8, 9)	0.516
Endometrial thickness (mm)	11 (10, 12)	11 (10, 12)	11 (9, 12)	11 (10, 12)	11 (10, 12)	0.331

Data were presented as median (Q1–Q3). Data were presented as a number of subjects and percentage (*n* (%)). Kruskal–Wallis tests were used for the numerical variable. Chi-square tests were used for the categorical variable

[a] Compared with group 4, $p<0.05$

[b] Compared with group 3, $p<0.05$

age with an overall average of 32 years. Other baseline variables were also comparable except for body mass index ($p=0.031$). Concordantly, there was no significant difference in the clinical parameters other than the etiology of infertility (tubal factor, $p=0.039$) and estradiol level on trigger day ($p=0.039$).

No significant difference was observed in the primary outcomes across all four groups, i.e., clinical pregnancy and miscarriage rate ($p=0.640$, *RR* 0.44 95% *CI* (0.40–0.48) and $p=0.141$, *RR* 0.98 (0.75–1.27) respectively) (Table 2). To underscore these primary findings, supplementary Table 1 provides the results of propensity score matching analysis for the primary outcomes of the current study. Multiple analyses (Table 2) showed that the likelihood of clinical pregnancy and miscarriage did not differ among the groups even after adjusting for potential confounders such as infertility duration, total gonadotropin usage, endometrial thickness, and BMI ($p=0.872$, *RR* 0.99 95% *CI* (0.91–1.08) and $p=0.345$, *RR* 0.977 95% *CI* (0.76–0.98), respectively).

The number of GV as well as MI stages were elevated following high immature proportion (p-value <0.001). Similarly, the number of injected and fertilized oocytes declined gradually from group 1 to 4. A similar descending trend was also confirmed in the embryonic development parameters in which the number and quality of cleavage- and blastocyst-stage embryos were significantly decreased from group 1 to 4 (Table 3). Furthermore, ET cancelation rates due to poor embryo quality were also significantly different across all groups; likewise, the number of embryos transferred on day 2/3. Nonetheless, comparable number of retrieved oocytes and embryos transferred on day 5/6 was noted in the secondary outcomes (Table 3).

Discussion

Our study highlights the insignificant impact of immature oocyte proportion in a cohort on clinical pregnancy and miscarriage rate. This finding agrees with a previous study which also observed similar pregnancy rate among studied cycles with different quantities of immature oocytes [14]. Nonetheless, increased immature oocyte proportion is related to less favorable embryo development at the fertilization up to the blastocyst stage. Natural embryo selection throughout the culture might account for the lack of association between the immature oocyte proportion in a cohort and the primary outcomes. Oocytes with impaired quality seemed to be eliminated at the beginning over a failed fertilization process or the incapability of developing into a viable embryo at the cleavage or blastocyst stage. This study also observed that a higher number of immature oocytes led to an elevated ET cancelation rate due to poor embryo quality. Interestingly, however, even though the embryo transfer cancelation rate due to poor embryo quality was high in group 4 with > 50% immature oocyte proportion, the comparable number of blastocysts transferred was observed in all groups.

In analyzing the baseline characteristics, we observe a trend of higher BMI in the group with a higher proportion of immature oocytes and, conversely, a lower BMI tendency in the other group (Table 1). This finding is in line with a study by Machtinger and colleagues who established the association between elevated BMI and a decreased number of retrieved MII oocytes [18]. In addition to reproductive hormones, it was hypothesized that an elevation in circulating glucose, insulin, free fatty acids, and adipokines in obese patients could likely contribute to the dysfunction of oocyte development and competency by disrupting the intricate molecular orchestration of ovarian dynamics [19].

The clinical characteristics of subjects revealed a substantial difference in the proportion of immature oocytes between tubal factor infertility (see Table 1). This finding is relevant to the previous observations which suggested a discrepancy in the quantity of mature oocytes between tubal and unexplained infertility factors, proposing a potential link between its condition and the oocyte maturation process [20]. Different physiological distinctions in the development of oocytes may be one of the contributors to its condition. Moreover, in line with the presumption of others suggested that defective intrinsic factors of oocytes in certain types of infertility cases could cause maturation arrests [21, 22], akin to what was presumed to occur in our study. Tubal factor infertility encompasses various causes of tubal damage, such as tubal blockage due to pelvic inflammatory disease resulting from sexually transmitted infections, acute salpingitis, endometriosis, and peritoneal factors [23]. These factors collectively comprise what is recognized as tubal factor infertility. The notable variances observed among the four studied groups may be attributed to varying background causes and the severity of tubal factor infertility.

Table 2 Primary outcome among studied groups

Primary outcome	Group 1 ($n=984$)	Group 2 ($n=326$)	Group 3 ($n=281$)	Group 4 ($n=40$)	Crude p-value	Adjusted p-value	Crude RR	Adjusted RR
Clinical pregnancy	433 (44%)	148 (45.4%)	127 (45.2%)	14 (35%)	0.640	0.872	0.44 (0.40–0.48)	0.99 (0.91–1.08)
Miscarriage	45 (4.6%)	24 (7.4%)	11 (3.9%)	1 (2.5%)	0.141	0.345	0.98 (0.75–1.27)	0.97 (0.76–0.98)

Data were presented as subjects and percentages (n (%)). Chi-square tests were used for statistical analysis

Table 3 Secondary outcomes according to immature oocyte proportion

Secondary outcomes	Group 1 ($n=1064$)	Group 2 ($n=369$)	Group 3 ($n=331$)	Group 4 ($n=62$)	*p*-value
Number of oocytes retrieved	11 (8, 15)	12 (9, 16)	11 (8, 15)	13 (8, 15)	0.349
Number of GV	0 (0, 1)[a,b,c]	1 (1, 2)[d,e]	2 (1, 4)[f]	4 (2, 7)	< 0.001
Number of MI	0 (0, 1)[a,b,c]	1 (0, 2)[d,e]	2 (1, 3)	2 (1, 4)	< 0.001
Number of injected oocytes	9 (7, 13)[a,b,c]	9 (6, 11)[d,e]	7 (5, 9)	6 (4, 9)	< 0.001
Number of fertilized oocytes	7 (5, 9)[a,b,c]	6 (3, 8)[d,e]	5 (3, 6)[f]	4 (2, 5)	< 0.001
Number of cleavage(s)	7 (5, 9)[a,b,c]	6 (3, 8)[d,e]	5 (3, 6)[f]	4 (2, 5)	< 0.001
Number of top-quality cleavage(s)	3 (2, 5)[a,b,c]	2 (1, 4)[d,e]	2 (1, 3)[f]	1 (0, 2)	< 0.001
Number of blastocyst(s)	6 (4, 8)[a,b,c]	5 (3, 7)	5 (3, 6)	4 (2, 5)	< 0.001
Number of top-quality blastocyst(s)	3 (2, 4)[c]	3 (1, 4)	3 (1, 4)	2 (1, 3)	0.001
Number of embryos transferred on day 2/3	2 (2, 2)[b,c]	2 (2, 2)[e]	2 (2, 2)	2 (1, 2)	< 0.001
Number of embryos transferred on day 5/6	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 1)	0.345
ET cancelation rate due to poor embryo quality	80 (7.5%)	43 (11.7%)	50 (15.1%)	22 (25.5%)	< 0.001
Number of total freezing embryo(s)	2 (1, 3)	2 (1, 3)	2 (1, 3)	1 (1, 2)	0.118

[a] Data were presented as median (Q1, Q3). [b]Data were presented as a number of subjects and percentage (*n* (%)). Kruskal–Wallis tests were used for the numerical variable. Chi-square tests were used for the categorical variable. *NS*, not significant. [a]Compared with group 2. [b]Compared with group 3. [c]Compared with group 4. [d]Compared with group 3. [e]Compared with group 4. [f]Compared with group 4. *GV*, germinal vesicle; *MI*, metaphase I; *ET*, embryo transfer

Other than the etiology of infertility, estradiol levels on trigger day were also found to decline with the increasing proportion of immature oocytes (Table 1). The principal hallmark of oocyte maturation is the formation of a haploid metaphase II oocyte. Luteinizing hormone (LH) has been identified as the driver of this meiotic progression by activating a cascade of ovulatory mediators [24, 25]. Following the mid-cycle surge, circulating LH binds to the G protein-coupled receptors on granulosa cells and activates the adenylate cyclase/cyclic AMP (cAMP)/cAMP-dependent protein kinase (PKA) pathway. cAMP spike in the follicular compartment subsequently suppresses C-type natriuretic peptide (CNP) and natriuretic peptide receptor 2 (NPR2) release which activates the EGF network and closes gap junctions. Consequently, meiosis I resumption is due to the reduction of cGMP, cAMP, and activation of phosphodiesterase 3A (PDE3A) and CDK1 resulting in MII oocytes formation [25]. As to this, reports suggest the mid-cycle LH surge is induced by circulating estradiol. The rise of estradiol at the end of the follicular phase is known to mediate positive feedback to the LH release due to neuro-progesterone synthesis [25, 26]. We assumed that a reduced level of estradiol in this study is inadequate to exert positive feedback to the hypothalamus causing an absence of LH surge resulting in maturation failure.

In the secondary outcomes of this study, both oocyte and embryo development were proven to be affected by the immature oocyte proportion in a cohort. The decline in the laboratory outcomes might be due to the overall decrease in the number of mature oocytes that could potentially develop to become good-quality embryos. Alternatively, as suggested by the previous study, an increased proportion of immature oocytes in a cohort is pertinent to a jeopardized fertilization and developmental capacity of sibling mature oocytes. The diminished fertilization and poor embryo development might also be caused by incomplete ooplasmic maturation or poor oolemma maturation. In conclusion, our study indicates that the presence of a high proportion of immature oocytes within a cycle cohort can significantly impede overall embryo development. However, if a single top-quality cleavage- or blastocyst-stage embryo is accessible for transfer during the cycle, similar clinical pregnancy and miscarriage rates among patients are anticipated, regardless of the varied proportion of immature oocytes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43043-024-00179-5.

Supplementary Material 1: Table 1. Results of propensity score matching analysis for the primary outcomes of the current study.

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Authors' contributions
NH constructed the study design, participated in statistical analysis, and revised the first draft of the manuscript. AMS helped to draft the first version of the manuscript. TA performed the statistical analysis. AB, AAP, BW, BS, and IS participated in its design and have commented on to draft to improve the scientific content accuracy. All authors have read and approved the final version of the manuscript.

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Availability of data and materials
The repository of the data that supports our findings in the current study is available in our private research institution affiliated with Morula IVF Jakarta Clinic. Potential data sharing is considered upon reasonable request to the corresponding author (NH).

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the Faculty of Medicine University of Indonesia (number of approval: KET-511/UN2.F1/ETIK/PPM.00.02/2022). Due to the nature of the retrospective study, waiver of informed consent has been granted by the Ethics Committee of the Faculty of Medicine University of Indonesia.

Consent for publication
Not applicable as none of personal information appeared in the manuscript.

Competing interests
The authors declare that they have no competing interests.

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