İstanbul Med J 2022; 23(3): 216-9
DOI: 10.4274/imj.galenos.2022.84748

Low Oocyte Maturity Rate and Asynchronous Follicle Development: Other Unnoticed Groups in the Bologna Criteria for Poor Responders?

Sinem Ertaş[1], Kayhan Yakın[2]

[1]American Hospital, Women's Health Center, İstanbul, Turkey
[2]Koç University Faculty of Medicine, Department of Obstetrics and Gynaecology, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to evaluate the prognosis of patients with low rates of oocyte maturity and compare those who are aforethought poor responders with respect to the Bologna criteria.

Methods: All assisted reproductive technology (ART) cycles conducted from 2004 to 2018 in a tertiary center in İstanbul were analyzed retrospectively. Patients were grouped into three accordingly the count of total retrieved oocytes and metaphase-II [(M-II) -mature] oocytes after denudation (group 1: ≤3 oocytes and ≤3 M-II oocytes; group 2: >3 oocytes and ≤3 M-II oocytes; group 3: >3 oocytes and >3 M-II oocytes). A Low oocyte maturity rate was diagnosed when ≤50% of all harvested oocytes were in the M-II stage before the fertilization procedure.

Results: During the study period 14,899 intracytoplasmic sperm injection cycles were evaluated. The study group's mean age was 32.6±5.3. The mean counts of total and mature oocytes were 9.8±5.9 and 7.3±4.5, respectively. A mean count of 2.38 embryos was transferred in 10118 cycles. The group 3 patients had a considerably higher live birth ratio compared to the group 1 and 2.

Conclusion: We propose oocyte maturity rate and the count of M-II oocytes as two diagnostic criteria for the case definition of asynchronous follicle growth. Based on our findings, stimulation cycles ending with low oocyte maturity rate (≤50%) and ≤3 M-II oocytes would be considered asynchronous follicle development. Patients with low oocyte maturity rate and asynchronous follicle development should be counseled and informed regarding potential poor prognosis of the treatment.

Keywords: Oocytes, fertilization in vitro, ovarian reserve, ovarian stimulation, metaphase

Introduction

Asynchronous follicle growth is a frequent finding in women with poor ovarian reserve and usually ends with a limited count of mature oocytes available for intracytoplasmic sperm injection. The ESHRE Working Group on Poor Ovarian Response proposed Bologna Criteria using the total count of oocytes as the primary determinant to define a poor responder (1). However, this definition is prone to overlook patients who do not fulfill the criteria based on the total count of harvested oocytes despite a limited count of mature ones. Clinical experience denotes that the prognosis of women with asynchronous follicle growth and low oocyte maturity rate is as poor as the Bologna defined as poor responders (2-5). Therefore, we designed this study to evaluate the prognosis of patients with low oocyte maturity rates and compare those who were evaluated as poor responders in accordance with the Bologna criteria.

Methods

All assisted reproductive technology (ART) cycles conducted between 2004 and 2018 in the tertiary in vitro fertilization (IVF) center of İstanbul were retrospectively analyzed. Data collected from the electronic database included female age, previous failed cycles, stimulation protocol, count of oocytes collected, count of mature oocytes and clinical outcome. Patients, who had undergone one of two commonly used stimulation protocols, i.e., long luteal GnRH agonist and GnRH antagonist protocols and had at least one mature oocyte following follicle aspiration were included in the study. Patients who underwent in vitro maturation, natural cycle, or modified natural cycle treatment, preimplantation genetic screening/diagnosis, and who used testicular sperm for fertilization were excluded. Following the exclusions, the final dataset included 14,899 ICSI cycles.

Details of stimulation protocols and ART laboratory procedures employed in our unit are reported elsewhere (6). A low oocyte maturity rate was diagnosed when ≤50% of all harvested oocytes were in the metaphase-II (M-II) stage before the fertilization procedure.

The Koç University Faculty of Medicine Local Research Ethics Committee authorized the count of total and M-II oocytes (approval number: 2022.132.IRB1.048, date: 05.04.2022).

Address for Correspondence: Sinem Ertaş MD, American Hospital, Women's Health Center, İstanbul, Turkey
Phone: +90 535 921 40 60 **E-mail:** drsinemertas@gmail.com **ORCID ID:** orcid.org/0000-0002-1699-616X

Cite this article as: Ertaş S, Yakın K. Low Oocyte Maturity Rate and Asynchronous Follicle Development: Other Unnoticed Groups in the Bologna Criteria for Poor Responders?. İstanbul Med J 2022; 23(3): 216-9.

Received: 07.04.2022
Accepted: 26.07.2022

Statistical Analysis

Continuous variables were defined by mean (±2 standard deviation) and categorical variables were defined by number and percentage. Two-tailed Pearson correlation test and linear regression analysis were conducted to determine confounding variables that are associated with live birth. Cycles were categorized into four groups with respect to female age (≤30, 31-35, 36-40, ≥40). The groups were compared using analysis of variance test with Bonferroni correction. Receiver operator characteristics (ROC) curves were constructed to evaluate predictive values for live birth. In the context of two-way hypothesis evaluation, $p<0.05$ was considered statistically significant. The Statistical Package for the Social Sciences software (SPSS version 22) was used to analyze the data and create the figures.

Results

The mean age of the study group was 32.6±5.3. The mean counts of total and M-II oocytes were 9.8±5.9 and 7.3±4.5, respectively. A mean count of 2.38 embryos was transferred in 10118 cycles.

The overall oocyte maturity rate was 74%. The proportion of mature oocytes to the total count of retrieved oocytes was similar among the four age groups (73.4% for ≤30 years, 74.2% for 31-35 years, 74.8% for 36-40 years, and 75% for >40 years).

However, the low oocyte maturity rate was increased with advancing female age ($p=0.001$) linearly (4.6%, 5.9%, 6.0%, and 7.9%), showing the highest rate in >40-year-old women.

Patients were grouped into three according to the count of total retrieved oocytes and M-II oocytes after denudation (Table 1).

The association with live birth ratio and the count of entire harvested and M-II oocytes is given in Figure 1.

Women who had more than 3 M-II oocytes available for fertilization (group 3) had considerably higher live birth ratio compared to those who had ≤3 M-II oocytes (group 1 and 2). Nevertheless, the live birth ratio was similar for women with ≤3 M-II oocytes regardless of the whole count of retrieved oocytes (group 1 and 2, respectively; 11.9 and 16.7%).

Figure 2 elucidates the association between live birth and oocyte maturity rates. Women who had ≤50% oocyte maturity rate have a significantly lower live birth ratio.

The live birth ratios according to the count of total and M-II oocytes concerning oocyte maturity rate are given in Table 2.

Live birth ratios were directly proportional to the count of both mature and entire harvested oocytes, being significantly higher for women with >3 M-II oocytes (group 3) ($p<0.01$). However, for a given count of M-II oocytes, the live birth ratio did not significantly differ according to the entire count of harvested oocytes, despite being lower in women with low oocyte maturity rates ($p>0.05$). The count of M-II oocytes was more predictive of a live birth than the whole count of retrieved oocytes.

Figure 3 shows ROC curves of the count of mature oocytes and the total count of collected oocytes for discriminating cycles resulting in a

Table 1. Patient groups according to the count of total retrieved oocytes and M-II oocytes

	Group 1	Group 2	Group 3
Total oocyte number	≤3	>3	>3
Count of M-II oocytes	≤3	≤3	>3

M-II: Metaphase-II

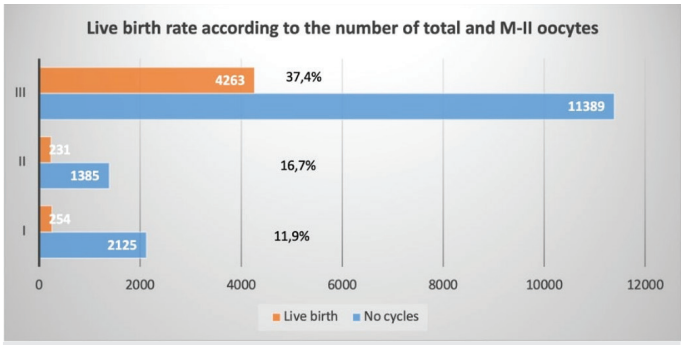

Figure 1. The live birth ratio according to the count of total harvested oocytes and M-II oocytes
M-II: Metaphase-II

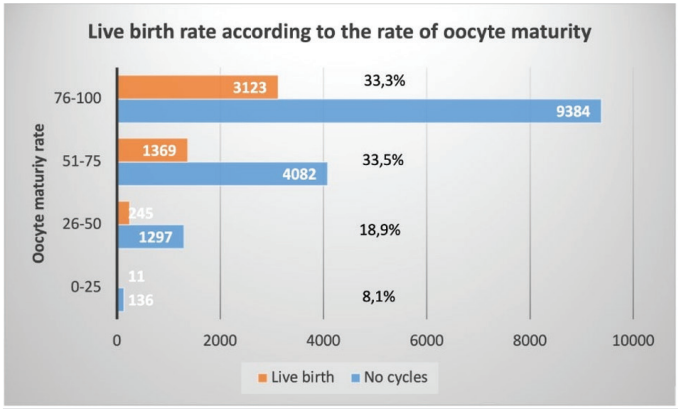

Figure 2. The live birth ratio according to the oocyte maturity rates

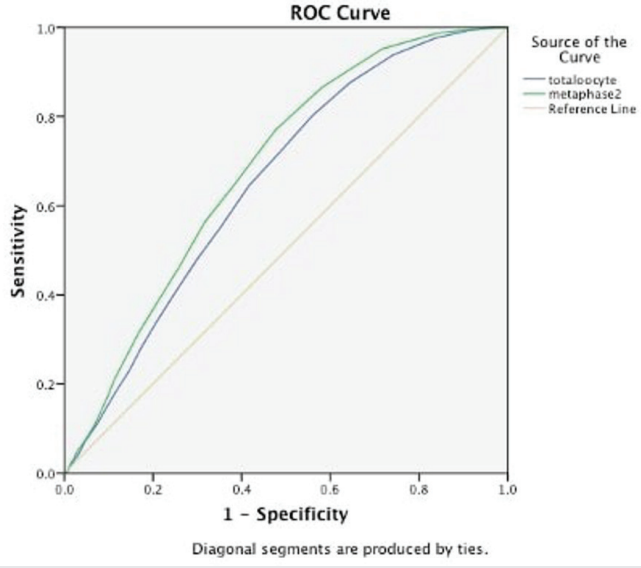

Figure 3. Receiver operating characteristic curves of the count of mature oocytes and the total count of collected oocytes for discriminating cycles resulting in live birth or non-live birth
ROC: Receiver operator characteristics

Table 2. Live birth ratios according to the count of M-II and total harvested oocytes

No M-II oocytes	Total harvested oocytes	Count of cycles	Embryo transfer cycles	Live birth (% per cycle)
1	≤3	957	589	52 (5.4%)
1	>3	90	42	4 (4.4%)
2	≤3	826	770	118 (14.3%)
2	≥4	376	309	38 (10%)
3	3	342	337	84 (24.6%)
3	4-5	651	639	138 (21.2)
3	≥6	268	247	51 (19.0%)
4	4-7	989	975	332 (33.6%)
4	≥8	110	106	30 (27.3%)
≥5	≥5	10,290	10,118	3,901 (37.9%)

M-II: Metaphase-II

live birth. In the prediction of live birth; the area under the ROC curve was 0.684 [95% confidence interval (CI): 0.671-0.697] for the count of mature oocytes and 0.653 (95% CI: 0.639-0.666) for the entire count of retrieved oocytes. These results showed that the count of M-II oocytes was better predictive of live birth than the entire count of harvested oocytes (p=0.0007).

Discussion

Marked discrepancies in follicular size during controlled ovarian stimulation would be damaging to pregnancy success since a considerable fraction of oocytes in the cohort will fail to complete the maturation process. In cases with low oocyte maturity; the count of M-II oocytes rather than the entire count of oocytes determines the patient's prognosis. Asynchronous follicle growth and subsequent low oocyte maturity are associated with a poor clinical outcome. The prognosis is similar to the Bologna criteria, defining poor responders if only ≤3 M-II oocytes are available within a pool of ≥3 retrieved oocytes. As the Bologna criteria fail to cover this group of patients, we suggest that this group of patients should be counseled accordingly.

Throughout controlled ovarian stimulation, the majority of the early antral follicles are expected to grow synchronously in reply to exogenous gonadotropins. However, 15-30% of recovered oocytes are reported to be immature (7-10). In our study group, 26% of the harvested oocytes were immature after denudation. Although these immature oocytes can be matured in vitro and fertilized, the derived embryos had a lower post-implantation developmental potential (11-13) and a higher incidence of cytogenetic abnormalities (14). In contrast to the physiological selection of the dominant follicle in a spontaneous cycle, ovarian hyperstimulation may lead to the rescue of follicles harboring intrinsically abnormal oocytes that would otherwise be destined to undergo atresia (15).

Immature oocytes may also stem from small antral follicles during oocyte retrieval or from large preovulatory follicles that do not respond adequately to hCG. A robust rate of oocyte immaturity was reported to be linked with ovarian stimulation protocols (8,9,16,17), inadequate timing, dose or activity of hCG (18), and early follicle aspiration (19). In contrast, we did not find a difference between stimulation protocols regarding oocyte maturity rate.

Asynchronous follicle growth and a higher rate of immaturity among retrieved oocytes are more frequently encountered in women with diminished ovarian reserve. A plausible explanation for this finding might be the earlier start of development of antral follicles due to the stimulatory effect of higher FSH levels during the late luteal phase of the previous cycle (20). We did not find a correlation between the overall rate of oocyte immaturity and female age. However, a low oocyte maturity rate was linearly correlated with advancing female age.

The Bologna criteria were proposed by the ESHRE Working Group on Poor Ovarian Response considering the entire count of oocytes retrieved as the major determinant to define a poor responder in addition to female age and ovarian reserve tests (1). According to these criteria, women who had ≤3 oocytes in one or two treatment episodes of ovarian stimulation (according to her age group) were poor responders. Several concerns have been raised about the design, reliability, applicability, and prognostic value of these criteria (21-25). Our findings will add further criticism to the Bologna criteria since the use of total count of oocytes as a criterion overlooks the group with asynchronous follicle growth. In cases with a limited count of growing follicles, the count of mature oocytes rather than the total count of oocytes will determine the prognosis of the patient.

Study Limitations

The retrospective design of our study was limitation. Although clinical heterogeneity within the dataset may be noted a drawback, such differences enhance the generalizability of our findings. Since female age was closely related to the chance of live birth, a post-hoc stratification according to different age groups was performed in the analysis phase. Since only ICSI cycles were included in the study, our findings cannot be translated into IVF cycles where oocyte maturity is not assessed before incubation with spermatozoa. However, indications for ICSI are becoming less stringent, and it is used more often, particularly in cycles with a low oocyte yield, exceeding 50% of all ART cycles in the U.S. (26).

Conclusion

Asynchronous follicle growth is a vaguely defined terminology. Much of the available literature includes a heterogeneous group of women, only some of whom have the condition of interest. Studies on risk

factors, diagnosis, management, and prognosis are hampered by a lack of uniform definition, either clinical or laboratory. We propose that oocyte maturity rate and the count of M-II oocytes as two diagnostic criteria for the case definition of asynchronous follicle growth. Based on our findings, stimulation cycles ending with low oocyte maturity rate (≤50%) and ≤3 M-II oocytes would be considered of asynchronous follicle development. Patients with low oocyte maturity rate and asynchronous follicle development should be counseled and informed regarding potential poor prognosis of the treatment.

Ethics Committee Approval: The Koç University Faculty of Medicine Local Research Ethics Committee authorized the count of total and M-II oocytes (approval number: 2022.132.IRB1.048, date: 05.04.2022).

Informed Consent: Our study design was retrospective; therefore, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., K.Y.; Concept: K.Y.; Design: K.Y.; Data Collection or Processing: S.E.; Analysis or Interpretation: K.Y.; Literature Search: S.E.; Writing: S.E., K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

References

1. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of 'poor response'to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011; 26: 1616-24.
2. Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel? Fertil Steril 2011; 96: 1058-61.
3. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011; 26: 1768-74.
4. Shu Y, Gebhardt J, Watt J, Lyon J, Dasig D, Behr B. Fertilization, embryo development, and clinical outcome of immature oocytes from stimulated intracytoplasmic sperm injection cycles. Fertil Steril 2007; 87: 1022-7.
5. Stoop D, Ermini B, Polyzos NP, Haentjens P, De Vos M, Verheyen G, et al. Reproductive potential of a metaphase II oocyte retrieved after ovarian stimulation: an analysis of 23 354 ICSI cycles. Hum Reprod 2012; 27: 2030-5.
6. Ata B, Yakin K, Balaban B, Urman B. Embryo implantation rates in natural and stimulated assisted reproduction treatment cycles in poor responders. Reprod Biomed Online 2008; 17: 207-12.
7. Lee JE, Kim SD, Jee BC, Suh CS, Kim SH. Oocyte maturity in repeated ovarian stimulation. Clin Exp Reprod Med 2011; 38: 234-7.
8. Nogueira D, Friedler S, Schachter M, Raziel A, Ron-El R, Smitz J. Oocyte maturity and preimplantation development in relation to follicle diameter in gonadotropin-releasing hormone agonist or antagonist treatments. Fertil Steril 2006; 85: 578-83.
9. Huddleston HG, Jackson KV, Doyle JO, Racowsky C. hMG increases the yield of mature oocytes and excellent-quality embryos in patients with a previous cycle having a high incidence of oocyte immaturity. Fertil Steril 2009; 92: 946-9.
10. Beall S, Brenner C, Segars J. Oocyte maturation failure: a syndrome of bad eggs. Fertil Steril 2010; 94: 2507-13.
11. De Vos A, Van de Velde H, Joris H, Van Steirteghem A. In-vitro matured metaphase-I oocytes have a lower fertilization rate but similar embryo quality as mature metaphase-II oocytes after intracytoplasmic sperm injection. Hum Reprod 1999; 14: 1859-63.
12. Strassburger D, Friedler S, Raziel A, Kasterstein E, Schachter M, Ron-El R. The outcome of ICSI of immature MI oocytes and rescued in vitro matured MII oocytes. Hum Reprod 2004; 19: 1587-90.
13. Vanhoutte L, De Sutter P, Van der Elst J, Dhont M. Clinical benefit of metaphase I oocytes. Reprod Biol Endocrinol 2005; 3: 71.
14. Strassburger D, Goldstein A, Friedler S, Raziel A, Kasterstein E, Mashevich M, et al. The cytogenetic constitution of embryos derived from immature (metaphase I) oocytes obtained after ovarian hyperstimulation. Fertil Steril 2010; 94: 971-8.
15. Levran D, Farhi J, Nahum H, Glezerman M, Weissman A. Maturation arrest of human oocytes as a cause of infertility: case report. Hum Reprod 2002; 17: 1604-9.
16. Bosch E, Vidal C, Labarta E, Simon C, Remohi J, Pellicer A. Highly purified hMG versus recombinant FSH in ovarian hyperstimulation with GnRH antagonists--a randomized study. Hum Reprod 2008; 23: 2346-51.
17. Greenblatt EM, Meriano JS, Casper RF. Type of stimulation protocol affects oocyte maturity, fertilization rate, and cleavage rate after intracytoplasmic sperm injection. Fertil Steril 1995; 64: 557-63.
18. Griffin D, Engmann L, Budinetz T, Kummer N, Nulsen J, Benadiva C. Dual trigger with gonadotropin releasing hormone agonist (GnRHa) and human chorionic gonadotropin (hCG) for the treatment of 'immature oocyte syndrome'(IOS). Fertil Steril 2012; 98(Suppl): 156.
19. Weiss A, Neril R, Geslevich J, Lavee M, Beck-Fruchter R, Golan J, et al. Lag time from ovulation trigger to oocyte aspiration and oocyte maturity in assisted reproductive technology cycles: a retrospective study. Fertil Steril 2014; 102: 419-23.
20. Fanchin R, Salomon L, Castelo-Branco A, Olivennes F, Frydman N, Frydman R. Luteal estradiol pre-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists. Hum Reprod 2003; 18: 2698-703.
21. Sallam HN, Ezzeldin F, Agameya AF, Abdel-Rahman AF, El-Garem Y. The definition of 'poor response': Bologna criteria. Hum Reprod 2012; 27: 627-8.
22. Frydman R. Poor responders: still a problem. Fertil Steril 2011; 96: 1057.
23. Papathanasiou A. Implementing the ESHRE 'poor responder'criteria in research studies: methodological implications. Hum Reprod 2014; 29: 1835-8.
24. Venetis CA. The Bologna criteria for poor ovarian response: the good, the bad and the way forward. Hum Reprod 2014; 29: 1839-41.
25. Polyzos NP, Sunkara SK. Sub-optimal responders following controlled ovarian stimulation: an overlooked group? Hum Reprod 2015; 30: 2005-8.
26. Simpson JL. Birth defects and assisted reproductive technologies. Semin Fetal Neonatal Med 2014; 19: 177-82.