RESEARCH ARTICLE

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Follicular fluid and serum Prostaglandin D2 level as a biomarker for ovarian reserve and response in IVF protocol

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ABSTRACT

Background: Poor responders are those with poor ovarian reserve test, usually old age group however, there are some young patients with adequate ovarian reserve test are unexpectedly poorly responding to Controlled Ovarian Stimulation protocol (COS) through In Vitro Fertilization (IVF) program. Follicular fluid and serum Prostaglandin D2 (PGD2) level has a role in ovarian function and response to COS protocol.

Aim of study: To find whether follicular fluid and serum PGD2 level is a potential biomarker of ovarian reserve and a predictor of ovarian response to hyper stimulation and to show a possibility in developing a therapeutic factor for poor ovarian responders.

Methods: The study included eighty infertile females less than 42 years old, their BMI less than 30 undergone Controlled Ovarian Stimulation (COS) protocol through IVF program. Forty of them with poor ovarian reserve (study group) defined according to ESHRE guidelines 2019; low Ati Mullerian hormones (AMH) and or low Antral Follicle Count (AFC), adding to them in my study Follicular Stimulating Hormone (FSH) level. Other forty with normal ovarian reserve test (control group). A third group extracted from control group, eight in number involving those with adequate ovarian reserve test and young age less than 35 years old, though showed unexpectedly poor response to COS protocol(total oocytes retrieved less than four). In our study we excluded women with endometriosis, immune disorder, endocrine disorders, women with endometriosis, women with polycystic ovarian syndrome and male factor infertility. We analysed PGD2 level using ELISA in both follicular fluid and patients serum on day of ovum pick up in both study group and control group, then we correlated the patients clinical parameters (age, BMI, ovarian reserve test),controlled ovarian stimulation / IVF program outcome (total oocytes retrieved, fertilisation rate and total embryos obtained) with follicular and serum PGD2 level. Finally we did comparison of all parameters mentioned above including follicular and serum PGD2 level among: (1) study group (poor ovarian reserve test) (2) new control group (normal ovarian reserve test and normal response with four oocytes retrieved and above) and (3) unexpected poorly responding group (normal ovarian reserve test, young less than 35 year and total oocytes retrieved less than four).

Results: Showed significant lowered PGD2 level in both follicular fluid and patient's serum in study group (poor ovarian reserve group) in comparison with control group (normal reserve test). When we do the comparison among the three groups, the result showed significant lower follicular fluid PGD2 level, non-significant lower serum PGD2 level in unexpected poor responder group (age less than 35yr, normal ovarian reserve test, and poor response, less than four total oocytes retrieved) in comparison to group(normal ovarian reserve test and normal responder with equal or more than four total oocytes retrieved). There was no significant difference in follicular fluid and serum PGD2 level between study group (poor ovarian reserve test) and the unexpected poor responder group.

Conclusion: We suggest that PGD2 is a potential biomarker to aid the tests of ovarian reserve and to enhance the diagnosis of poor ovarian response and this data may show the possibility of developing a therapeutic factor for poor ovarian responders by enhancing follicular function that can be used to establish new individualised COS protocol in women with poor ovarian response

Keywords: Poor Ovarian Reserve, Follicular, Serum PGD2

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INTRODUCTION

Ovarian reserve is a term which refers to woman's reproductive potential. Ovarian Reserve Tests (ORT); have been shown to be accurate predictors of quantitative aspects of ovarian reserve and predict the ovarian response to Controlled Ovarian Simulation (COS); however they are not accurate predictors of the qualitative aspect of ovarian reserve and not good predictor of pregnancy outcome after In Vitro Fertilisation (IVF)[1]. Both AMH and AFC have equal accurate predictive value for ovarian response to hyper stimulation according to ESHRE guidelines 2019[2]. AMH mainly predicts the reproductive life span and it's not applicable for the prediction of fecundity. Chronological female age though informative for pregnancy prospects in assisted reproduction, it will not always correctly express a woman's reproductive potential[3-6]. Low responders according to Poseidon definition combines both quantitative and qualitative parameters namely: the age, AMH, AFC. Group 1and 2 of the Poseidon classification include those with unexpected poor ovarian response, group 1 with age less than 35 years old , group 2 with equal or more than 35 years old, both with adequate ovarian reserve tests (AMH = or more than 1.2 ng/ml and AFC = or more than 5), and both groups subdivided according to their response to COS protocol to: 1a; less than 4 oocytes retrieved and 1b: 4-9 oocytes retrieved . One of the explanations of this discrepancy between ovarian reserve and response might be due to genetic polymorphism in FSH receptors (FSHR), LH Receptor (LHR) or LH, which associated with higher FSH consumption, thus characterizing patients requiring higher doses of gonadotropins in the COS for IVF[7-10].

Folliculogenesis is under control of growth factors and two pituitary gonadotropines hormones; Follicular Stimulating Hormones (FSH) and Luteinising Hormones (LH). These glycoprotein bind in the ovary to specific G-protein coupled receptors; FSHR and LHR respectively to facilitate growth and differentiation of ovarian cells and also to control the production of two steroids hormones progesterone and estradiol[11-13]. Prostaglandins (PGs) derived from polyunsaturated fatty acids, belonging to the super family of eicosanoids, these molecules act locally in an autocrine and or paracrine manner and their action are complex[14,15]. Prostaglandins D2 (PGD2) is produced by two prostaglandin D synthases; (PGDS) responsible for mediating the final regulatory step in the biosynthetic pathway of PGD2 production one is the lipocalin-type PGDS (L- PGDS), the second is hematopoietic type PGDS(H- PGDS)[16,17].

There is evidence about the role of H – PGDS produced PGD2 – signalling in the FSH signalling via the increase of FSHR and LHR receptors expression , leading to activation of steroid genic Cyp11a1 and Star gene expression and subsequently to progesterone secretion activity of granulose cells[18-20]. In our study we tried To find whether follicular fluid and serum PGD2 level is a potential biomarker of ovarian reserve so in the future its level specially in the serum can be used to assess ovarian reserve, and whether PGD2 level is a predictor of ovarian response to controlled ovarian stimulation. Finally to show a possibility in developing a therapeutic factor for poor ovarian responders especially in young age group.

MATERIALS & METHODS

The study was conducted from March 2022 to June 2023 in Infertility centres in Baghdad / Iraq. All women underwent COS protocol through IVF program. We investigated eighty infertile women's follicular fluid PGD2 using ELISA test which was harvested during ovum pick up and serum PGD2 which was taken just prior to ovum pick up. ELISA reader at ambient temperature, (Version-21- 2019), which uses EIA photometric as the measuring mode. Up to 8 standards can be loaded per time.

Sensitivity: 4.34 pg per ml. All was approved by Institutional Research and Ethical Committees of Al Nahrain University, Baghdad/ Iraq.

Inclusion Criteria:

- Women with less than 42 years old.
- Body Mass Index (BMI) less than 30.
- Forty of them with poor ovarian reserve test (study group) defined according to ESHRE guidelines 2019 as those with low AMH level less than 1.1ng/ml and or AFC less than 5. Adding to them in our study follicular stimulating hormone FSH level,(patients serum taken day 2 or 3 of cycle) ; considering 10 IU/L as cut off level, considering those with serum FSH level more than 10 iu\l as poor ovarian test. The other forty with normal ovarian reserve (control group). From the control group we extracted a third group (un expected poor responder), who were having normal ovarian reserve test, their age less than 35 years old though the total number of oocytes retrieved was less than four.

Exclusion Criteria:

- Age more than 42 years old, BMI equal and above 30.
- Women with endometriosis, genetic disease, autoimmune disease and endocrine disorders.
- Women with polycystic ovarian syndrome.
- Previous history of chemotherapy, radiotherapy and extensive ovarian surgery.
- Male factor infertility.

We compared follicular fluid and serum PGD2 level between study group and control group, also compared the patients clinical parameters (age, BMI, AMH, AFC, FSH), Controlled ovarian stimulation COS protocol and IVF outcome (total oocytes retrieved, fertilisation rate, total embryos obtained) between study group and control group, then we did correlation between follicular fluid, serum PGD2 level and the all above parameters (clinical parameters and COS/IVF protocol outcome. Finally we

did comparison of all the parameters and the follicular fluid, serum PGD2 level among the three groups which are: 1. study group (women with poor ovarian reserve test), 2.New control group (women with normal ovarian reserve test and normal response with 4 and above oocytes retrieved), 3.Unexpected poor responder (with normal ovarian reserve test , young age less than 35 year, though poorly responding, less than four oocytes retrieved).

RESULTS

Forty infertile female with poor ovarian reserve (Study group) were compared with another 40 infertile female with good ovarian reserve (Control group) in the present case control study. According to the results, regarding (AMH, FSH, AFC): There was significant lower serum AMH level and AFC in poor ovarian reserve group vs. control group. On the contrary there was significant higher serum FSH level in poor ovarian reserve group. This is already explained by the definition of poor ovarian reserve tests.

Regarding controlled ovarian stimulation protocol and IVF outcome (total oocytes retrieved, fertilization rate, total embryos outcome); the results showed significantly lower total oocytes retrieved, $p<0.001$ and total embryos obtained(Grade 1 and 2), $p< 0.001$ in poor ovarian reserve group vs. control group, whereas there was not significant lower fertilization rate in poor ovarian reserve group, $p= 0.058$.

Poor ovarian reserve group showed significantly lower both serum and follicular fluids prostaglandin D2 levels (12.34 ± 2.03 vs. 22.56 ± 4.46; $p=0.041$) and (13.33 ± 2.03 vs. 22.84 ± 4.28; $p=0.043$) respectively **Table 1**.

There were insignificant negative correlations between serum and follicular fluids prostaglandin D2 with both age and body mass index.

There was a significant positive correlation between serum AMH with both serum and follicular fluids prostaglandin D2 ($r=0.438$ & $p < 0.001$) and ($r=0.404$ & $p=0.001$) respectively **Figure 1**, there was also a positive significant correlation between antral follicles count with both serum ($r=0.354$ & $p=0.003$) and follicular fluids prostaglandin D2 ($r=0.295$ & $p=0.014$); in addition there was a significant negative correlation between serum FSH and follicular fluids prostaglandin D2 ($r=-0.296$ & $p=0.014$).

Furthermore there was a significant positive correlation between total oocytes retrieved with both serum ($r=0.471$ & $p< 0.001$) and follicular fluids prostaglandin D2 ($r=0.410$ & $p< 0.001$) **Figure 2** and with total embryos ($r=0.410$ & $p< 0.001$) and ($r=0.410$ & $p< 0.001$) respectively. There was no significant correlation between fertilization rate with both serum and follicular fluids prostaglandin D2 **Table 2.**

Eight women from control group were unexpectedly poorly responded to COS protocols with less than four oocytes retrieved although they have adequate ovarian reserve test and young age group less than 35 year old. Accordingly the women were subdivided into three groups; poor ovarian reserve, unexpected poor ovarian responders and new N control groups (adequate ovarian reserve test with four and above oocytes retrieved).

According to the above classification, the results showed significant differences of serum prostaglandin D2 (12.34 ± 2.03 vs. 9.54 ± 7.66 vs. 25.94 ± 5.11; $p=0.02$) and follicular fluids prostaglandin D2 (13.33 ± 2.03 vs. 6.48 ± 3.22 vs. 27.34 ± 5.04; $p=0.005$) between poor reserves, poor responders and control groups as demonstrated in **Table 3**.

Post hoc test of ANOVA **Table 3,4** were used to identify which particular differences between pairs of means were significant. Regarding prostaglandin D2 levels in serum, there was significant difference between poor ovarian reserve group and N control groups ($p=0.026$); furthermore there were no significant differences between poor ovarian reserve group and unexpected poor responders group ($p=0.938$), in addition to unexpected poor responders and N control groups ($p=0.132$).

Comparison of follicular fluids prostaglandin D2 showed a significant differences between poor ovarian reserve and N. control groups ($p=0.012$) and between unexpected

Table 1. Comparison of Clinical data between Study and Control groups.

Parameters (Mean±SD)	Study group n=40	Control group n=40	p value
Age (years)	34.10 ± 7.07	33.40 ± 5.63	0.625 NS
BMI (Kg/m^2)	25.78 ± 2.61	25.73 ± 2.17	0.926 NS
AMH (ng/ml)	0.79 ± 0.31	2.12 ± 0.52	< 0.001 S
FSH (mIU/ml)	12.79 ± 2.15	7.96 ± 1.39	< 0.001 S
Antral follicles count	5.55 ± 1.24	12.15 ± 2.95	< 0.001 S
Total oocytes count	3.48 ± 1.15	8.45 ± 3.6	< 0.001 S
Fertilization rates	72.39 ± 30.34	83.48 ± 19.49	0.058 NS
Total embryos	2.08 ± 1.56	6.05 ± 2.71	< 0.001 S
Serum prostaglandin D2 (pg/ml)	12.34 ± 2.03	22.56 ± 4.46	0.041 S
F.F. prostaglandin D2 (pg/ml)	13.33 ± 2.03	22.84 ± 4.28	0.043 S

SD: Standard deviation; NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$)

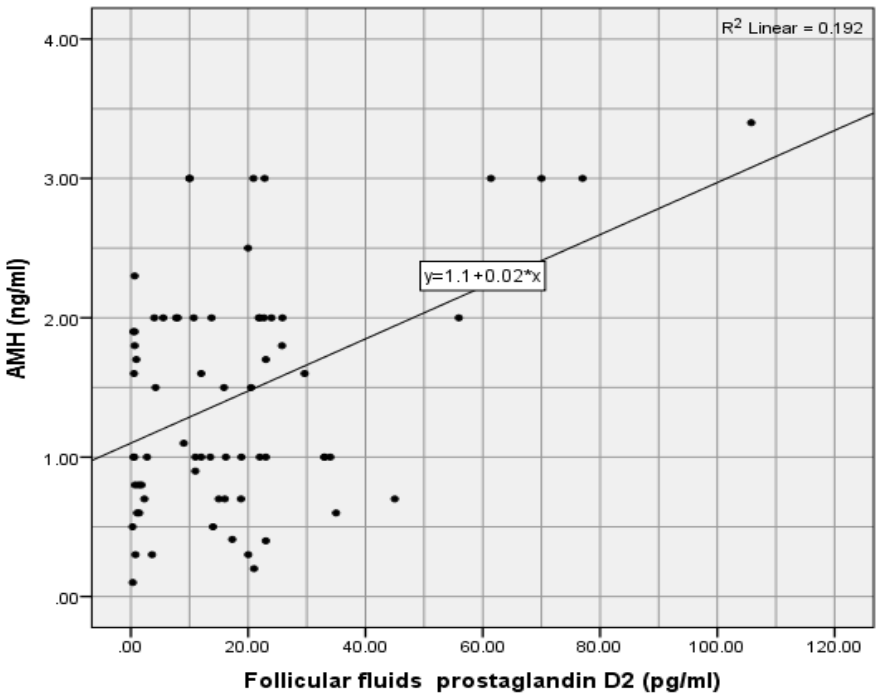

Figure 1: Correlation between follicular fluids prostaglandin D2 and serum AMH.

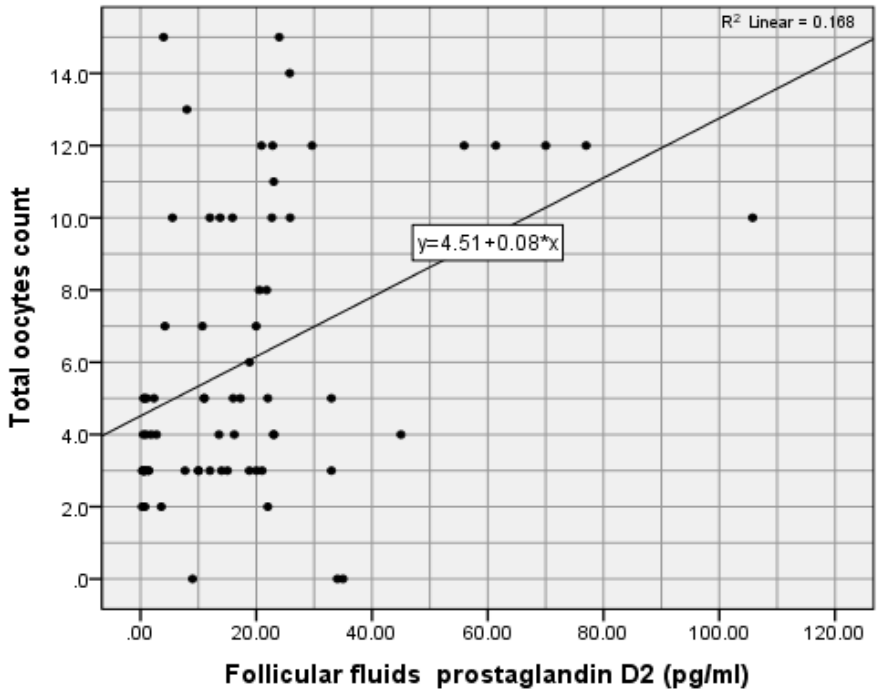

Figure 2: Correlation between follicular fluids prostaglandin D2 with total oocytes count.

poor responders and N. control groups ($p=0.026$). There was no significant differences between poor ovarian reserve group and unexpected poor responders patients ($p=0.640$).

Statistics: The data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 and Microsoft office 2010.The descriptive statistics including frequency, range, mean and standard deviation were measured to describe the data .The groups were compared by applying independent sample t-test (Unpaired t-test compare between two groups) and analysis of variance (ANOVA for comparison of more than two different groups). Post hoc tukey test of ANOVA were used to identify which particular differences between pairs of groups were significant. The degree of association between continuous variables was calculated by Pearson's correlation coefficient (r) and the results were considered statistically significant when *p* value was less than or equal to 0.05.

Table 2. Correlation between Serum and Follicular Fluids Prostaglandin D2 with patient's clinical parameters.

		Serum prostaglandin D2	Follicular Fluids prostaglandin D2
AGE	r	-0.191	-0.197
	p value	0.120 NS	0.105 NS
BMI	r	-0.105	-0.013
	p value	0.393 NS	0.915 NS
AMH	r	0.404	0.438
	p value	0.001 S	< 0.001 S
FSH	r	-0.205	-0.296
	p value	0.095 NS	0.014 S
Antral follicles count	r	0.354	0.295
	p value	0.003 S	0.014 S
Total oocytes retrieved	r	0.471	0.410
	p value	< 0.001 S	< 0.001 S
Fertilization rate	r	0.048	0.022
	p value	0.700 NS	0.858 NS
Total embryos	r	0.475	0.416
	p value	< 0.001 S	< 0.001 S

r: Pearson correlation coefficient; NS: Not significant($p>0.05$); S: Significant ($p\leq0.05$).

Table 3. Comparison of Clinical Parameters among Poor Ovarian Reserve Patients, Unexpected Poor Responders and N Control Group.

Parameters (Mean ± SD)	Poor ovarian reserve group n=40	Unexpected Poor ovarian responders n=8	N Control group n=32	p value
Serum prostaglandin D2 (pg/ml)	12.34 ± 2.03	9.54 ± 7.66	25.94 ± 5.11	0.020 S
Follicular fluids prostaglandin D2 (pg/ml)	13.33 ± 2.03	6.48 ± 3.22	27.34 ± 5.04	0.005 S

S; Significant ($p \leq 0.05$)

Table 4: Post hoc test for Paired groups' significance.

Parameters	Paired groups interaction		*p* value
Serum prostaglandin D2	Poor ovarian reserve group	N.Control group	0.026 S
	Poor ovarian reserve group	Unexpected Poor responders	0.938 NS
	Unexpected Poor responders	N.Control group	0.132 NS
Follicular fluids prostaglandins D2	Poor ovarian reserve group	N.Control group	0.012 S
	Poor ovarian reserve group	Unexpected Poor responders	0.640 NS
	Unexpected Poor responders	N.Control group	0.026 S

NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$)

DISCUSSION

Discrepancy between ovarian reserve and actual ovarian response that is expected from the selected stimulation protocol in IVF program particularly in young women, still represent a dilemma in our practice. Although many strategies to improve ovarian response in those group of women have been proposed, most of them have not been significantly effective in improving ovarian response[14,9]. Prostaglandins' D2 (PGD2) roles in female reproduction have been evaluated in several studies. PGD2 play an important role in the proliferation and modulate the differentiation of granulose cells and in steroid genic activity of the ovary[15,16] . In July 2021 a study done by KH Choi et al. compared follicular fluid PGD2 level between patients with normal ovarian response and those with poor ovarian response and the result showed significantly lower PGD2 level in the poor ovarian responder group than in the follicular fluid of young and old patients with normal ovarian response [21] . Other study in September 2021 done by Kim Yu Jin et al. , on association of PGD2 in follicular fluid level with poor ovarian responders, the data showed the same results that had been obtained by KH Choi et al, suggesting that PGD2 support ovarian function and female fertility[22] .

In our study; the results support the above two studies in demonstrating significant lower follicular fluid PGD2 in poor ovarian reserve , but in our study we measured also PGD2 level in patients serum in addition to follicular fluid to strengthen the association of lower both serum and follicular fluid PGD2 level in poor ovarian reserve women which might reflect its role in ovarian function and the possibility of using serum PGD2 as a potential biomarker to support the diagnosis of poor ovarian reserve. In our study also we extracted subgroup from control group who are young age with normal ovarian reserve test, but showed unexpected poor response to COS protocol. We found in this subgroup significantly lower follicular fluid PGD2 and lower not significant serum PGD2 level in comparison to control group who have both adequate ovarian reserve and adequate response; this might suggest the important role of PGD2 in ovarian response to controlled ovarian stimulation. Although the discrepancy between ovarian reserve and actual response have been studied by several studies; no one explanation have reached level of evidence and in our study we tried to highlight one of these explanation suggesting the possibility of PGD2 in enhancing ovarian response to hyper stimulation and developing a therapeutic factor for poor ovarian responders. In our study also did correlation between serum and follicular fluid PGD2 level and biomarkers of ovarian reserve (AMH, FSH, AFC), and with COS/IVF protocol outcome (total oocytes retrieved, fertilization rate, total embryos). There was significant positive correlation with AMH, AFC, total oocytes retrieved and total embryos suggesting an overall possible role of PGD2 in the diagnosis of poor ovarian reserve and its role in modulating ovarian response to COS, putting in mind that both fertilization rate and number of embryos are affected by other factors like sperm fertilization potential and the condition of culture media. Salleh N et al. in 2014 studied Prostaglandins' role in embryo implantation through increase vascular permeability, stromal decasualization and blastocyst growth[14]. Review article done by Moira Rossito et al. 2015; on the multiple role of PGD2 signaling pathway in reproduction physiology specially in females[13].Other studies demonstrated the role of PGD2 together with prostaglandins PGE2 and PGI2 in conjunction with other mediators such as histamines in the immune system and inflammation process[23,24].

CONCLUSION

We suggest that PGD2 is a potential biomarker to aid the tests of ovarian reserve and to enhance the diagnosis of poor ovarian response and this data may show the possibility of developing a therapeutic factor for poor ovarian responders by enhancing follicular function that can be used to establish new individualised COS protocol in women with poor ovarian response.

RECOMMEDATION

We recommend doing further studies to highlight the role of prostaglandins D2 as:

1. Potential biomarker of ovarian reserve in either follicular fluid or serum.
2. Enhancing ovarian response to COS protocol in those with low level of PGD2 in either follicular fluid or serum as a possible developing therapeutic factor for poor ovarian responders.

REFERENCES

1. Gardner DK, Weissman A, Howles CM, Shoham Z. Textbook of assisted reproductive techniques. Taylor Francis Group. 2018.
2. Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Hum Reprod Open. 2020;2020(2):hoaa009.
3. Rao KA, Rao VA, Devi R. Principles and Practice of Assisted Reproductive Technology: Three Volume Set. Jaypee Brothers Medical Publishers. 2023.
4. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Upd. 2014;20(1):124-40.
5. Chinta P, Antonisamy B, Mangalaraj AM, Kunjummen AT, Kamath MS. POSEIDON classification and the proposed treatment options for groups 1 and 2: time to revisit? A retrospective analysis of 1425 ART cycles. Hum Reprod Open. 2021;2021(1):hoaa070.
6. No CO. Female age-related fertility decline. Fertility Sterility. 2014;101(3):633-4.
7. Jirge PR. Poor ovarian reserve. J Hum Reprod Sci. 2016;9:63-9.
8. Zhang Y, Zhang C, Shu J, Guo J, Chang HM, Leung PC, et al. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Upd. 2020;26(2):247-63.
9. Grisendi V, Mastellari E, La Marca A. Ovarian reserve markers to identify poor responders in the context of poseidon classification. Front Endocrinol. 2019;10:384468.
10. Haahr T, Esteves SC, Humaidan P. Individualized controlled ovarian stimulation in expected poor-responders: an update. J Endocrinol Reprod. 2018;16:1-9.
11. Pier B, Edmonds JW, Wilson L, Arabshahi A, Moore R, Bates GW, et al. Comprehensive profiling of prostaglandins in human ovarian follicular fluid using mass spectrometry. Prostaglandins Other Lipid Mediat. 2018;134:7-15.
12. Grisendi V, Mastellari E, La Marca A. Ovarian reserve markers to identify poor responders in the context of poseidon classification. Front Endocrinol. 2019;10:384468.
13. Rossito M, Ujjan S, Poulat F, Boizet-Bonhoure B. Multiple roles of prostaglandin D2 signaling pathway in reproduction. Reproduction. 2015;149(1):R49-58.
14. Salleh N. Diverse roles of prostaglandins in blastocyst implantation. Sci World J. 2014;2014.
15. McKnight K, Hoang HD, Prasain JK, Brown N, Vibbert J, Hollister KA, et al. Neurosensory perception of environmental cues modulates sperm motility critical for fertilization. Science. 2014;344(6185):754-7.

16. Tootle TL. Genetic insights into the in vivo functions of prostaglandin signaling. Int J Biochem Cell Biol. 2013;45(8):1629-32.

17. Lim W, Bae SM, Jo G, Bazer FW, Choi Y, Song G. Prostaglandin D2 synthase related to estrogen in the female reproductive tract. Biochem Biophys Res Commun. 2015;456(1):355-60.

18. Le Faouder P, Baillif V, Spreadbury I, Motta JP, Rousset P, Chêne G, et al. LC–MS/MS method for rapid and concomitant quantification of pro-inflammatory and pro-resolving polyunsaturated fatty acid metabolites. J Chromatogr B Biomed Appl. 2013;932:123-33.

19. Jacob KD, Hooten NN, Trzeciak AR, Evans MK. Markers of oxidant stress that are clinically relevant in aging and age-related disease. Mech Ageing Dev. 2013;134(3-4):139-57.

20. Humaidan P, La Marca A, Alviggi C, Esteves SC, Haahr T. Future perspectives of POSEIDON stratification for clinical practice and research. Front Endocrinol. 2019;10:464190.

21. Choi KH, Kim YJ, Kang KY, Park EA, Kim YS, Kim MJ, et al. P–657 Prostaglandin D2 is correlated with follicles development and a reliable marker of ovarian reserve of poor ovarian responder patients. Hum Reprod. 2021;36(1):deab130-656.

22. Kim YJ, Kang KY, Choi KH, Park EA, Kim YS, Kim MJ, et al. Prostaglandin d2 association with poor ovarian responder in female infertility. Fertil Steril. 2021;116(3):e372.

23. Luo W, Salih SM, Bormann CL, Wiltbank MC. Induction of chemokines and prostaglandin synthesis pathways in luteinized human granulosa cells: potential role of luteotropin withdrawal and prostaglandin F2α in regression of the human corpus luteum. Reprod Bio. 2015;15(4):247-56.

24. Boots CE, Jungheim ES. Inflammation and human ovarian follicular dynamics. Reprod Med. 2015;33(4) :270-275. Thieme Medical Publishers.