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Research Article

Correlation Study of Inflammatory Factors and Ovarian Reserve Decline in Infertile Women

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Abstract

Purposes: To investigate the correlation between inflammatory factors and ovarian reserve decline in infertile women and to study the pathogenesis of ovarian reserve decline.

Methods: Retrospective analysis of the basic data and blood routine level of infertile women who underwent IVF/intracytoplasmic single sperm injection-embryo transfer (IVF/ICSI-ET) in the Reproductive Medicine Center of Dongguan Maternal and Child Health Hospital from January 2019 to December 2023, According to the infertile women (Anti-Mullerian Hormone, AMH) values and the number of sinus follicles (Antral Follicle Count, AFC) is Divided into Ovarian Reserve decline group (DOR group) (AMH <1.1ng/ml, AFC <6) and normal ovarian reserve group (non-DOR group) (AMH 1.1 ng/ml, AFC 6 units), Analyzing the basic data and blood routine results of both groups, The Association of Monocyte count (MONO), Neutrophil Count (NEUT), Mean Platelet Volume (MPV) and ovarian reserve decline were assessed.

Results: DOR group was 0.49(0.36-0.55) 109/L, Lower than the non-DOR group 0.55(0.42-0.64) 109/L, The difference was statistically significant (P <0.001); The median NEUT in the DOR group was 5.26(4.02-6.12) 109/L, Lower than the non-DOR group 6.57(5.12-7.73) 109/L, The difference was statistically significant (P <0.001); MPV, PCT, PDW, PLT in DOR group compared with non-DOR group, No differences were statistically significant, respectively (P >0.05); Multivariate Logistic regression analysis, NEUT was associated with ovarian reserve decline (OR = 1.570, P <0.001).

Conclusions: There is a positive correlation between neutrophils as inflammatory factors and decreased ovarian reserve function in infertile women.

Keywords: Inflammatory factors; Neutrophil count; Ovarian reserve; Correlation

Introduction

Ovarian reserve function decreased (Diminished Ovarian Reserve, DOR) refers to the oocyte number and (or) the quality of declining, caused by the serious shortage of ovarian reserve function, further cause fertility decline, accompanied by a variety of hormone level adjustment, such as: resistant hormone levels, sinus follicle count, basic follicle stimulating hormone level increased [1,2]. DOR is divided into physiological and pathological, in which physiological age is related to advanced age, while pathological age and pathological age are related [3-5]. As is known to all, with the gradual aging of age, the decline of female ovarian reserve function with the aging of age is irreversible, but according to the decreasing trend, the degree of development to premature ovarian failure (Premature Ovarian Failure, POF) varies greatly [6,7]. DOR and POF can affect the reproductive capacity of girls, and on the other hand, they can increase the incidence of cardiovascular disease and osteoporosis. At present, the etiology of DOR is still unclear, and its risk factors mainly include the following aspects: age, immunity, genetics and other factors. Several clinical trials have shown that [8-10], the level of proinflammatory cytokines in the peripheral blood is significantly increased in DOR patients, which may be involved in the related process of reduced ovarian reserve function, and may have a correlation. Therefore, this paper analyzed and compared the ovarian reserve function and the inflammatory factors that might affect the ovarian reserve function.

Methods

Patients

From January 2019 to December 2023, the basic data of patients were treated in the Reproductive Medicine Center of Dongguan Maternal and Child Health Hospital, and 2,066 patients were included. Among them, 112 patients Diagnosed with Ovarian Reserve decline (DOR group) and 1954 patients with non-ovarian reserve decline (non-DOR group) had no significant average infertility age 0 and physical index (P >0.05). The median age of the two groups was 31.00 (29-33) and 30.08 (28-33) years, respectively (P<0.05).

Inclusion criteria: All the patients were admitted to the Reproductive Medicine Center of Dongguan Maternal and Child Health Hospital, and the ovarian reserve function decline was mainly diagnosed by AMH and AFC indicators. Elimination criteria: 1) malignant tumors, autoimmune diseases, infectious diseases; 2)

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patients with anemia (such as thalassemia, iron deficiency anemia, megaloblastic anemia, etc.); 3) patients with long-term drug history (including drugs to control blood pressure, blood glucose and lipids); 4) patients with long or recently taking anticoagulant drugs or antibiotics; 5) patients with polycystic ovary syndrome; 6) patients with chronic pelvic inflammatory disease sequelae; 7) patients with previous history of ovarian surgery. This paper has been approved by the Ethics Committee of Dongguan Maternal and Child Health Hospital, and the ethical batch number is (Lun Approval 2022 (39).

Approach

All patients had blood routine, AMH and sex hormones one month before identifying IVF/ICSI-ET filing, and their peripheral blood was drawn on an empty stomach. The comparison of two types of primary infertility and secondary infertility. The inflammatory indexes in both groups of blood routine were observed and analyzed.

Statistical analysis

All the data were analyzed using SPSS for Windows version 17.0. Data are presented as the mean±standard deviation. Categorical variables are presented as frequencies and percentages. The chi-square test and *t* test were used to establish significance among two and single categorical data groups, respectively, and P <0.05 was considered statistically significant.

Results

Compared with the type of infertility in the DOR and non-DOR groups, there was no statistically significant difference (P>0.05), (Table 1), median MONOO, NEUT, and lower DOR than non-DOR (P<0.05); but the DOR group, such as WBC, LYMH, PLT, PLR, MPV, PCT, PCT, PDW and P-LR, compared with the two groups (P>0.05) (Table 2).

Table 1: Comparison of infertility types in the two groups.

Variables	DOR (n=112)	Non-DOR (n=1954)	Result (X^2)	*P*
Primary infertility	68 (60.71%)	1015 (51.94%)	3.266	0.071
Secondary infertility	44 (39.29%)	939 (48.06%)		

DOR group: ovarian reserve function decreased
Non-DOR group: normal ovarian reserve function.

Table 2: Comparison of infertility types in the two groups.

Variables	DOR (n=112)	Non-DOR (n=1954)	Result (Z)	*P*
WBC (10^9/L)	4.45 (4.18, 4.74)	4.51 (4.28, 4.75)	-0.95	0.341
LYMPH (10^9/L)	2.17 (1.78, 2.71)	2.17 (1.80, 2.59)	-0.52	0.601
MONO (10^9/L)	0.43 (0.36, 0.55)	0.52 (0.42, 0.64)	-4.20	<.001
NEUT (10^9/L)	4.91 (4.02, 6.12)	6.41 (5.12, 7.73)	-7.15	<.001
EO (10^9/L)	0.10 (0.06, 0.13)	0.10 (0.06, 0.16	-1.42	0.154
PLT (10^9/L)	268.50 (235.00, 323.25)	270.00 (231.00, 316.00)	-0.86	0.806
MPV (fL)	10.30 (9.47, 11.00)	10.30 (9.70, 10.90)	-0.24	0.807
P-LCR (%)	27.15 (20.38, 33.00)	27.00 (22.10, 32.20)	0.34	0.737

*WBC represents white blood cell count, LYMPH lymphocyte count, MONO monocyte count, NEUT neutrophil count, EO eosinophil count, PLT platelet count, PLR represents the ratio of platelet count to lymphocyte count, and MPV mean platelet volume.

Table 3: Comparison of infertility types in the two groups.

Variables	β	*S.E.*	Wald	*P*	*OR*	*95%CI*
Age	-0.120	0.037	10.698	<0.001	0.885	0.824~0.951
Infertility years	0.069	0.048	2.074	0.151	1.071	0.975~1.177
Infertility type	-0.699	0.215	10.529	<0.001	0.497	0.326~0.758
BMI (kg/m^2)	-0.072	0.027	7.033	0.008	0.93	0.882~0.981
Endometriosis	0.047	0.366	0.017	0.898	1.048	0.511~2.150
MONO (109/L)	-0.466	0.703	0.158	0.507	0.627	0.158~2.486
NEUT (109/L)	0.451	0.071	1.366	<0.001	1.570	1.366~1.805

*MONO represents monocyte count; NEUT neutrophil count.

Age, number of infertility years, infertility type, BMI, endometriosis, MONO (10^9/L), NEUT (10^9/L) were included to construct multifactor Logistic regression equations. The results found that age, infertility type, constitution index and NEUT had statistically significant effects on ovarian reserve decline and were independent factors of clinical pregnancy. The results were statistically significant by the multifactor model (X^2=20.299, *P*=0.009) (Table 3).

Discussion

Ovarian reserve function is a measure of the quantity and quality of ovulation in female ovaries, which can directly affect fertility. Current methods for assessing ovarian reserve include hormonal assessments, such as measuring serum levels of anti-mullersonian hormone (Anti-Muller Hormone AMH) and follicular stimulating hormone (Follations Stimulate Hormones FSH), and the imaging technique for transvaginal ultrasound counting [2-4]. Despite advances in these techniques, significant gaps remain in understanding the complex biological mechanisms governing ovarian reserve and its decline with age or pathological conditions. How to seek a valid indicator to evaluate, and this indicator is easily accessible, this is the objective of this study.

Between DOR patients and non-DOR patients, we compared the counts of various indicators in blood routine (Table 2). Median MONO and NEUT, DOR group were lower than non-DOR group, the difference was statistically significant (P <0.001). Through multivariate logistic regression analysis, the effect of NEUT on ovarian reserve function was an independent influencing factor of clinical pregnancy. Although the median MONO was statistically significant in group comparisons, the multivariate logistic regression analysis was not an independent influence of clinical pregnancy and could be influenced by other factors (Table 3). Although the specific regulatory network and mechanisms involved in NEUT in this process are still unclear, further studies are needed to clarify its role in ovarian reserve decline. However, it has reflected its importance in this study, and combined with previous studies, there is a possible correlation between inflammatory factors and ovarian reserve decline, suggesting that chronic inflammation may affect the physiological state of ovary through several mechanisms, such as by changing the endocrine environment or directly damaging ovarian tissue [11]. It causes significant harm to reproductive health, especially in pregnant women, the decline of ovarian function will lead to ovulation disorders, pregnancy complications and abortion problems [12]. In turn, chronic intestinal inflammation is very likely to affect the physiological function of the ovary, and then affect the maintenance of ovarian reserve function in [13-15]. Chronic inflammation may adversely affect ovarian function and the overall success of ART. Studies have shown that elevated levels of proinflammatory cytokines are associated with reduced response to ovarian stimulation and decreased pregnancy rate after entering the sperm injection flow, highlighting the complex relationship between inflammation and fertility outcomes [16-18]. In this study, excluding women with significant PCOS or other inflammatory conditions, we found between DOR and non-DOR infertility (P >0.05), but in the median of NEUT of conventional blood inflammatory indicators, indicating a more clear link between subclinical inflammation and reproductive outcomes, suggesting that even mild inflammatory status can negatively affect

fertility. In addition, this study used regression analysis to find NEUT as an independent factor affecting clinical pregnancy, which is of great significance. We may find a way to solve inflammatory conditions and tailored treatment to reduce their effects may improve the success rate, which deserves further exploration in subsequent studies. Several previous studies have shown that polycystic ovary syndrome is a low-grade chronic inflammatory [11] with metabolic dysfunction. At present, the occurrence and development mechanism of inflammatory factors and decreased ovarian reserve function still need to be explored in depth. There may be individual differences in the effects of different types of ovarian diseases, inflammatory status and chemotherapy on ovarian reserve, so these factors need to be taken into account when developing treatment options. Future studies should focus on exploring how inflammatory factors influence ovarian reserve through different pathways and finding potential intervention strategies to actively address the fertility challenges of ovarian reserve decline.

NEUT has a correlation with ovarian reserve, and the lower NEUT is more prone to DOR. The specific mechanism needs further investigation. However, this study still has some limitations. First, patients with endometriosis were not excluded from this study, and previous studies have confirmed the possible correlation between inflammatory factors and endometriosis [19,20]. In addition, the sample size of DOR group still needs to be further expanded.

The sample size gap between DOR group and non-DOR group in this study is large, and more sample data of DOR is still needed to support, which can be solved by multi-center study; Second, the findings may still not be applicable to all infertility subgroups, such as those with unexplained infertility or other specific causes; Furthermore, the exclusion of women with Polycystic Ovary Syndrome (PCOS) may limit the applicability of our findings to populations exhibiting ovarian hyperresponsiveness, thus potentially oversimplifying the complex interplay between inflammation and ovarian reserve in different clinical situations. Finally, the cross-sectional nature of the study limits the causal inferences, as the temporal relationship between inflammatory cytokines and ovarian responses remains to be elucidated. Recently, inflammatory factors have played crucial roles in various molecular biology as well as in pathological processes, including the regulation of ovarian reserve function. Studies have shown that there may be a correlation between inflammatory factors such as monocyte count and neutrophil count and decreased ovarian reserve function.

The chronic inflammatory state may lead to blocked follicle development and decreased egg quality by affecting cellular mechanisms within the ovary [16-18]. However, the relationship between NEUT and ovarian reserve function is still not completely defined, and the specific regulatory mechanisms need further investigation. Moreover, therapeutic strategies for decreased ovarian reserve function need to be explored to overcome drug resistance [21-23].

In conclusion, this study concluded that NEUT, as a simple and clinically measurable routine blood parameter, has a correlation with ovarian reserve decline. And has some correlation with ovarian reserve decline, but its deep mechanism still needs further research.

Author Statements

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Authors contributions

Jing Cai, performed the data analyses and wrote the manuscript; Li Ya Song performed the surgeries and contributed significantly to analysis and manuscript preparation; Yan Sun, Kun Wang and Jia jun Zeng helped perform the analysis with constructive discussions. All authors reviewed the manuscript.

Declaration of conflicting interests

Jing Cai, Yan Sun, Kun Wang and Jia jun Zeng have no conflicts of interest or financial ties to disclose.

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