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Association between diminished ovarian reserve and recurrent pregnancy loss: a comparative study

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ABSTRACT

Objective. To assess diminished ovarian reserve prevalence in patients with recurrent pregnancy loss.
Patients and Methods. Included 100 females were subjected to evaluation for diagnosis of the cause of recurrent pregnancy loss, we divided our patients into 2 groups each group contains 50 patients; the first group included patients with unexplained recurrent miscarriage and the second group included healthy females with no recurrent pregnancy loss that acts as a control group.
Results. The levels of FSH in the recurrent miscarriage group were higher than the control group ($p = 0.005$). The levels of AMH in the recurrent miscarriage group were lower than the control group ($p = 0.002$). The levels of LH, E2 and FSH/LH ratio were nearly similar in both groups.
Conclusions. We found that diminished ovarian reserve as denoted by high FSH levels and low AMH levels was associated with higher risk of recurrent pregnancy loss.

INTRODUCTION

Spontaneous miscarriage is considered the commonest pregnancy complication, with about 9-20% of pregnancies are terminating with miscarriage. Risk of occurrence of miscarriage is markedly increasing with increasing maternal age reaching up to 40% in females aged 40 years old. Recurrent pregnancy loss, which is defined as losing three pregnancies consecutively, is a less common condition [1]. Most cases of miscarriage and recurrent pregnancy loss have unknown explanation, but it was found that embryonic aneuploidy the commonest cause of miscarriage in the first-trimester which is increased with increasing age of the mother [2, 3].
Ovarian reserve demonstrated the reproductive potential of the ovary regarding number and quality of the present oocytes [4].
It was found that diminished ovarian reserve is associated with aneuploidy and recurrent pregnancy loss in young females [5, 6]. Although there are many studies regarding association between diminished ovarian reserve and recurrent pregnancy loss, but tests for diminished ovarian reserve is not

routinely used as a diagnostic workup of recurrent miscarriages as suggested by American Society for Reproductive Medicine (ASRM). The current routine diagnostic workup of recurrent miscarriages as recommended by ASRM are karyotyping analysis of parents, antiphospholipid syndrome screening, examination of the uterus for any congenital anomalies and evaluations of presence of any hormonal disturbances [1]. It was found that after application of all these tests, about half of the recurrent pregnancy losses have unexplained causes [7]. The objective of our study was to assess diminished ovarian reserve prevalence in patients with recurrent pregnancy loss.

PATIENTS AND METHODS

Included patients in the current study were subjected to evaluation for diagnosis of the cause of recurrent pregnancy loss in Gynecology and Obstetrics Department, Faculty of Medicine, Zagazig University, in the period from May 2015 and May 2020. Patients were subjected to routine ASRM evaluation in addition to ovarian reserve testing.
We obtained an approval before starting the study from institutional review board.

Inclusion criteria

The inclusion criteria were females with spontaneous recurrent pregnancy loss and healthy normal conceiving females without pregnancy loss.

Exclusion criteria

The exclusion criteria were female patients who were diagnosed as polycystic ovarian syndrome or having endometriosis, patients with a previous history of ovarian surgery, pelvic radiotherapy, chemotherapy, having irregular menstruation, having premature ovarian failure or using any hormonal therapy or oral contraceptives within 3 months before the study.

Laboratory analysis

We have taken samples from the venous blood of included patients in the period between 8:00 AM and 9:00 AM in days 2-4 which is the early follicular phase of the menstrual cycle. The routinely recommended ASRM workup, included TSH, prolactin, HbA1c testing, searching for antiphospholipid antibodies, evaluation of uterine cavity defects and assessment of and chromosomal translocations in both parents. Unexplained recurrent pregnancy loss was the term used when no apparent abnormality in any of the previously mentioned tests were found. Testing for ovarian reserve tests include serum follicle-stimulating hormone (FSH) levels, serum antimullerian hormone (AMH) levels.
We evaluated ovarian volume and numbers of follicles that measured 2-10 ml in diameter (antral follicle count) were evaluated by the same operator, who was blinded to patient information.
We considered an increasing the baseline levels of FSH to become > 10 mIU/mL and decreasing basal levels of AMH to become < 1 ng/mL as markers for decreased ovarian reserve [4].
Levels of FSH and E2 were measured using electrochemiluminescent immunoassay while levels of AMH were measured using ELISA [8, 9].
After application of exclusion and inclusion criteria of patients, we divided our patients into 2 groups, each group contain 50 patients. The first group was composed by females patients who have unexplained recurrent miscarriage, and the second group was composed by healthy females with no recurrent pregnancy loss who will act as control.
We collected patients' demographic data as age, body mass index, parity, times of pregnancy loss, period of each pregnancy and ovarian reserve findings as serum levels of FSH, AMH, E2, LH, and FSH/LH ratio. We recorded ovarian volumes at both sides for both groups of included patients then we compared between both groups regarding all these parameters.
Our manuscript the Enhancing the Quality and Transparency Of health Research (EQUATOR) network guidelines.

Statistical analysis

Data analysis was performed by Chi square test, Mann-Whitney U test and Student t-test considering P-value of < 0.05 as statistically significant. Data analysis was performed by IBM's SPSS software (SPSS version 15.0).

RESULTS

The descriptive and demographic data of patients and ovarian reserve functions data were found in

Table 1. We detected no significant differences between both included groups of patients regarding length of menstrual cycle or the body mass index.
The levels of FSH in the recurrent miscarriage group were higher than the control group (p = 0.005 and Confidence interval (CI) = 95%).
The levels of AMH in the recurrent miscarriage group were lower than the control group (p = 0.002 and Confidence interval (CI) = 95%).
The levels of LH, E2 and FSH/LH ratio were nearly similar in both groups.
We detected no significant differences between both included groups of patients regarding ovarian volumes on both sides.

DISCUSSION

It was found that the commonest cause of recurrent miscarriage is aneuploidy and diminished ovarian reserve particularly in females above the age of 35 years [10].
We found in the current study that ovarian reserve parameters were decreased in females with recurrent miscarriage other than healthy females without pregnancy loss which were similar to data detected by previous reports [1, 4].
Wald *et al*. [1] found that most patients having unexplained recurrent pregnancy loss has diminished ovarian reserve particularly in females aged 38 years old.
So they recommended adding tests of ovarian reserve parameters to routine investigations in those patients to explain the reason of recurrent pregnancy loss.
Similarly, Trout *et al*. [11] and Gurbuz *et al*. [12] reported that females having recurrent unexplained miscarriage have elevated levels of FSH, E2 and FSH/LH ratios which denoted decreased ovarian reserve in those patients.
A recently introduced parameter of assessment of ovarian reserve is the level of AMH which was found to be a more accurate parameter than FSH [1].
In the present article we found that AMH is decreased in females with recurrent pregnancy loss than the control group.
Previous studies showed that there is a significant association between levels and quality of AMH levels and oocytes quality [13], while these findings were still controversial by some studies [14].
Advanced ovarian age which is detected by diminished ovarian reserve is considered an accurate determinant of risks of aneuploidy which is associated with recurrent miscarriages [15]. Atasever *et al*.'s [4] study found that the number of females with low levels of AMH was higher in the recurrent miscarriage group than the healthy control group which was in line with finding detected by the current study.
For management of unexplained recurrent pregnancy loss performing IVF with embryonic chromosomal analysis before implantation could be

Table 1. *Correlations between patients with recurrent pregnancy loss and healthy control.*

	Recurrent pregnancy loss n = 50 (%)	Healthy control n = 50 (%)	P-value
Age (years)			
Mean ± SD	26.3 ± 12.18	27.25 ± 12.41	0.808
Range	20-35	20-35	
Gravity	3.7 ± 0.9	1.7 ± 0.6	0.049
Parity	0.2 ± 0.4	1.5 ± 0.7	0.043
BMI	24 ± 3.2	25 ± 3.9	1
Cycle length (d)	28.3 ± 2.2	28.5 ± 1.5	1
FSH	8.6 ± 3.7	7.1 ± 1.9	0.005
LH	5.2 ± 2.2	5.4 ± 2.4	0.043
AMH	2.9 ± 1.7	3.6 ± 1.7	0.002
Estradiol	42.2 ± 15.1	45.5 ± 30.2	0.004
FSH/LH	1.7 ± 0.7	1.6 ± 1.1	0.3
Comorbid medical problems			
Present	5 (33)	4 (43)	0.1
Absent	45 (67)	44 (57)	

considered a recent treatment option [16], moreover transplantation of euploid embryo was associated with decreased incidence of miscarriage and a high rate of success [17, 18].
It was found that patients with diminished ovarian reserve have little number of eggs and little number of euploid embryos than patients with normal ovarian reserve. Due to the high IVF costs, it is better to make ovarian reserve tests to increase the chance of having euploid embryos and increase the success rate.
Preoperative ovarian reserve must be assessed in infertile females underwent ovarian cystectomy to ensure effects of different haemostasis methods on the ovarian reserve and fertility outcome [19].
Different results were found by recent studies: several biomarkers of ovarian reserve have been proposed as predictors of ovarian reserve. Peluso *et al*. evaluated age, FSH, AMH, antral follicle count (AFC). They showed that none of the ovarian reserve tests showed a good predictive capacity for hypo-response, while the ovarian response prediction index (ORPI) was the strongest predictor of hyper-response in norm-ovulatory infertile women [20].
Additionally, Di Paola *et al*. showed that the application of nomogram in IUI cycles lead to a more tailored FSH starting dose and improved cost-effectiveness, although in PCOS women, with high AMH, it does not seem adequate [21].

CONCLUSIONS

In the current study we assessed the tests used for accurate assessment of ovarian reserve, correlating between females with recurrent pregnancy loss and healthy females regarding ovarian reserve and we found that diminished ovarian reserve as denoted by high FSH levels and low AMH levels was associated with higher risk of recurrent pregnancy loss.
Moreover, we showed that ovarian reserve tests should be routinely used in the diagnostic workup of unexplained recurrent miscarriages to allow early treatment and in patients who want to perform IVF in addition to performing routine chromosomal analysis to increase rates of success.

Points of strength

We have chosen an important point of research which is significant to infertile females which is assessment of ovarian reserve in Egyptian females.

We pointed to benefits of routine assessment of tests for diminished ovarian reserve as diagnostic workup of recurrent miscarriages.

Points of weakness

We included a relatively a few number of patients as the study was performed in a single institution and this is the rate of flow of patients.

Recommendations

We recommend performing a larger study included a huge number of patients to confirm our findings and gives possible management strategies for unexplained recurrent pregnancy loss.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors: Conceptualization, data curation, project administration, resources, software, supervision, validation, visualization, writing, original draft, review, editing, formal analysis, investigation, methodology, conceptualization, data curation and funding acquisition.

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None.

Study registration

Zag 1012000.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethical Approval was obtained from local ethical committee of Faculty of Medicine Zagazig University.

Informed consent

A written informed consent was obtained from all participants in the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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