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High basal estradiol level and FSH/LH ratio in unexplained recurrent pregnancy loss

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Abstract *Background:* The potential role of diminished ovarian reserve in unexplained recurrent pregnancy loss (RPL) in a retrospective comparative analysis. *Methods:* Eighty women with RPL underwent routine work-up to exclude known associations of RPL. Serum FSH, LH and E₂ levels were assessed on the 3rd day of the menstrual cycle. Following investigation, 58 women failed to reveal an identifiable cause and are therefore classified as unexplained RPL. Control group consisted of women in whom the cause of abortions was known such as uterine septum and parental chromosomal abnormalities. Mean age, gravidity, parity, presence of infertility, previous number of miscarriages, duration of marriage were similar in both groups. Day 3 serum levels of FSH, E₂ and FSH:LH ratios were compared in the two groups. *Results:* Elevated FSH concentrations were equally distributed in the unexplained RPL and control groups. Both day 3 E₂ and FSH:LH ratio were elevated in the unexplained RPL group compared with the control group ($p=0.0066$ and $p=0.0187$ respectively). The percentage of women with elevated FSH and/or E₂ levels on day 3 were significantly higher in the unexplained RPL group than in controls ($p=0.0045$). *Conclusions:* Unexplained RPL may be associated with diminished ovarian reserve and should be considered in the workup of RPL.

Keywords Ovarian reserve · Unexplained recurrent pregnancy loss (RPL)

Introduction

Recurrent pregnancy loss is the loss of three or more spontaneous and consecutive pregnancies at less than 20 weeks of gestation and fetal weight less than 500 g. It is a heterogeneous condition with a number of possible underlying causes, such as anatomical defects (8%); genetic factors (4%); autoimmune diseases (3%) and endocrinopathies (8%) [10, 11]. Despite thorough investigation according to various clinic protocols, the underlying cause remains unexplained in about 70% of cases.

The increased risk of pregnancy loss due to genetic abnormalities of the fetus, most often aneuploidy, is well known in older women with poorer ovarian reserve [13]. Although ovarian reserve diminishes with age, young women with RPL may have diminished ovarian reserve. Basal serum FSH, E₂ levels and FSH:LH ratio may indirectly reflect the poor quality and quantity of the oocytes [2, 3, 5, 6, 8, 9].

We investigated the potential role of diminished ovarian reserve in unexplained RPL.

Materials and methods

Study and control subjects

The records of all 80 women who were evaluated for recurrent pregnancy loss at the our hospital were assessed. Recurrent pregnancy loss is defined as at least three successive first trimester losses without an intervening live birth or live birth at any time before the start of the study, all with the same partner. The patients underwent initial investigations, which included a chromosomal analyses of both partners, levels of prolactin, TSH, anticardiolipin antibody, lupus anticoagulant, antinuclear antibody and coagulation studies, pelvic ultrasonography and hysterosalpingogram. Hysteroscopic assessment was not part of the routine investigations but was performed if the hysterosalpingogram or pelvic ultrasound indicated structural anomalies affecting the uterine cavity. Serum LH, FSH and E₂ levels were measured on the 3rd day of the

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menstrual cycle. Of these 80 women, 58 women in whom all testing had normal results were identified as having unexplained recurrent pregnancy loss (Group 1). Control group consisted of 22 women in whom the cause of abortion was known (such as uterine septum, chromosomal abnormalities and anti-phospholipid syndrome). This group was assigned the diagnosis of explain RPL (Group 2).

Day 3 serum levels of FSH, E₂ and FSH:LH ratio were compared in the two groups. An elevated day 3 level was defined as a serum FSH level ≥ 10 mIU/ml (immulite) or a serum E₂ level ≥ 50 pg/ml (immulite) [1, 7, 12] and FSH:LH ratio of more than 3.6 was designated as the cut-off values between patients with poor follicular reserve and those with physiologically normal ovaries [6].

We compared the incidence of elevated day 3 serum FSH, E₂ levels and elevated FSH:LH ratios between two groups.

Hormone analysis

Serum FSH, LH and E₂ concentrations were measured by commercial chemiluminescent assay (Immulite; Euro/Diagnostic Product Corporation, Gwynedd, United Kingdom).

Statistical analysis

The statistical analysis was performed using the Chi-square test, Mann-Whitney U test and Fisher exact test where applicable. Statistical significance was determined at $p \leq 0.05$.

Results

There were no statistically significant differences in age, gravidity, parity between unexplained RPL and explained RPL groups. The previous number of miscarriages, duration of marriage and history of infertility also did not differ significantly between groups (Table 1).

Table 2 shows the serum levels of FSH, LH and E₂ in unexplained RPL and control patient. FSH, LH and E₂ concentrations were significantly higher in the unex-

plained RPL group than in controls, although serum concentrations of all hormones were within the normal range. Elevated FSH concentrations were equally distributed in the unexplained RPL and control groups ($p=0.658$). The percentage of women with elevated E₂ concentrations ($p=0.0066$) and elevated FSH and/or E₂ concentrations on day 3 were significantly higher in unexplained RPL group than in controls ($p=0.0045$).

We observed high basal LH level (≥ 11.6 mIU/ml) in only 1 woman (1.7%) and polycystic ovarian (PCO) morphology in 4 patients (6.9%) in the study group. None of the patients in controls had high levels of LH and PCO. There were no differences in the frequency of these parameters between two groups ($p>0.05$).

We determined a cut off value for the FSH:LH ratio ≥ 3.6 to identify patients with poor ovarian reserve and those with normal ovaries. The percentage of women with FSH:LH ratio ≥ 3.6 was significantly higher in unexplained RPL group than in controls ($p=0.034$).

Discussion

Basal serum FSH and E₂ levels measured on days 2–4 of the menstrual cycle are an indirect measure of ovarian reserve. Diminished production of inhibin by the granulosa cells of the remaining follicles, the resultant elevated FSH, and the premature rise in E₂ may indirectly reflect the lower quality and quantity of the remaining oocytes [2, 3, 5, 6, 8, 9].

Although ovarian reserve diminishes with age, young women with RPL may have diminished ovarian reserve. Oocytes of women with advanced maternal age are predisposed to a greater risk for fetal aneuploidy. Nasseri

Table 1 Maternal demographic findings

| | Controls $n=27$ | Unexplained $n=58$ | p value ^c | Explained $n=22$ | p value ^d |
|------------------------------|-----------------|--------------------|------------------------|------------------|------------------------|
| Age in years ^a | 30.2 (23–40) | 30.5 (22.0–40.0) | ns | 30.0 (26.0–40.0) | ns |
| Gravidity ^a | 3 (2.0–4.0) | 3.0 (3.0–10.0) | ns | 3.0 (3.0–10.0) | ns |
| Parity ^a | 3 (2.0–4.0) | 0.0 (0.0–3.0) | <0.05 | 0.0 (0.0–3.0) | <0.05 |
| Pregnancy loss ^a | 0 | 3.0 (3.0–10.0) | <0.05 | 3.0 (3.0–8.0) | <0.05 |
| Duration of marriage (years) | 7 (4–18) | 6.0 (1.5–22.0) | ns | 7.0 (3.0–19.0) | ns |
| Infertility ^b | 0 | 14 (24.1%) | <0.05 | 4 (18.2%) | <0.05 |

^a Median (minimum and maximum), ^b n , %, ^c Unexplained vs. controls, ^d Explained vs. controls

Table 2 Serum hormone levels and distribution of the cases according to different FSH, LH and E₂ levels between explained and unexplained recurrent pregnancy loss groups

| | Controls $n=27$ | Unexplained $n=58$ | p value ^c | Explained $n=22$ | p value ^d |
|---|-------------------|--------------------|------------------------|-------------------|------------------------|
| E ₂ ^a (pg/ml) | 43.10 \pm 19.20 | 63.24 \pm 45.56 | 0.007 | 42.99 \pm 18.13 | ns |
| FSH ^a (mIU/ml) | 6.32 \pm 3.22 | 8.29 \pm 2.99 | 0.008 | 6.59 \pm 2.71 | ns |
| LH ^a (mIU/ml) | 3.57 \pm 1.20 | 4.60 \pm 2.04 | 0.001 | 3.38 \pm 1.64 | ns |
| FSH ≥ 10 mIU/ml ^b | 4 (14.4%) | 20 (34.5%) | ns | 3 (13.6%) | ns |
| E ₂ ≥ 50 mIU/ml ^b | 5 (18.5%) | 25 (43.1%) | 0.038 | 4 (18.2%) | ns |
| FSH ≥ 10 mIU/ml and/or E ₂ ≥ 50 mIU/ml | 5 (18.5%) | 31 (53.4%) | 0.004 | 4 (18.2%) | ns |
| FSH/LH ≥ 3.6 mIU/ml ^b | 7 (25.9%) | 28 (48.5%) | 0.033 | 5 (25.8%) | ns |

^a Mean \pm SD, ^b n , %, ^c Unexplained vs. controls, ^d Explained vs. controls

et al. showed that baseline serum FSH and/or E₂ concentrations may be valuable as predictors of fetal aneuploidy [7]. In our study, day 3 serum FSH, LH and E₂ concentrations were significantly higher in the unexplained RPL group than in controls, although serum concentrations of all hormones were within the normal range. Standard limits for FSH or E₂, although reasonable markers for ovarian response, may be too high for predicting the quality of remaining oocytes; and a decline in oocyte quality may occur long before any significant elevations in serum concentrations of these hormones are encountered. It is accepted that the patients with day 3 FSH level ≥ 10 mIU/ml and E₂ level ≥ 50 pg/ml have diminished ovarian reserve [1, 7, 12]. The percentage of women with elevated FSH levels on day 3 was higher than in controls but statistically insignificant. Day 3 serum levels of E₂ were elevated in the unexplained RPL group compared with the control group. Basal E₂ concentrations may be useful in evaluating these patients. As E₂ levels rise, circulating gonadotrophin (FSH) concentrations decline, potentially providing a misleading estimate of the hormonal balance. When combined, FSH or E₂ levels, or both, the percentage of women with elevated hormone levels were significantly higher in unexplained RPL group than in controls. Trout and Seifer demonstrated that women with unexplained RPL have a greater incidence of elevated day 3 serum FSH and E₂ levels than do women with a known cause of RPL [12]. Lenton et al. demonstrated that serum FSH increases several years before elevations in serum LH, and, as a result, the first intimation of a diminished ovarian reserve may be an elevated FSH: LH ratio [5]. Mukherjee et al. showed that in patients with a normal day 3 FSH level, an FSH:LH ratio ≥ 3.6 had a sensitivity of 85% and a specificity of 95% for predicting a poor response to controlled ovarian hyperstimulation [6]. This parameter, to our knowledge, has not been assessed as a marker of diminished ovarian reserve in women with unexplained RPL. In our study, the percentage of women with FSH: LH ratio ≥ 3.6 was significantly higher in unexplained RPL group than in controls.

The clomiphene citrate (CC) challenge test was designed to unmask poor ovarian reserve in patients with a normal basal FSH. Hoffman et al. showed that women with unexplained RPL had a similar incidence of

abnormal CC challenge test compared with the case of a large general infertility population [4]. Our control group comprised women in whom the cause of miscarriages was known.

In conclusion we observed an increased rate of diminished ovarian reserve in women with unexplained RPL. We believe that evaluation of ovarian reserve in women with unexplained RPL should be considered in the routine work-up.

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