

## Unexplained Recurrent Abortion and Diminished Ovarian Reserve

Dr. Nafiseh Saghafi

Assisted professor of university

Department of OB & GYN

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### سقط مکرر توجیه نشده و کاهش ذخیره تخمدانی

#### خلاصه

**هدف:** تعیین میزان اثر کاهش ذخیره تخمدان در ایجاد سقط مکرر توجیه نشده.

**مواد و روشها:** از میان ۱۱۶ بیمار مراجعه کننده به علت سقط مکرر به بخش زنان بیمارستان قائم (عج) پس از بررسی علل سقط، تعداد ۲۵ زن با تشخیص سقط مکرر توجیه نشده به عنوان گروه کنترل و تعداد ۲۵ زن با سابقه حاملگی طبیعی به عنوان گروه شاهد انتخاب شدند. میانگین سنی، طول سن قاعدگی، سابقه نازائی و اندازه گیری FSH و E2 در روز سوم دوره ماهانه در تمام آنها بررسی شد و نتایج با یکدیگر مقایسه شد.

**نتایج:** میزان FSH یا E2 سرم در روز سوم دوره ماهانه در زنان با شکایت سقط مکرر توجیه نشده بالاتر از گروه کنترل بود (۶۰٪ در مقابل ۱۶٪)  $P < 0.005$ . سایر معیارهای مورد بررسی در میان دو گروه تفاوت مشخصی نداشت.

**بحث و نتیجه گیری:** میزان FSH و E2 روز سوم دوره ماهانه در زنان با شکایت سقط مکرر توجیه نشده بالاتر از زنان با سابقه حاملگی طبیعی بود. بنابراین کاهش ذخیره تخمدانی ممکن است در سقط مکرر دخالت داشته باشد و بایستی به عنوان قسمتی از ارزیابی این گونه بیماران مد نظر قرار گیرد.

**کلمات کلیدی:** سقط مکرر توجیه نشده - حاملگی نرمال - استرادیول - FSH.

#### Correspondence:

Ghaem Hospital

Medical university

Mashhad - IRAN

Tel: 0511-8417493

Fax: 0511-8409612

Email: n\_saghafi@yahoo.com

**Introduction :**

Recurrent abortion is classically defined as 3 or more consecutive spontaneous abortion. Recurrent abortion is a multifactorial problem associated with : Genetic abnormalities, environmental toxins , anatomical causes, endocrine dysfunction , infection causes, Thrombophilia , advanced maternal and paternal age and Autoimmune diseases. All of these diagnoses result in pregnancy loss without live birth.(1) Unfortunately, no determinable cause can be found in most couples with recurrent abortion (70%).(2) Women with unexplained recurrent abortion probably represent a heterogeneous group with several contributing causes (2). It is well known that fetal aneuploidy can result in first – trimester spontaneous abortions and is more common in older women with poorer ovarian reserve (2) . In addition, just as women enter menopause at different ages, reductions in ovarian reserve seem to occur at different rates. Such factors as pelvic surgery, chemotherapy, and radiotherapy, as well as unknown factors ,that may directly affect the ovary, can adversely affect ovarian reserve(2). Therefore, even young women with recurrent miscarriage may have diminished ovarian reserve.(2) Ovarian reserve screening has been used by many fertility centers to evaluate a woman’s reproductive potential, both in the general infertility population and for couples undergoing IVF (3) .Not the potential to become pregnant but the ability to produce a live – born infant. Ovarian reserve screening usually involves measurement of early follicular phase FSH levels with or without an E2.(3) All studies to date using ovarian reserve screening have demonstrated that with elevated early follicular FSH levels, The

likelihood of live birth with self oocytes is very small, even with aggressive treatment using assisted reproductive technologies (3). Because diminished ovarian reserve is not limited to older women and can contribute to first – trimester spontaneous abortion. We examined the possible link between diminished ovarian reserve and recurrent abortion. We tested the hypothesis that diminished ovarian reserve, as reflected by elevated day 3 serum FSH and E2 levels, may contribute to recurrent abortion.

**Materials and Methods :**

116 women with complaint of recurrent abortion referred to Ghaem hospital , (from 1999 to 2002) . Work – up Performed by the Pregnancy Loss Evaluation Service consisted of detailed history, which included a complete obstetrical history, medical , surgical , family gynecologic history, and review of symptoms. Level of prolactin, TSH, Lupus anticoagulant , anticardiolipin antibody , antinuclear antibody were measured in all women and a uterine evaluation was done by using hysterosalpingography, after this evaluation, If no cause could be found for the pregnancy losses , the women was assigned the diagnosis of unexplained recurrent abortion.

By these criteria , there were 25 women with diagnose of unexplained recurrent abortion (test group). The other group (n:25) which represented as control, consisted of women in whom a history of a normal pregnancy was known. Two groups were compared on age, menstrual cycle length, the history of infertility and menstrual day 3 FSH and E2.

An elevated day 3 level is defined as a serum FSH Level  $\geq 10$  mIU/ml or a serum E2 level  $\geq 50$  pg/ml. Theses

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criteria for elevated FSH and E2 levels are based on data from previous reports (4). Day 3 serum FSH and E2 levels were measured at one laboratory and with the same method. Data were compared by using the  $\chi^2$  or Fisher exact test, as appropriate, p value of 0.05 was considered statistically significant.

**Results :**

The mean age in test group was :  $28 \pm 4.2$  years and in control group was  $24 \pm 3.9$ . The control group were younger (P:0.05). Two groups had similar menstrual cycle lengths ( $29 \pm 6$  days). The history of infertility was not statistically significant difference between the two groups (table).

Comparison of demographic and day 3 serum levels of FSH and E2 in women with unexplained recurrent abortion and women with a normal pregnancy history. Ghaem hospital (1999-2002)

Parameter	Women with unexplained recurrent abortion (n=25)	Women with a normal pregnancy history (n=25)	P value
No. (%) with day 3 FSH level > 10 mIU/ml	6 (24%)	1 (4%)	<.02
No. (%) with day 3 E2 level > 50 pg/ml	9(36%)	3 (12%)	.05
No. (%) with day 3 E2 level > 50 pg/ml and/or day 3 FSH level > 10 mIU/mL	15 (60%)	4 (16%)	<.004
Age (year)	$28 \pm 4.2$	$24 \pm 3.9$	0.05
Cycle Length (day)	$29 \pm 6$	$28 \pm 5.6$	0.13

Of 25 women with unexplained recurrent abortion, 15 (60%) had elevated serum levels of FSH or E2 on day 3. Of these 15 women , 9 had elevated E2 levels , 6 had elevated FSH

levels. Of 25 women in control group , 4 had an elevated serum levels of FSH or E2 on day 3 (16%). One of the 4 had an elevated FSH levels and 3 had elevated E2 levels . The percentage of women with elevated FSH levels (P<0.02), elevated E2 levels ( P = 0.05), and elevated FSH or E2 (P<.004) levels on day 3 was significant (Table).

**Discussion :**

Recurrent Pregnancy loss has multiple etiologies that must be independently investigated before treatment for the recurrent loss can be initiated. Currently , the common diagnostic categories are hormonal dysfunction, structural uterovaginal anomalies, genetic, infectious, environmental, and immunologic etiologies (1). The end treatment goal is a successful live birth. Although women with recurrent abortion are not infertile but, they suffer from the same inability to have a live – born child with self oocytes , as the infertile women.

It is well established that as a woman ages, her reproductive potential declines (2). This is in part because of an increase in the miscarriage rate, presumably because of the increased incidence of aneuploidy, and diminished ovarian reserve, which each may be related to the other. Attempts to identify women with diminished ovarian reserve have historically evaluated early follicular phase FSH concentrations with or without E2 levels (3). In particular, a recent study suggested that in the general infertility population, a significant number of women with the diagnosis of unexplained infertility demonstrated diminished ovarian reserve and that the incidence of diminished ovarian reserve in women with unexplained infertility was independent of maternal age (4). In this study there

were diminished ovarian reserve in 58% of women with unexplained recurrent abortion (in our study it was 60%). A recent study has demonstrated a high incidence of oocyte derived aneuploidy in younger women as well, particularly those with a poor prognosis for IVF (5). Recently, it has been suggested that the incidence of genetic abnormalities in spontaneously aborted fetuses was higher in women with diminished ovarian reserve compared with the women with normal ovarian reserve (6). In other study, It is well established that even younger women with diminished ovarian reserve might also have a higher incidence of genetic abnormalities of the fetus resulting from aneuploidy of the oocyte, which may account for their pregnancy losses.(7)

The above - cited studies prompted this investigation into the association of diminished ovarian reserve and recurrent abortion. Women with recurrent abortion are often relatively young, and for some, no firm etiology for their recurrent abortion can be established. Thus, we hypothesized that some women with recurrent abortion may indeed have diminished ovarian reserve as their diagnosis and, as such, would have a significantly reduced chance of a live birth compared with the case of woman with normal ovarian reserve.

Our data showed that unexplained recurrent abortion is associated with diminished ovarian reserve, as measured by serum day 3 FSH and E2 levels, Thus, women who had unexplained recurrent abortion were approximately four times more likely than women with a normal pregnancy history to have an elevated day 3 serum level of FSH or E2. Susan.W et al reported the women who had

unexplained recurrent abortion were approximately six times more likely than women with normal pregnancy (2). (In our study it was four times).

**Conclusion :**

We believe that diminished ovarian reserve may contribute in part to unexplained recurrent abortions. Consideration should be given to measuring day 3 serum FSH and E2 during evaluation of a couple presenting with recurrent miscarriage.

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## Abstract

**Objective:** To Determine the incidence of diminished ovarian reserve in unexplained recurrent abortion.

**Materials and Methods:** among 116 women with complaint of recurrent abortion who referred to Ghaem hospital, after evaluation, 25 women with unexplained recurrent abortion were chosen as the test group and the control group (n=25) were women with a history of normal pregnancy. Mean age, day 3 serum FSH and E2 levels, presence or absence of a history of infertility and menstrual cycle lengths were compared between two groups.

**Results:** Day 3 FSH and E2 Levels were higher in the unexplained recurrent abortion group compared with the control group (61% VS 16%)  $P < 0.005$ . Other factors did not differ between two groups.

**Conclusion:** Women with unexplained recurrent abortion have a greater incidence of elevated day 3 serum FSH and E2 levels than do women with a normal pregnancy history. Therefore diminished ovarian reserve may contribute to recurrent pregnancy loss and should be considered as a part of the work - up for unexplained recurrent abortion.

**Key Words:** Unexplained recurrent abortion - Normal pregnancy - Estradiol - FSH.

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