The Role of Endocrine and Endometrial Factors in Cases of Recurrent Miscarriage: A Tertiary Center Experience

Tekrarlayan Düşükte Endokrin ve Endometrial Faktörler: Üçüncü Basamak Bir Hastane Deneyimi

Tekrarlayan Düşükte Endokrin ve Endometrial Faktörler / Endocrin and Endometrial Factors in Recurrent Abortion

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Özet

Amaç: Tekrarlayan gebelik kayıplarında endometrial ve endokrin problemleri araştırmak. Gereç ve Yöntem: Tekrarlayan gebelik kaybı olan hastalarda, klinik ve sonografik görünümler, genetik, immünolojik ve anatomik faktörler, hormon profilleri, endometrial örneklemler incelendi. Kromozom anormallikleri ve uterus anaomalileri çalışma kapsamı dışında tutuldu. Bulgular: Tekrarlayan gebelik kaybı olan 57 hastanın 8'inde (14%) düşük progesteron seviyeleri bulundu. Bir hastada (1.75%) yüksek androjen seviyesi, 2 (3.5%) hastada prolaktin yüksekliği, 2 (3.5%) hastada insülin seviyelerinde yükseklik tespit edildi. Dört olguda (7%) oral glikoz tolerans testinin 2 parametresi yüksek bulundu. Endometrial örnekleme yapılan 51 olgunun sadece 1 tanesinde gecikmiş endometrial gelişim görüldü. Tartışma: Tekrarlayan gebelik kaybının hem endokrin hem endometrial faktörleri de içeren kompleks bir etiyolojiye sahip olduğu düşünüldü.

Anahtar Kelimeler

Tekrarlayan Gebelik Kaybı; Tekrarlayan Düşük; Endokrinolojik Faktör; Endometrial Faktör

Abstract

Aim: To investigate endocrinologic and endometrial factors in cases of recurrent abortions. Material and Method: In cases of recurrent abortions, clinical and ultrasonographic features, genetic, anatomic and immunologic factors, hormonal profiles and endometrial samplings were assessed. Chromosomal abnormalities and uterine anomalies were excluded. Results: In 8 (14%) of 57 cases with recurrent abortions, there were low progesterone levels. In 1 (1.75%) case there was a high androgen level. In 2 (3.5%) cases there was hyperprolactinemia and in another 2 (3.5%) cases there were high insulin levels. In 4 (7%) cases two scores of OGTT were high. In 51 cases where endometrial sampling was performed, only one (1.75%) case had delayed endometrial development. Discussion: We conclude that recurrent abortions have a complex etiology related to endocrinologic and endometrial factors.

Keywords

Recurrent Abortions; Habitual Abortion; Habitual Miscarriages; Endocrinological Factor; Endometrial Factor

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Introduction

The most frequent complication in gestation is spontaneous abortion. Habitual miscarriages are defined as two or more sequential pregnancy losses in the first 20 weeks of gestation. In the etiology of recurrent abortions, anatomic, genetic, endocrinologic, immunologic and infectious factors may have a role. In most cases the etiology cannot be set forth accurately [1, 2].

In this study, endocrinologic and endometrial factors in habitual miscarriages were assessed and the role of these factors in the etiology was investigated.

Material and Method

This study was carried out at the gynecology department of the tertiary care hospital. The study group was composed of individuals who applied to the outpatient clinic of our hospital due to three or more sequential pregnancy losses in the first 20 weeks of gestation. The informed constant was taken from all percipients and ethical approval was taken from our hospital' ethical committee. Non-consecutive abortions, pregnancy loss due to severe maternal disease and chemical pregnancies were excluded from the study. Detailed history was recorded for all cases. Gynecological examinations and ultrasonographic analyses were performed. Menstrual cycle features, gravida and parities were recorded. Cycles of 21-35 days were assessed as normal. The cases in which over 10 peripherally localized cysts with a size of 2-8 mm were detected with dense stroma in ultrasonographic examination were diagnosed as polycystic ovary syndrome (PCOS) [3].

Feriman Gallwey scoring of the cases with hirsutism symptoms was performed. In the 7th-9th days of cycle, hysterosalpingography (HSG) was conducted for all cases. For cases with pathology in the HSG results, laparoscopy and hysteroscopic procedures were applied.

Endocronologic evaluations were performed during the early days (3rd-5th days) of cycle in all cases. Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin (PRL),

Thyroid-stimulating hormone (TSH), Free testosterone (sT), and Dehydroepiandrosterone sulphate

(DHEAS-s) values were examined in blood samples taken in the morning (8:30-9:30) on an empty stomach. Progesterone measurements were done on the 21st day of cycles and ovulation findings were evaluated in the pipelle samples taken on the 26th day of the cycle. Insulin levels were measured in the blood samples taken in the morning on an empty stomach. Levels up to 29 m iu/ml were accepted as normal for insulin. 100g oral glucose tolerance tests (OGTT) were conducted. Fasting levels were accepted as in a normal range at 105, 1st hour < 190, 2nd hour < 165, and 3rd hour <145. Antinuclear antibody levels (ANA) and activated partialthromboplastin times (aptt) (25''-40'') were measured and recorded. Besides these examinations performed in our hospital, sT and DHEAS-s levels of the cases were measured in private laboratories having contracts with the social insurance institution. Insulin levels were evaluated in our hospital. Parent chromosome analyses of all cases were performed in private genetic diagnosis centers (Gentan-CDF).

The cases in which chromosome abnormalities including balanced translocations in mother and/or father were found, cases with uterine abnormalities that could have an effect in abortion etiology, such as septum and bicornis filling defects, except for uterus actuate, and cases for which recurrent aborts were positive were not included in the study.

Results

A total of 57 cases completed the study protocol. The average age was 30.60±6.23. Gravida average of the cases was 3.98±1.40 (3-8) and the parity average was 0.48±0.91 (0-4). While 53 cases had normal menstrual cycles (25-35 days), 4 cases had oligomenorrhoea.

There were Hirsutism complaints for 3 cases and the modified Feriman Gallwey scoring of these cases was over 8. The average BMIs of the 57 cases was 25.41±4.34 kg/m². The BMI was ≥25 kg/m² in 28 cases (49.1%). In the hormonal examinations performed, FHS and LH levels were within normal ranges for all cases. In only 1 case, the LH/FSH rate was >2. The PRL levels were higher 35 ng/ml in 2 cases (3.5%). TSH values were higher 5.0 mIU/ml in one case. sT3 and sT4 values of this case were found to be within a normal range. sT levels in 4 cases and DHEAS-s levels in 1 case were detected as over the normal value (35-450 µg/dl). For the progesterone measurements made on the 21st day of cycle, the progesterone levels were lower 4 ng/ml in 8 cases (8.77 %). These cases were diagnosed as anovulation. In the endometrial samplings of 51 cases performed on the 26th day of cycle, proliferative phase was detected in 8 cases. In one case (1.75%) endometrial development retardation over 2 days was identified.

ANA was negative in all cases. Aptt values were above the normal range in one case. When insulin levels were examined, insulin values in 2 cases (3.5%) were higher 29 mIU/ml. It was observed that only in 4 cases (7.01 %), were 2 or more values over the normal range in the results of OGTT. The demographic characteristics of the cases and the prevalence of abnormal results are summarized in Table 1.

Table 1. Demographic characteristics and the prevalence of abnormal results in women with habitual miscarriages. Values are given as n (%).

Demographic Characteristic	Mean Range	
Age	30.60±6.23	
Gravidity	3.98±1.40	
Parity	0.48±0.91	
BMI (kg/m²)	25.41±4.34	
Abnormality	Numerous of "n" in 57 Cases	Rate (%)
Oligomenorrhea	4	7.01
Hirsutism	3	5.25
Low Progesterone Level	8	14.0
High Androgen Level	5	8.77
Hyperprolactinemia	2	3.5
High Insulin Level	2	3.5
Abnormal OGTT	4	7.01
Endometrial Development Retardation	1	1.75

Discussion

In present study suggested that the etiology of habitual miscarriages does not seem to connect a single factor.

Many researchers have considered the causes of habitual miscarriages and have carried out studies on this subject; however the etiology could not be conclusively determined. Endocrine and endometrial factors are among the leading causes implicated in recurrent abortions. In this matter, the hypersecretion of luteinizing hormone is just one of the factors blamed in the etiology. It was asserted in some studies that PCOS and high LH levels play a role. The rate of PCOS identification in cases with recurrent abortion was reported as between 0% and 56% in different studies [2-4]. In our series composed of 57 patients, the rate of cases with BMI ≥ 25 was 49.1%. We did not encounter any patient showing typical PCOS characteristics in ultrasonographic examination in our series.

In one of the largest series performed on this subject, 2199 cases with recurrent abortion were examined and the PCOS prevalence was reported as 40.7 %. However, no statistically significant difference between the recurrent abortion rate in cases with PCOS (60.9%) and the cases with normal ovary morphology (58.5%) was determined in terms of live birth rates. The authors concluded that the morphology of polycystic ovary is not determinant in cases with recurrent abortion which can become pregnant ovulatory and spontaneously [1].

In different research studies in which LH/FSH rates were accepted as over 2, this rate was reported to be between 1.9 and 14 % in cases with recurrent abortion [2, 5, 6]. Radioimmunoassay measurements present higher and more accurate results than immunometric measurements [7]. In our study, only in one case (1.75%) was LH measured at 13.22 mIU/ml in the single LH measurement performed with radioimmunoassay. There was only one case with LH/FSH > 2. Although the first studies [8, 9] reported that high LH levels exceeding 10 mıu/ml was an important parameter in cases with recurrent abortion, other reports stated that this does not indicate a significant cause and effect relation [10]. Some study groups published guidelines stating that suppressing high LH levels in cases with PCOS does not increase the rate of live birth, in 2003 and 2006 [11,12].

In spite of all these results, many recent researchers reported that giving metphormin to cases with PCOS and LH hyper-secretion in the first trimester of pregnancy increases the rate of live birth [13-15].

Hyperprolactinemia may also play a role in the etiology of recurrent abortion. While

Hirahara [16] achieved healthy pregnancies at a rate of 85.7 % with bromocriptine treatment he gave to 64 hyperprolactinemic women with 2 or more abortions; this rate was 52.4 % in the control group. But later researchers not only found the hyperprolactinemy definition as inaccurate but also had the criticism that bromocriptine is a troublesome medicine in terms of abnormalities in the first trimester [17]. In our study, in 2 cases the prolactin levels were higher than normal. In some researches the authors investigated whether ANA and Aptt might play a role in thrombophilia syndromes. In our series ANA was negative in all cases and Aptt values were above the normal range in one case [18].

The delayed growth of the endometrium in luteal deficiency may depend on deficient estrogen levels in the follicular phase or insufficient progesterone production in the luteal phase. For diagnosis, classically, endometrial histological examination is performed. Tuccerman et al. asserted in the study they performed in a series of 36 patients with unexplained recurrent abortion in 2004 that 23 (23/36) cases had normal endometrium and 13 patients had a luteal phase defect (LPD) as a result of endometrial biopsies. Consequently, they stressed the importance of the timing of the biopsy performed to diagnose the LPD [19].

When midluteal progesterone levels of the 57 cases in our study group were examined, deficient progesterone levels in the luteal phase were defined for 5 cases. A proliferative phase was found in 8 of 51 cases for which endometrial sampling was performed, and in one case a delayed luteal phase was found. Only in 1 of the 5 cases thought to have luteal deficiency according to progesterone level could a histological diagnosis be performed. The reason for this may be that the evaluation of endometrial samples was done by different pathologists and inadequate care may have been shown for chronological determination. Recent reports have stated that since LPD is a known factor in habitual miscarriages and since it is desired to avoid expensive and invasive procedures for patients, it is recommended when considering LPD to use a simple progesterone determination where the efficiency is well known [17, 20, 21].

In summary, we conclude that habitual miscarriages have a complex etiology that may be related to different endocrinologic and endometrial factors.

Competing interests

The authors declare that they have no competing interests.

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