Dicle Tıp Dergisi /
Dicle Medical Journal

2013; 40 (3): 374-378
doi: 10.5798/diclemedj.0921.2013.03.0292

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

The evaluation of diagnostic and clinical findings in grand multiparous patients with endometrial cancer

Endometriyum kanserli grand multipar hastalarda tanı ve klinik bulguların değerlendirilmesi

Ali Özler[1], Abdulkadir Turgut[1], Elif Ağaçayak[1], Mehmet Sait İçen[1], Ulaş Alabalık[2], Serdar Başaranoğlu[1], Nurullah Peker[1], Talip Gül[1]

ÖZET

Amaç: Bu çalışmanın amacı grand multipar, endometrium kanserli hastaların tanısal ve klinik özelliklerini diğer endometrial kanserli hastalar ile karşılaştırarak değerlendirmektir.

Yöntemler: Kliniğimizde Ocak 2006-Ağustos 2012 tarihleri arasında endometrium kanseri nedeniyle opere edilen 34 hasta dahil edildi. Hastalar doğum sayısına göre üç gruba ayrıldı; Grup 1 (doğum yapmamış hastalar, n=8), Grup 2 (doğum sayıları 1'den 4'e kadar olan hastalar, n=14), Grup 3 (grand multipar hastalar, n=12). Grand multipar hastaların tanısal, klinik ve histopatolojik verileri diğer gruplardaki hastalar ile karşılaştırıldı.

Bulgular: Grup 3 (grand multipar) hastaların yaş ortalaması diğer gruplara göre anlamlı yüksek bulundu ($p<0,05$). Tüm gruplar tümörün myometrial invazyon derinliği açısından karşılaştırıldığında ise anlamlı bir farklılık tespit edilmedi ($p>0,05$). Grup 1, 2 ve 3' deki Evre 1A tümörlü hastaların oranlarının sırasıyla %75, %64,2 ve %83,3 olduğu bulundu. Ayrıca, bütün grand multipar hastaların evre 1 tümöre sahip oldukları bulunmuştur.

Sonuç: Sonuç olarak, grand multipar hastaların tanıları daha geç yaşlarda konmakta, fakat erken evrede ve endometrioid tip endometrial kanser tanılarını almışlardır. Son doğumdan itibaren geçen süre endometrial kanser riski üzerine etkili bir faktör olabilir.

Anahtar kelimeler: Endometrium kanseri, grand multiparite, nulliparite, gebelik

ABSTRACT

Objective: The aim of the present study is to evaluate differences in diagnostic and clinical characteristics of the grand multiparous patients with endometrial cancer comparing with the other patients with endometrial cancer.

Methods: A total of 34 patients that operated for endometrial cancer between January 2006 and August 2012 in our clinic were included. The patients were divided into three groups according to the number of births; group 1 (nulliparous patients, n=8), group 2 (the number of delivery from one to four, n=12), group 3 (grand multiparous patients, n=12). The diagnostic, clinical and histopathological data of the patients in the group 3 (grand multiparous patients) were compared with those of the other groups.

Results: The mean age of the patients in group 3 (grand multipara) was found to be significantly higher than those of the other groups ($p<0.05$). There was no significant difference in the depth of myometrial invasion of the tumor between all groups ($p>0.05$). The percentages of patients with the tumor stage 1A in the groups 1, 2 and 3 were found to be 75%, 64.2% and 83.3%, respectively. All of the grand multiparous patients (group 3) were found to have stage 1 tumor.

Conclusion: In conclusion, grand multiparous patients were diagnosed at advanced age but their diseases were endometrioid type endometrial cancer at an early stage. The protective effect of pregnancies against endometrial cancer decreases at advanced age. The period of time after last birth may be a factor on the risk of endometrial cancer.

Key words: Endometrial cancer, grand multiparity, nulliparity, pregnancy

[1] Dicle University, School of Medicine, Department of Obstetrics and Gynecology, Diyarbakır, Turkey
[2] Dicle University, School of Medicine, Department of Pathology, Diyarbakır, Turkey

***Yazışma Adresi /Correspondence:** Ali Özler,*
Dept. of Ob&Gyn, Medical Faculty of Dicle University, Diyarbakır, Turkey Email: draliozler@gmail.com
Geliş Tarihi / Received: 17.07.2013, Kabul Tarihi / Accepted: 01.08.2013

INTRODUCTION

Endometrial cancer is the most common carcinoma originating from the female genital organs in the developed countries, and its incidence has recently increased [1,2]. Worldwide, endometrial cancer is the 2nd most common gynecological cancer after cervical cancer [3]. In the recent years, the gynecological cancer showing the most frequent increase was endometrium cancer in southeast Turkey [4]. Endometrial cancer is divided into two general groups according to the relationship between estrogen exposures [5]. While type 2 tumors seem largely unrelated to estrogen, type 1 endometrial cancers are related to unopposed estrogen exposure. High plasma levels of bioavailable estrogens, insufficiently counterbalanced by progesterone, are thought to increase the mitotic activity of endometrial cells [6]. Therefore, reproductive factors, leading to changes in endogenous estrogen and progesterone are closely related to endometrial cancer risk.

There are a lot of epidemiological studies reporting that nulliparous women have more endometrial cancer risk than those of parous [7,8]. However, there are few studies investigating differences in diagnostic and clinical characteristics of the grand multiparous patients with type 1 endometrial cancer [9]. The term grand multiparity (GM) defines women who have undergone at least 5 full-term pregnancies [10]. The aim of the present study is to evaluate differences in diagnostic and clinical characteristics of the grand multiparous patients with endometrial cancer comparing with the other cases with endometrial cancer.

METHODS

The study protocol was approved by the Ethics Committee of Dicle University, School of Medicine. A total of 52 patients that operated for uterine corpus cancer between January 2006 and August 2012 at the Clinics of Department of Obstetrics and Gynecology, Dicle University, School of Medicine were included. The final results of histological type of cancer, size and grade of the tumor, depth of myometrial invasion, cervical, adnexal and lymphatic invasion were obtained from the archives of pathology laboratory. The 8 patients with leiomyosarcoma, 3 patients with Malignant Mixed Mullerian Tumor, 2 patients with endometrial stromal sarcoma and the patient with angiosarcoma were excluded from the study. A total of 34 patients diagnosed with Endometrial adenocarcinoma (n=28), serous adenocarcinoma (n=3), clear cell carcinoma (n=2) and mucinous adenocarcinoma (n=1) were evaluated retrospectively. The patient information related to initial complaint, age, reproductive (gravidity, parity and infertility), last menstrual period, history of chronic diseases, surgical history, serum levels of tumor markers and intraoperative observations were retrospectively retrieved from hospital records. The patients were re-staged based upon the FIGO 2009, evaluating all the data.

The patients were divided into three groups according to the number of births; group 1 (consisted of nulliparous patients), group 2 (consisted of patients have the number of delivery from one to four), group 3 (consisted of grand multiparous patients). The clinical and histopathological data of the patients in the group 3 (grand multiparous patients) were compared with those of the other groups.

Statistical analysis

Data were presented as means, standard deviations and percentages. Categorical variables were analyzed by the Chi square test and Fisher exact test. Normality of variance was tested with Kolmogorov-Smirnov test. Variables showing non-parametric distribution were compared between groups by using Mann-Whitney U test. SPSS 15.0 statistical package (SPSS Inc., Chicago, IL) was used to perform all calculations, and P values less than 0.05 were considered statistically significant.

RESULTS

The demographic data of the patients included in the study of are presented in Table 1. The mean ages (range) of the patients in the groups 1, 2 and 3 were 40.5 (30-51), 56.8 (44-69) and 69.1 (53-81), respectively. Compared the groups in terms of age, the mean age of the patients in group 3 (grand multipara) was found to be significantly higher than those of the other groups ($p < 0.05$). The mean number of deliveries of the patients in Groups 2 and 3 were 3.0±1.1 and 7.4±2.3, respectively). The rates of menopause, hypertension and diabetes in the groups 2 and 3 were higher than those of the group 1 (nulliparous) ($p < 0.05$). In all groups, the most common initial complaints were menometrorrha-

gia or postmenopausal vaginal bleeding (82.3%). The other initial complaints were abdominal pain (7.8%), postcoital bleeding (5.8%) and abdominal mass (3.9%), respectively. The advanced stage of tumor was in one of the patients presented with a mass.

Compared to all the groups in terms of the depth of myometrial invasion of the tumor, there was no significant difference ($p > 0.05$). The percentages of patients with the tumor stage 1A in the groups 1, 2 and 3 were found to be 75, 64.2 and 83.3%, respectively. The rates of patients detected elevated level of CA 125, which is an indicator of advanced disease, showed no statistically significant differences between the groups ($p > 0.05$). When the patients were re-staged according to FIGO 2009 the criteria, the distribution of patients in the groups are shown in Table 2. All of the grand multiparous patients (group 3) were found to have stage 1 tumor. The advanced tumors were detected in two nulliparous patients of group 1 and in four patients of group 2.

Table 1. The demographic and clinic data of the patients with endometrial cancer

	Group 1 (Nulliparous) (n=8)	Group 2 (0< births ≤4) (n=14)	Group 3 (Grand multiparous) (n=12)
Age (years)	40.5 (30-51)	56.8 (44-69)*	69.1 (53-81)*,#
Parity (n)	0	3.0±1.1*	7.4±2.3*,#
Menopause (%)	12.5	71.4*	91.7*
Hypertension (%)	25.0	28.6	58.3*
Diabetes Mellitus (%)	0	28.6*	50.0*,#
Myometrial invasion<1/2 (%)	25.0	35.7	16.7
CA 125 > 35 U/ml (%)	12,5	42,9	25,0

*p<0.05 comparing with Group 1 (nulliparous)
# p<0.05 comparing with Group 2 (0< births ≤4)

Table 2. The distribution of patients in the groups after re-staging according to FIGO 2009 criteria

Grade		Group 1	Group 2	Group 3	Total, %
Grade 1	1A	6	9	10	82.3
	1B	-	1	2	
Grade 2	2	-	-	-	5.9
Grade 3	3A	1	1	-	11.7
	3B	0	1	-	
	3C	0	2	-	
Grade 4	4A	-	-	-	2.9
	4B	1	-	-	

DISCUSSION

The incidence of gynecologic cancers varies from country to country. According to Globacan 2008 data, endometrial cancer is the most common gynecologic cancers in our country, and it is followed by ovarian and cervical cancer, respectively [3]. Endometrial cancer constitutes 11% of all cancers in women and, 45% of gynecologic cancers [11]. Endometrial cancer is strongly associated with unopposed estrogen. Many risk factors have been identified for endometrial cancer. Early menarche (< 12 years), late menopause (> 50 years), chronic anovulation, infertility, nulliparity, obesity, diabetes mellitus, hypertension, estrogen replacement therapy, tamoxifen therapy, hereditary non-polyposis colorectal cancer (HNPCC) and a history of familial gynecological malignancy are considered the risk factors. One of the factors that reduce the risk of endometrial cancer is the number of pregnancies. Compared with those who have had fewer births, the risk tends to be lower for those who have had

more births [8]. An epidemiological study has been reported that grand multiparity (≥ 5 births) reduces the risk of endometrial cancer by 43%.9 Compared to other cases with endometrial cancer, there is limited information about the clinical and pathological findings of grand multiparous patients in literature. In this study, the findings of grand multiparous patients compared to those of the other endometrial cancer patients.

Age at diagnosis, stage of disease, histological grade and type, ploidy, and estrogen and progesterone receptor status have been identified as prognostic markers in endometrial cancer. In literature, there are many studies investigating molecular-biological features of endometrial cancer and their prognostic values, but their clinical results are not yet clear [12]. As previously mentioned, nulliparity has been considered to be a strong risk factor for endometrial cancer [13]. However, few previous studies have focused on a potential prognostic effect of parity. The protective effect of pregnancy on endometrial cancer depends on suppression of estrogenic effect on endometrial tissue. Increase in the number of pregnancy enhances the protective effect on endometrium by reducing the exposure of estrogen [14]. The main effect of progesterone on the endometrium is reduction of cellular differentiation [8,14]. Albrektsen et al reported that nulliparity women with endometrial cancer have significantly poorer prognosis than parous women [15]. Similar results have been reported in two studies published previously [16,17]. Diagnostic delay among nulliparous women was considered as a possible explanation in these studies. Grand multipara cases have included in present study as a separate group. Compared prognostic clinical and pathological parameters, no significant difference were found between the nulliparous and multiparous and grand multiparous cases.

Compared in terms of the ages, we found a significant difference between the groups. While nulliparous cases were diagnosed at an earlier age, grand multipara cases were diagnosed at postmenopausal age. In a study comparing patients who had a birth and patients who have not given birth, it was found that childless women were at a higher risk of endometrial cancer [18]. It was suggested that the risk was stronger in younger (< 50 years) than in older (50+ years) women in the same study [18]. Advanced stage at diagnosis of endometrial cancer has been associated with increasing age, higher tumor grade, and more aggressive histology [19]. In our study, grand multiparous patients were diagnosed at advanced age but they diagnosed histological type of tumor with good prognosis at an early stage. These results suggest that the protective effect of pregnancies against endometrial cancer decreased at advanced age. In an epidemiological study, it was found that women having at least a difference of 10 years between their first and last birth have significantly lower risk for endometrial cancer [20]. In the light of all this information, the period of time after last birth may be considered a factor effecting on the risk of endometrial cancer.

In conclusion, grand multiparous patients were diagnosed at advanced age but their diseases were endometrioid type endometrial cancer and at an early stage. The protective effect of pregnancies against endometrial cancer decreases at advanced age. The period of time after last birth may be considered a factor effecting on the risk of endometrial cancer.

Acknowledgments

None

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16:481-488.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-2917.
4. Turgut A, Ozler A, Sak ME, et al. Retrospective analysis of the patients with gynecological cancer: 11-Year Experience. J Clin Exp Invest 2012;3:209-213.
5. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983;15:10-17.
6. Key TJ, Pike MC. The dose-effect relationship between «unopposed» oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer 1988;57:205-212.
7. Kvåle G, Heuch I, Ursin G. Reproductive factors and risk of cancer of the uterine corpus: a prospective study. Cancer Res 1988;48:6217-6221.

8. Pocobelli G, Doherty JA, Voigt LF, et al. Pregnancy history and risk of endometrial cancer. Epidemiology 2011;22:638-645.

9. Hinkula M, Pukkala E, Kyyrönen P, et al. Grand multiparity and incidence of endometrial cancer: a population-based study in Finland. Int J Cancer 2002;98:912-915.

10. Solomons B. The dangerous multipara. Lancet 1934;II:8-11.

11. White LN. An overview of screening and early detection of gynecologic malignancies. Cancer 15 1993;71:1400-1405.

12. Salvesen HB, Akslen LA. Molecular pathogenesis and prognostic factors in endometrial carcinoma. APMIS 2002;110:673-689.

13. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2001;15:341-354.

14. Henderson BE, Ross RK, Pike MC, et al. Endogenous hormones as a major factor in human cancer. Cancer Res 1982;42:3232-3239.

15. Albrektsen G, Heuch I, Tretli S, et al. Is the risk of cancer of the corpus uteri reduced by a recent pregnancy? A prospective study of 765,756 Norwegian women. Int J Cancer 1995;61:485-490.

16. Salvesen HB, Akslen LA, Albrektsen G, et al. Poorer survival of nulliparous women with endometrial carcinoma. Cancer 1998;82:1328-1333.

17. Hachisuga T, Fukuda K, Hirakawa T, et al. The effect of nulliparity on survival in endometrial cancer at different ages. Gynecol Oncol 2001;82:122-126.

18. Lambe M, Wuu J, Weiderpass E, et al. Childbearing at older age and endometrial cancer risk (Sweden). Cancer Causes Control 1999;10:43-49.

19. Albrektsen G, Heuch I, Wik E, et al. Parity and time interval since childbirth influence survival in endometrial cancer patients. Int J Gynecol Cancer 2009;19:665-669.

20. Bevier M, Sundquist J, Hemminki K. Does the time interval between first and last birth influence the risk of endometrial and ovarian cancer? Eur J Cancer 2011;47:586-591.