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Association Between Gestational Diabetes History with Endometrial Hyperplasia and Cancer

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ABSTRACT

Background & Objective: Gestational diabetes mellitus (GDM) is also defined as a metabolic disease associated with relative insulin resistance during pregnancy, and elevated circulating insulin may increase the risk of EH and EC development. This study aimed to investigate the association between GDM and the incidence of EH and EC.

Materials & Methods: We conducted a retrospective case-control study, including 300 women with abnormal uterine bleeding (AUB) referred to Ayatollah Rouhani Hospital in Babol. Cases (n=152) were patients with HC and EC based on medical records, and the controls (n=148) were individuals without HC and EC. The groups were compared according to demographic information, GDM or diabetes mellitus (DM) history, and body mass index (BMI). The Chi-square, independent t-test, and logistic regression analyses were performed to compare groups.

Results: Of 300 women studied, 72 people (24.1%) had a GDM history, and 64 people had a diabetes mellitus history. There was a significant difference between the incidence of EC and EH with GDM (*P*=0.001). Both GDM and DM were associated with the increased EC (OR: 17.98, 95% CI: 6.73-48.08, and OR: 1.84, 95% CI: 1.26-2.68, respectively). GDM was also associated with the increased risk of EH (OR: 6.68, 95% CI: 2.77-16.10), whereas diabetes mellitus had not a significant role in the increased risk of EH (*P*=0.14).

Conclusion: This study indicated that a GDM history is significantly associated with HC and EC. Therefore, to prevent and control these two complications in the future, management and monitoring of diabetes during pregnancy should be considered.

Keywords: Gestational diabetes, Endometrial cancer, Endometrial hyperplasia, Insulin resistance

Introduction

Endometrial cancer (EC) is the second most prevalent gynecological malignancy affecting females. Endometrial hyperplasia (EH) is an uncontrolled proliferation of endometrial glands, resulting in EC's precursor lesions. EC is classified into two types based on histopathological observations, metabolic features, and clinical manifestations **(1)**. Type I EC accounts for 70%-80% of cases and typically represents endometrioid histology. This type is commonly described as a low-grade tumor, which is estrogen-dependent and is often associated with simple and complex atypical hyperplasia **(2-4)**.

Based on epidemiological findings, multiple risk factors are associated with EC, including increased body mass index (BMI), anovulation, infertility, estrogen replacement therapy, a family history of EC, aging, and diabetes mellitus **(5-7)**. Insulin resistance, observed in diseases like type-2 diabetes, obesity, and polycystic ovary syndrome (PCOS), is an important risk factor for EC **(8, 9)**. Extensive studies have been conducted on the role of insulin resistance as an influential factor in EC, most of which indicate a significant relationship between diabetes and the incidence of this cancer **(10, 11)**. Gestational diabetes mellitus (GDM), a disease with relative insulin resistance during pregnancy, is also a risk factor in developing type-2 diabetes **(12, 13)**. GDM is estimated to affect 3%-10% of pregnant women depending on some parameters, such as the population studied, dietary patterns, and lifestyle. There are limited studies

on the GDM role in EH and EC risk, which have been associated with conflicting results **(14-16)**. A study by Wartko *et al.* in 2017 found that EH and EC had a significant relationship with GDM after matching data for gender/ethnicity and maternal age during pregnancy **(14)**. Another study reported an association between GDM and EH/EC in obese women, suggesting the possible role of augmented circulating insulin in obese women with GDM in EC development **(17)**. Given the fact that GDM may be a fast marker for insulinopathy, we investigated the relationship between GDM, EH, and EC incidence.

Methods

This retrospective case-control study was performed on the medical records of 335 women with abnormal uterine bleeding (AUB) who were referred to Ayatollah Rouhani Hospital in Babol, Iran. Among them, 35 cases were excluded from the study due to infertility and abortion. Finally, 300 people were reviewed, and their demographic information, clinical features, and the history of gestational diabetes mellitus (GDM) and diabetes mellitus (DM) were collected in a checklist. The cases included all patients diagnosed with hyperplasia Cancer (HC) and endometrial cancer (EC) based on the pathology reports, and the controls were individuals without HC and EC (Figure 1). The inclusion criteria entailed a history of at least one delivery after the 29th week of pregnancy. The exclusion criteria included a diagnosis of prenatal EH, DM before 29th weeks, young age, the lack of parity, hysterectomy at delivery, stillbirth, the lack of information about GDM, and insufficient information.

All data were obtained from medical records, including age (years), menarche age, weight, height, BMI, parity, pharmacologic treatment, the presence of DM or GDM, underlying diseases, menstrual cycle pattern, taking oral contraceptive pill (OCP), a family history of DM or GDM, the number of pregnancies, current hormonal replacement therapy (HRT), infertility, a history of abortion, insulin and tamoxifen use, and duration of AUB.

Case and control groups were matched in terms of hormone consumption, age (±3 years), and parity. Based on the information obtained from the patients' medical records, the case and control groups were compared in terms of GDM and DM history. It should be noted that the definition of GDM in this center was based on the latest edition of the guidelines provided by the American Diabetes Association (ADA) and was recorded in the patient records.

Statistical Analysis

All results were analyzed using the SPSS software version 18 (IBM, Chicago, IL., USA). The normality of data distribution was evaluated based on the Kolmogorov-Smirnov test. Quantitative variables were expressed as mean±standard deviation (SD), and qualitative variables were expressed as numbers and percentages. The chi-Square and analysis of variance (ANOVA) were used to analyze the qualitative and quantitative variables, respectively. $P<0.05$ was considered significant. Moreover, logistic regression analysis was used to test the odds ratio (OR) of the risk of GDM and DM on EH and EC with a 95% confidence interval.

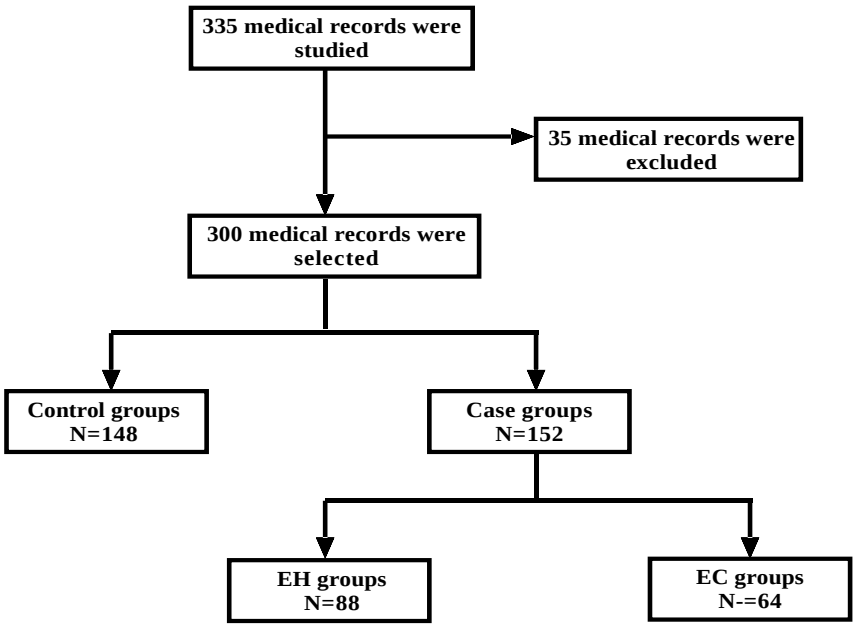

Figure 1. Schematic view of the study group selection. EC: endometrial cancer; EH: endometrial hyperplasia.

Results

Demographic Characteristics

Out of 300 participants, 88 patients had EH and 64 had EC. We observed that 148 participants did not have these two lesions in the control group. Demographic information for all three groups is given in Table 1. Our findings showed that the mean age of the EC group was 56.6±9.7 years. Moreover, the number of pregnancies, deliveries, live births, and stillbirths was significantly higher in patients with EC than in the other groups (*P*=0.001) Patients with EH had a higher BMI compared to other groups (*P*=0.023). The mean age of menarche in normal people was higher than in the EH and EC groups (*P*=0.023). There was no significant difference between different groups in terms of the mean number of abortions (Table 1).

Table 1. Comparison of demographic information and reproductive behaviors

Groups Variables	EH (n=88) Mean±SD	EC (n=64) Mean±SD	Controls (n=148) Mean±SD	P-value
Age (years)	47.8± 8.1	56.6± 9.7	51.08± 9.31	0.001
BMI (kg/m^2)	34.2±20.5	32.42± 7.05	29.83± 4.7	0.023
Gravity	3.37± 1.97	4.6± 2.25	3.83± 2.04	0.002
Parity	2.94± 1.81	4.2± 2.05	3.59± 3.05	0.01
Number of live births	2.85± 1.69	3.92± 1.8	3.25± 1.74	0.001
Number of abortions	0.44 ± 0.7	0.39± 0.79	0.42 ± 0.78	0.93
Number of stillbirths	0.1 ± 0.34	0.32 ± 0.73	0.19 ± 0.53	0.039
Menarche age	11.52± 1.68	12.12± 1.81	12.13± 1.71	0.023

Frequency Distribution of the Clinical Features of the Participants

Among 300 subjects, 227 (75.9%) had no GDM history, of which 138 patients (93.9%) belonged to the normal group. The current study results showed that 72 patients (24.1%) had a GDM history, and GDM prevalence in the group with EC was significantly higher than in others (*P*=0.001). In addition, 236 cases (78.7%) had no diabetes history, while 64 patients (21.3%) had diabetes. This rate was significantly higher in patients with EC compared to others (*P*=0.001). We found that 20 (22.7%) of women with EH, 13 (20.6%) of cases with EC, and 16 (10.8%) of normal individuals had a familial diabetes history (*P*=0.034). Furthermore, hyperplasia and EC had statistically significant relationships with age (*P*=0.001), gravity (*P*=0.001), history of underlying disease (*P*=0.016), age of GDM (*P*=0.001), and time of GDM (*P*=0.001). On the other hand, hyperplasia and EC had no significant relationship with a history of insulin use, OCP consumption, infertility, AUB, PCOS, and tamoxifen use in the study population.

The difference in the duration of oral diabetes medication use was statistically significant between three groups of EH, EC, and healthy controls (*P*=0.004). The EH, EC, and controls distribution and frequency are presented in Table 3 based on diabetes duration, in which the three groups were significantly associated (*P*=0.001). The highest frequency of the EC group was in people who had diabetes for more than 10 years (14.1%). Moreover, EH, EC, and controls had a significant relationship with underlying diseases (*P*=0.001). Patients with EC (53.2%) had underlying diseases for a more extended period than other groups. We found that EH, EC, and controls did not have a significant relationship with infertility, insulin use, HRT, and OCP in the study population.

DM and GDM Increase the Risk of EC and EH Compared to the Control Group

According to the information recorded in Table 2, the unadjusted and adjusted ORs of EC in people with a history of DM compared to healthy individuals were 3.67 (CI 95%: 1.86-7.22; *P*= 0.001) and 1.84 (CI 95%: 1.26-2.68; *P*=0.001), respectively. The unadjusted and adjusted ORs of EC risk in people with a GDM history compared to the healthy individuals were 14.4 (CI 95%: 6.25-33.1; *P*=0.001) and 17.98 (CI 95%: 6.73-48.08; *P*=0.001), respectively. Therefore, the presence of a history of GDM and DM significantly increased EC development (Table 2). According to Table 2, the unadjusted and adjusted ORs in people with DM compared to healthy individuals were 1.37 (CI 95%: 0.68-2.75; *P*=0.37) and 1.36 (CI 95%: 0.9-2.05; *P*=0.014), respectively. These results suggest that DM did not significantly affect the risk of developing EH. In contrast, the data presented in Table 2 show that GDM significantly increased EH risk (at least six-fold). The unadjusted and adjusted ORs in GDM compared to the healthy individuals were 8.76 (CI 95%: 3.92-19.5; *P*=0.001) and 6.68 (CI 95%: 2.77-16.1; *P*=0.001), respectively.

Table 2. The unadjusted and adjusted odds ratio of history of diabetes mellitus and GDM at risk of EH and EC compared with the normal group

	Independent variable	Unadjusted odds ratio (CI 95%)	*p-value*	Adjusted odds* ratio (CI 95%)	*p-value*
EC group	Diabetes mellitus	3.67 (1.86-7.22)	0.001	1.84 (1.26-2.68)	0.001
	GDM	14.4 (6.25-33.1)	0.0001	17.98 (6.73-48.08)	0.001
EH group	Diabetes mellitus	1.37 (0.68-2.75)	0.37	1.36 (0.9-2.05)	0.14
	GDM	8.76 (3.92-19.5)	0.001	6.68 (2.77-16.1)	0.001

Relationship of DM and GDM History with EH and EC

According to Table 3, 64 (21.3%) people in the study population had a DM history (type 1 and type 2 diabetes), and 236 (78.7%) individuals had no DM history. Out of 64 people with DM, 42 cases belonged to the case groups (EH and EC individuals), and 22 people were in the control group (healthy individuals). The incidence of EH and EC in the people with DM were 26.6% and 39.1%, respectively. In addition, 72 (24.1%) subjects had a positive history of GDM, and 227 (75.9%) did not have a GDM history. The incidence of EH and EC in people with a positive history of GDM was 44.4% and 43.1%, respectively.

According to Table 4, 49 (16.3%) people in the study population had a positive family history of type1 and type2 DM, and 250 (83.7%) individuals did not have a DM family history. Among 49 people with a family history of diabetes, 33 cases were in the case group (EH and EC groups), and 16 people were in the control group. The EH and EC incidence in people with a family history of diabetes was 40.8% and 26.5%, respectively

Comparison of Hyperplasia and Endometrial Cancer Incidence According to BMI and GDM History

According to Table 5, out of 72 people with a history of GDM, 55 (76.3%) were overweight (BMI>25), and 17 (23.7%) were average weight. The number of people with EH and EC who were overweight and had a history of GDM was 26 and 24, respectively. There was a statistically significant relationship between obesity and the incidence of EH and EC in people with a history of GDM (*P*=0.001). The findings of the present study demonstrated that 47.3% of overweight people and 35.3% of normal-weight people had EH. Furthermore, 43.6% of overweight and obese and 41.2% of normal-weight people had EC. The incidence of EH and EC in overweight and obese people without a history of GDM was 31.1% and 16%, respectively (*P*=0.001).

Table 3. Comparison of the history of GDM and diabetes mellitus with the incidence of EH and EC in the subjects

Groups	History of GDM N (%)		History of diabetes mellitus N (%)		P-value
	Positive	Negative	Positive	Negative	
EH group	32 (44.4)	56 (24.7)	17 (26.6)	71 (30.1)	0.001
EC group	31 (43.1)	33 (14.5)	25 (39.1)	39 (16.5)	
Control group	9 (12.5)	138 (60.8)	22 (34.4)	126 (53.4)	

Table 4. Comparison of the diabetes mellitus family history with the EH and EC incidence in the subjects

Groups	Family history of diabetes N (%)		P-value
	Positive	Negative	
EH group	20 (40.8)	68 (27.2)	0.034
EC group	13 (26.5)	50 (20)	
Control group	16 (32.7)	132 (52.8)	

Table 5. Comparison of the incidence of EH and EC according to BMI and history of GDM

Groups	Positive history of GDM		Negative history of GDM		P-value
	BMI < 25 kg/m2	BMI> 25 kg/m2	BMI < 25 kg/m2	BMI > 25 kg/m2	
EH group	6 (5.3%)	26 (47.3%)	18 (16.8%)	37 (31.1%)	0.001
EC group	7 (41.2%)	24 (43.6 %)	14 (13.1%)	19 (16%)	
Control group	4 (23.5%)	5 (9.1%)	75 (70.1%)	63 (52.9%)	

Discussion

In the current research, we observed that a history of GDM was significantly associated with EH and EC, and history of DM was significantly associated with EC. The association between EH/EC and GDM and between EC and DM was also statistically significant after adjusting for age, parity, abortions, menarche age, menopause, BMI, HRT, and OCP history.

Histologically, EH refers to the increased proliferation of the endometrial glands and is the most common EC cause, mainly in postmenopausal women **(18)**. An essential hypothesis involved in the etiology of EH is the exposure of endometrial tissue to large amounts of estrogen along with the deficiency of progesterone, which augments the mitogenic activity of endometrial cells **(3, 19)**. After hormone replacement therapy, progesterone protects the endometrium tissue against the mitogenic effects of estrogen in women. Consequently, factors that reduce progesterone are also associated with a higher risk of EC **(20)**. EC's most important known risk factors are a family history of EC, anovulatory cycles, estrogen therapy, and certain diseases in which estrogen levels are elevated in the body, such as estrogen-producing ovarian tumors and PCOS **(20, 21)**. In addition, some metabolic factors, such as obesity, insulin resistance, and hyperinsulinemia, may also be associated with EC development, as insulin might play a vital role in altering the blood levels of estrogen and androgen and stimulating the proliferation of endometrial cells **(1, 22, 23)**. GDM is a metabolic disorder with relative insulin resistance during pregnancy, a known risk factor for developing type 2 diabetes **(12, 14)**. It occurs when the function of insulin receptors is impaired, or they become insensitive and resistant to this hormone, which can eventually lead to elevated blood glucose levels and gestational diabetes **(24)**. A study by Peng *et al.* in 2019 revealed that women with a history of GDM were significantly more likely to develop laryngeal, lung, kidney, breast, and thyroid cancers **(25)**. Limited studies have been performed on the relationship between GDM and the risk of EH and EC. Wartko *et al.* showed a significant relationship between EH/EC and GDM after adjustment for gender, ethnicity, and maternal age during pregnancy **(14)**. A systematic review and meta-analysis by Saed *et al.* suggested that GDM increases EC risk by 1.72 times **(26)**. The data of our study were in line with the results of previous studies. However, in this study, we investigated the role of GDM in the incidence of EH and EC in women. Our results indicated that 24.1% and 21.3% of participants had a positive history of GDM and DM, respectively. The history of DM in the group with EC (39.1%) was also significantly higher than in other groups. According to our study results, DM and GDM were considered the risk factors for EC and increased the chance of developing EC by 1.84 (CI 95%: 1.26-2.68) and 17.98 (CI 95%: 6.73-48.08) times, respectively.

Moreover, the current investigation showed that DM did not significantly affect the chances of developing EH, while GDM increased the risk of EH by almost seven-fold. Wartko *et al.* also reported the significant association of EH and EC with a history of GDM in obese women (OR=1.31). They revealed that GDM could be associated with an increased risk of EH and EC by elevating insulin levels, which may synergistically raise estrogen levels in the body **(17)**. The results of Lucenteforte *et al.* demonstrated that EC risk in people with diabetes and obese diabetic women was 1.7 and 1.5 times higher than in non-diabetic women, respectively **(27)**. The findings of these studies are consistent with our research. We evaluated the association of EH and EC with BMI. The incidence of EH and EC in obese women with a history of GDM was 91.9%, while this rate in normal-weight women with a history of GDM was 76.5%. As a result, EH and EC incidence were observed to have a significant relationship with BMI and GDM history.

A possible hypothesis that could justify and confirm our findings and the results of other studies is the role of insulin in stimulating endometrial cell growth **(1)**. Type 2 DM and GDM are the disorders of insulinopathy in which circulating insulin levels increase **(28, 29)**. Higher circulating insulin might stimulate the proliferation of endometrial stromal cells in several ways: **(1)** inducing cell proliferation by insulin binding to its receptors on the surface of endometrial cells **(30)**, reducing the levels of the globulin-binding hormone that increase the active estrogens serum levels **(31)**, decreasing the levels of insulin-like growth factor-1 protein (IGFBP-1) and raising the levels of IGF-1, which act as mitogen agents and cause abnormal endometrial cell proliferation **(32)**, and activating mitogen-activated protein kinase and

phosphoinositide 3-kinase pathways downstream of insulin receptors on the surface of endometrial cells, which are involved in the pathogenesis of ECs **(33)**.

The small number of patients and the lack of histological data for EH and EC groups were the limitations of the present study. However, physical activity status before pregnancy, GDM treatment, pre- and post-pregnancy obesity status, smoking history, the progression of type 2 diabetes after pregnancy, and insulin resistance status during pregnancy were not evaluated in this study.

Conclusion

In this case series, among 25 women with confirmed According to the results of this study, the history of diabetes mellitus and GDM are significantly effective in the incidence of EC. Therefore, women with a history of GDM are considered a high-risk group and should be managed and followed up. This study's findings can be used as a fundamental study to conduct more prospective studies on EH and EC's etiology and pathogenesis. It is recommended that prospective studies be performed with a larger sample volume and multicenter to obtain more reliable results.

Author's Contributions

ZB, AGH, MR, TM, and KH conceived the research question, designed the protocol, and were involved in the literature search, study selection, and data extraction. ZB, AGH, MR, TM, and KH contributed to data acquisition, analysis, and interpretation. ZB and KH created the tables, figures, and ZB, AGH, and TM contributed to both the draft and final versions of the manuscript. Contributed to study design/conduct/analysis: ZB, AGH, MR, TM and KH

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Ethical Approval

Our study proposal was approved by the ethics committee of the Babol University of Medical Sciences, Babol, Iran. Ethics number: IR.MUBABOL.HRI.REC.1397.268

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Informed Consent

Written informed consent was obtained from all participants after explaining the objectives of the study.

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