Association of endometrial hyperplasia or cancer with a history of gestational diabetes- results from a population-based study in Washington State, 1987-2013

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Abstract

Association of endometrial hyperplasia or cancer with a history of gestational diabetes - results from a population-based study in Washington State, 1987-2013

Paige D Wartko

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Stephen Hawes, Associate Professor
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Purpose: Excess circulating insulin may contribute to endometrial cancer (EC) development. Some, but not all, studies suggest increased risk of EC in women with type 2 diabetes mellitus. We investigated the association of gestational diabetes mellitus (GDM) with EC and its precursor, endometrial hyperplasia (EH).

Methods: We conducted a population-based case-control study of women in Washington State with a live birth or fetal death record from 1987-2013. Cases were women with a hospital discharge record indicating presence of EH/EC after delivery (n=588). Controls were selected from remaining deliveries, frequency matched 10:1 with cases on delivery year and age (n=6013). Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), stratified by body mass index and adjusted for birth year, maternal age, and race/ethnicity.

Results: EH/EC was associated with GDM in obese women (both obese class I: OR 2.89, 95% CI 1.94-4.31 and obese class II&III: OR 4.17, 2.87-6.05), but not in normal and underweight (OR 1.41, 95% CI 0.67-2.97) or overweight women (OR 1.31, 95% CI: 0.92-1.86). Similar results were observed when considering EH and EC separately.
**Conclusions:** We observed evidence of an association between EH/EC with GDM in obese women. Excess circulating insulin may act synergistically with the excess endogenous estrogen associated with obesity, increasing risk of EH/EC. Future research with improved exposure and outcome measurement, a longer latency/induction period, and more complete information on body mass index will help to confirm this relationship.
ACKNOWLEDGEMENTS

Tiffany Beck and Susan Reed contributed substantially to this project. We thank the Washington State Department of Health for access to this data, and Bill O’Brien for programming assistance.
DEDICATION

I would like to thank my parents, Sanny and Tony Wartko, for their unconditional love and support.
Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the US, with an incidence of 25 per 100,000 woman-years. Endometrial hyperplasia (EH) is the proliferation of cells that acts as the precursor to EC. The histologic subtypes of simple, simple atypical, complex, and complex atypical hyperplasia represent a progressive spectrum with complex atypical hyperplasia being the immediate precursor to EC. Simple and simple atypical hyperplasia seldom progress to cancer, whereas complex and complex atypical hyperplasia are more likely to progress to EC if untreated.

The main biological mechanism leading to development of EH/EC is thought to be prolonged excessive (exogenous or endogenous) estrogen exposure, which stimulates growth of the endometrium. Factors that increase the risk of EC include high body mass index (BMI), anovulation and nulliparity, whereas tobacco use decreases risk. Several studies reported that adult onset type 2 diabetes mellitus (T2DM) was associated with an increased risk of developing EC, even after controlling for obesity. The proposed mechanism is the hyperinsulinemia pathway, in which excess circulating insulin stimulates the overgrowth of cells in the endometrium, leading to EH and EC. Studies performed in the US and internationally have reported a 1.3 to nearly 8-fold increased risk of EC in patients with T2DM as compared to those without T2DM.

We hypothesize that gestational diabetes mellitus (GDM) is also associated with EH/EC. GDM is one of the most common pregnancy complications; it currently affects six percent of pregnancies in the US, and the prevalence is increasing. It is a disease of relative insulin resistance in pregnancy and is a recognized risk factor for development of T2DM. Risk factors for GDM include high BMI, advanced maternal age, Hispanic ethnicity and being of certain
racial groups, including Asian/Pacific Islanders and American Indian/Alaska Natives.\textsuperscript{15,17} The purpose of our study was to compare the history of GDM among a sample of parous women with and without EH/EC identified in Washington State from 1987-2013.

**Methods**

We conducted a population-based, case-control study of the association between EH/EC and a history of GDM in Washington State. This analysis was considered exempt from formal Institutional Review Board review because the data were de-identified.

Potential cases included all parous women hospitalized with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code indicating the presence of EH/EC in Washington State hospital discharge data for years 1987-2013. This included all non-federal, inpatient hospital discharge data in Washington State. Cases were restricted to women whose record could be linked to a prior birth or fetal death record from 1987-2013 for gestations >28 weeks. We excluded women with earlier deliveries because standard prenatal screening for GDM occurs between 24 and 28 weeks gestation. We selected each case’s most recent delivery over the study period. Ninety-seven percent of cases were linked to both a birth/death certificate and a hospital discharge record at the time of delivery, while the remaining three percent were linked only to a birth certificate. We included women with complex hyperplasia without atypia (ICD-9-CM code 621.32), endometrial hyperplasia with atypia (either simple or complex, 621.33), endometrial hyperplasia, unspecified (621.30), endometrial intraepithelial neoplasia (a type of advanced endometrial hyperplasia; 621.35) and endometrial cancer (182.0). The relatively benign, early finding of simple hyperplasia without
atypia was not included as most of those women are managed medically and have a low rate of progression to EC.²,¹⁸

Controls were randomly selected (control:case ratio 10:1) from all other women with deliveries resulting in birth/fetal death certificates indicating >28 weeks gestation during 1987-2013. If a control mother had multiple births over the time period, the most recent birth was used to be consistent with case selection. Eighty-seven percent of controls had a linked birth/death certificate and hospital discharge record at the time of delivery, whereas the remaining 13% had only birth certificate information. Both cases and control deliveries were restricted to singleton gestations. Controls were frequency matched to cases by year of delivery and on maternal age at delivery (<20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥45 years).

Subjects were considered exposed to GDM if they had either of the following: a marked GDM checkbox on the birth certificate or an ICD-9-CM diagnostic code for GDM (648.8) from the hospital discharge record. For the 3% of cases and 13% of controls who were not linked to a hospital discharge record at the time of delivery, the birth/death certificate alone determined GDM status. The screening and diagnostic procedure for GDM did not change during the study period and consisted of two parts: a 1-hour, 50 g screening glucose tolerance test, which, if abnormal, was followed by a 3-hour 100 g diagnostic glucose tolerance test. Abnormal findings on the second test resulted in a GDM diagnosis.¹⁹ Although standard prenatal screening for GDM occurs between 24 and 28 weeks of pregnancy, we included women with inadequate or late initiation of prenatal care because they had the opportunity for GDM diagnosis during a later prenatal visit or a test of capillary blood glucose on presentation to the hospital in labor. To verify this, we noted there were women in our sample with inadequate or late initiation of prenatal care with a GDM diagnosis. Gestational age at delivery was calculated from last
menstrual period. Where discrepancies existed between gestational age from last menstrual period and clinically estimated gestational age in weeks, comparisons were made with birth weight of the infant to determine whether the estimated or calculated value for gestational weeks was most plausible. For women who did not have information on last menstrual period but did have a clinical estimate of gestational age, the latter was used. Women were excluded if their birth/fetal death certificate indicated a history of pregestational Type 1 or Type 2 diabetes, or GDM status was missing (Figure 1).

We generated odds ratios (ORs) with 95% confidence intervals (CIs) using unconditional multivariable logistic regression. We frequency matched on and adjusted for year of delivery and maternal age (years) at delivery based on an a priori hypothesis of confounding. Variables assessed as data-driven confounders included parity (0, 1, 2, ≥3 prior births) and maternal race/ethnicity (White non-Hispanic, Asian/Pacific Islander, and other), as well as education (<12, 12, ≥13 years) and insurance status (private, Medicaid/Medicare, other) as proxies for socioeconomic status. We evaluated BMI as both a potential confounder (evaluated continuously) and effect modifier (evaluated categorically: normal and underweight: ≤24.9, overweight: 25.0-29.9; obese class I: 30.0-34.9, obese class II&III: ≥35.0). Confounding was defined as a substantial change from the crude OR of approximately 10% or greater in the presence of an association between the potential confounder and GDM, as well as EH/EC. Effect modification was evaluated by comparison of stratum-specific ORs and consideration of Wald tests of the interaction terms.

We used multiple imputation by chained equations to generate values for missing data in covariates, as described by Azur, et al. Some variables were not added to the birth certificate until 1992 or 2003, and even in years when variables were on the birth certificate, incomplete
reporting was prevalent. Missing values were imputed for BMI (no data before 2003, 12% missing from 2003 on), prepregnancy weight (no data before 1992, 20% missing from 1992 on), pregnancy weight gain (16% missing), maternal education (no data before 1992, 8% missing from 1992 on), and income (8% missing) using linear models; for smoking (4% missing) and obesity during pregnancy (no data before 1992, 20% missing from 1992 on) using logistic models; maternal race/ethnicity (3% missing), small for gestational age (5% missing), and insurance status (12% missing) using nominal logistic models; and parity (2% missing) using an ordinal logistic model. These variables were used in addition to GDM, EH/EC, birth year, and maternal age at delivery, which had no missing values, to estimate values. We assumed data was missing at random, after conditioning on the variables included in models. All analyses were conducted in Stata (version 13.0; StataCorp, College Station, TX). Missing data was imputed using the MI IMPUTE function, and ORs were calculated using the MI ESTIMATE function. We completed 20 imputations to account for the between-imputation aspect of variability.21 Race/ethnicity was identified as an additional confounder. The ORs varied substantially by BMI stratum, so we considered BMI an effect modifier. The formal test for interaction was not statistically significant, but this may have been due to small numbers within the strata.

To assess potential differential associations of GDM as it relates to EH versus EC, we conducted sub-analyses to separately evaluate associations between a history of GDM and EH, and history of GDM and EC.

After exclusions for pregestational diabetes, missing GDM data, and delivery prior or equal to 28 weeks (Figure 1), we ascertained 6013 controls and 588 cases, including 254 EH cases and 334 EC cases, to include in our analyses. Cases had a median of 14 years between the index delivery and EH/EC diagnosis (interquartile range: 9.5-18.0).
Results

Characteristics of cases and controls at the time of delivery were generally similar with respect to maternal age, race/ethnicity, insurance status, education, parity, and gestational age (Table 1). Cases were more likely than controls to be non-Hispanic white, to not have smoked during pregnancy, and to be obese. Among cases, 7.5% had a history of GDM, while 5.1% of controls had a history of GDM (data not shown).

We observed an association between EH/EC and a history of GDM in obese women, after adjustment for birth year, maternal age, and maternal race/ethnicity (OR 3.50, 95% CI 2.54-4.81; Table 2). This association held for both obese class I (OR 2.89, 95% CI 1.94-4.31) and obese class II&III women (OR 4.17, 95% CI 2.87-6.05). There was not evidence of a strong association between EH/EC and GDM among normal weight and underweight (OR 1.41, 95% CI 0.67-2.97) or overweight women (OR 1.31, 95% CI 0.92-1.86). These findings were consistent for EH and EC subtypes.

Discussion

In the present study, we observed an association between EH/EC and a history of GDM in obese women. While we are not aware of any other studies assessing this association, three meta-analyses reported significant associations between EC and T2DM, with RRs ranging between 1.81 and 2.10. Friberg et al. assessed the association between EC and T2DM stratified by BMI; the authors found a significant association in obese women (RR 2.65, 95% CI 1.37-5.15), but not in non-obese women (RR 1.55, 95% CI 0.83-2.91). This was consistent with other studies that found a positive association between diabetes and EC in obese but not overweight or non-overweight women.
The proposed biological mechanism linking T2DM with EC is hyperinsulinemia, in which excess insulin stimulates proliferation of endometrial cells. GDM may be an earlier marker of this insulinopathy. Excess circulating insulin is thought to increase proliferation of endometrial stromal cells through various pathways: (1) by attaching to insulin receptors on the endometrial cells (2) by lowering levels of sex hormone binding globulin, which raises the levels of bioactive estrogens and (3) by decreasing levels of insulin-like growth factor binding protein 1, which increases the amount of circulating insulin-like growth factor 1. The circulating level of an insulin-sensitizing hormone, adiponectin, is associated with obesity, diabetes, and endometrial cancer, and likely plays a role in our observed association. The association between GDM and EH/EC was specific to obese women, potentially because excess circulating insulin acts synergistically with the excess endogenous estrogen associated with obesity.

This study is the first investigation, to our knowledge, of the association between GDM and EH/EC. It is strengthened by the population-based design. Although this is a case-control study, the exposure was determined from medical records, so it is not affected by the recall bias that affects many case-control studies.

A limitation of our control ascertainment method is that controls may have emigrated from Washington State, resulting in loss to follow up. A similar case-control study assessing the association of a perinatal exposure and cancer outcome through Washington State records found that 64% of control women could be identified through driver’s licenses as living in Washington State within 5 years of the matched cases’ cancer diagnosis. It is possible that some of the remaining study controls were misclassified, as they may have been diagnosed with cancer outside of the state. However, the incidence of EC and EH is so low, at 25 per 100,000 woman-
years for EC and 80 per 100,000 woman-years for the subtypes of EH included in our study,\textsuperscript{1,18} respectively, that we would only expect about six controls to be misclassified. The bias that could have been introduced through this small amount of (likely non-differential) misclassification of cases as controls is minimal.

We ascertained cases solely through hospital inpatient records, which limits our study. We likely captured most EC cases through a diagnostic code from inpatient hospital discharge records, as studies report the majority undergoes hysterectomy (an inpatient procedure) as the primary form of treatment. EH cases were less likely to be ascertained, as studies report only 50%-80\% of women with atypical EH undergo hysterectomy as primary or secondary treatment, and others are treated pharmacologically or with outpatient procedures.\textsuperscript{2,18} We captured some portion of those with either EH or EC who did not undergo surgery through inpatient hospital records for evaluation of symptoms, such as abnormal uterine bleeding,\textsuperscript{34} that resulted in a diagnostic code for EH or EC. There may be concern about differential misclassification of cases as controls if factors that affect risk of surgery for EH are associated with GDM. However, as discussed previously, the low incidence of EH limits the bias that could have been introduced. This was also addressed through assessment of EH cases separately from EC cases.

Lydon-Rochelle et al. reported on the misclassification of gestational diabetes in Washington State birth records.\textsuperscript{35} When exposure was defined as gestational diabetes recorded on either the birth certificate or hospital discharge record from delivery, sensitivity was 93.3\% and specificity was 99.1\% (using the medical record as a “gold standard”). When exposure was defined as gestational diabetes recorded on the birth certificate alone, sensitivity was 64.3\% and specificity was 99.2\%. In our study, GDM status was identified from both birth certificates and hospital discharge data in 97\% of cases and 87\% of controls, while the remaining observations
determined GDM status only from the birth certificates. We used a weighted average to
determine the sensitivity and specificity for these two groups: cases had a sensitivity of 92.5%
and a specificity of 99.1%, and controls had a sensitivity of 89.5% and a specificity of 99.1%.
These values are relatively high and the differences are minimal between cases and controls, so it
is unlikely that the OR is substantially biased by misclassification.

Our study period, with a 26-year maximum span between exposure and outcome, was
shorter than a normal latency/induction period. The median age of cases at diagnosis was 46 for
EH and 48 for EC. At the time of most recent birth (index delivery), EH cases were on average
32 years old and EC cases were 33. The median lag time between index delivery and disease
ascertainment was 14 years for both EH and EC cases, which is 10-15 years younger than is
typical.36 These younger cases may have had a different susceptibility to a hyperinsulinemia
insult compared to women diagnosed at older ages. Younger age of onset of EC is more often
attributed to a genetic cancer predisposition, such as Lynch Syndrome.37 Buchanan et al. reported
that among women with EC, 10% of those under age 50 have Lynch syndrome.38 In our study,
61% of EC cases were in this age group, although we did not have information on whether our
subjects had a Lynch syndrome diagnosis. When there is another major risk factor present in a
study, such as Lynch syndrome, the sensitivity to observe the increased relative risk associated
with other factors, such as gestational diabetes, is diminished. The potential presence of this
strong risk factor in our relatively young study population likely attenuated the risk estimate.

We were not able to assess the number of study subjects who developed T2DM after
having a GDM-affected pregnancy and before an EH/EC diagnosis. This is not a limitation to our
hypothesis-generating study because we see GDM as a potentially important risk factor for
EH/EC whether T2DM mediates the association or is independent of it. Further studies should
clarify the role of T2DM in the association between GDM and EH/EC to better understand the scientific mechanisms and clinical implications.

Treatments for GDM include nutrition therapy, as well as insulin injections and/or oral medications, such as metformin, for more advanced cases.\textsuperscript{39} Through the proposed hyperinsulinemia pathway, the use of insulin to manage GDM may have had an added proliferative effect on the endometrium.\textsuperscript{5,40} Information on GDM treatment was not available from our data sources.

There was substantial missingness in covariates because certain fields were not added to the birth certificate until later years; Due to the late addition of certain variables and incomplete reporting even after variables were on the birth certificate, we were unable to use a complete case analysis approach. We addressed the missing data through use of multiple imputation, and thus were able to adjust for the confounding effect of race/ethnicity, and to stratify by BMI. Analysis of an imputed dataset only requires the assumption that the data were missing at random, whereas a complete case analysis, the most common approach, requires the much stronger assumption that the data were missing completely at random.

Our findings should be confirmed in older women with more complete assessment of body weight over time, GDM treatment, diagnosis of Lynch syndrome, and information on other factors occurring post-pregnancy. As rates of obesity and T2DM increase in the US and abroad, EC rates are also anticipated to increase.\textsuperscript{41} There is an urgency to identify additional early and modifiable risk factors for EC if we are to prevent the associated morbidity, mortality, and costs.
FIGURE 1: Case and control selection and exclusion process.

Cases: 657
- EH/EC<sup>a</sup> hospital discharge record in WA
- Birth record in WA

Subjects Excluded
- Pregestational diabetes: 6
- Missing GDM<sup>b</sup> data: 56
- Less than 28 weeks gestation: 7

Eligible Cases: 588
  - EH<sup>a</sup>: 254
  - EC<sup>a</sup>: 334

Controls: 6570
- No EH/EC<sup>a</sup> hospital discharge record in WA
- Birth record in WA, frequency matched 10:1 on year of delivery and maternal age at delivery

Subjects Excluded
- Pregestational diabetes: 7
- Missing GDM<sup>b</sup> data: 507
- Less than 24 weeks gestation: 43

Eligible Controls: 6013

<sup>a</sup>EH: ICD-9-CM 621.30, 621.32, 621.33, 621.35; EC: ICD-9-CM 182.0
<sup>b</sup>Gestational diabetes mellitus
TABLE 1. Characteristics of parous women in WA at time of index delivery with or without endometrial hyperplasia or endometrial cancer (EH/EC), 1987-2013.

<table>
<thead>
<tr>
<th></th>
<th>EH/EC Cases (n = 588)</th>
<th>Controls (n = 6013)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>50</td>
<td>(8.5)</td>
</tr>
<tr>
<td>25-34</td>
<td>329</td>
<td>(56.0)</td>
</tr>
<tr>
<td>35-39</td>
<td>142</td>
<td>(24.1)</td>
</tr>
<tr>
<td>≥40</td>
<td>67</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Maternal race/ethnicity</td>
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<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>492</td>
<td>(85.9)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>7</td>
<td>(1.2)</td>
</tr>
<tr>
<td>American Indian/Alaska</td>
<td>7</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Native</td>
<td>7</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>32</td>
<td>(5.6)</td>
</tr>
<tr>
<td>NH OPI</td>
<td>7</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Hispanic</td>
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<td>(4.9)</td>
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<tr>
<td>Maternal education (years)*</td>
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<tr>
<td>&lt;12</td>
<td>37</td>
<td>(11.2)</td>
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<tr>
<td>12</td>
<td>84</td>
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<td>≥13</td>
<td>210</td>
<td>(63.4)</td>
</tr>
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<td>Insurance status†</td>
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<td>Private</td>
<td>279</td>
<td>(49.0)</td>
</tr>
<tr>
<td>Medicaid/Medicare</td>
<td>108</td>
<td>(19.0)</td>
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<tr>
<td>Self-pay</td>
<td>10</td>
<td>(1.8)</td>
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<td>(30.4)</td>
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<td>Parity</td>
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<td>0</td>
<td>128</td>
<td>(22.1)</td>
</tr>
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<td>1</td>
<td>215</td>
<td>(37.1)</td>
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<tr>
<td>2</td>
<td>124</td>
<td>(21.4)</td>
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<td>3+</td>
<td>113</td>
<td>(19.5)</td>
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<td>Gestational age (weeks)</td>
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<td>29-36</td>
<td>54</td>
<td>(9.4)</td>
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<td>37-40</td>
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<td>(68.9)</td>
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<td>≥41</td>
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<td>Smoking during pregnancy</td>
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<td>-------</td>
<td>-------</td>
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<td>Yes</td>
<td>64</td>
<td>(11.2)</td>
</tr>
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<td>507</td>
<td>(88.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>17</td>
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<tr>
<td>Body mass index‡ (median, standard deviation)</td>
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<td>7.5</td>
</tr>
<tr>
<td>Normal weight/underweight</td>
<td>13</td>
<td>(27.1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>11</td>
<td>(22.9)</td>
</tr>
<tr>
<td>Obese</td>
<td>24</td>
<td>(50.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>540</td>
<td></td>
</tr>
</tbody>
</table>

*NHOPI*, Native Hawaiian or Other Pacific Islander

*Maternal education was added to the birth certificate in 1992.

†Medicaid/Medicare includes charity payer; private includes Indian Health Service.

‡Body mass index was added to the birth certificate in 2003.
<table>
<thead>
<tr>
<th></th>
<th>All subtypes (EH/EC)</th>
<th>EH</th>
<th>EC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR* 95% CI</td>
<td>Adjusted OR* 95% CI</td>
<td>Adjusted OR* 95% CI</td>
</tr>
<tr>
<td>Normal and underweight</td>
<td>1.41 (0.67-2.97)</td>
<td>1.17 (0.31-4.38)</td>
<td>1.54 (1.02-2.38)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.31 (0.92-1.86)</td>
<td>1.31 (0.81-2.10)</td>
<td>1.30 (0.84-2.01)</td>
</tr>
<tr>
<td>Obese</td>
<td>3.50 (2.54-4.81)</td>
<td>3.50 (2.27-5.10)</td>
<td>3.54 (2.38-5.26)</td>
</tr>
<tr>
<td>Obese class I</td>
<td>2.89 (1.94-4.31)</td>
<td>2.84 (1.78-4.54)</td>
<td>2.87 (1.61-5.14)</td>
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<tr>
<td>Obese class II&amp;III</td>
<td>4.17 (2.87-6.05)</td>
<td>4.02 (2.39-6.76)</td>
<td>4.25 (2.65-6.83)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval
*Adjusted for known and imputed values of birth year, maternal age, and race/ethnicity.

2. Lacey JV, Jr., Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas 2009;63:39-44.


