HHS Public Access

Author manuscript

Curr Obstet Gynecol Rep. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Curr Obstet Gynecol Rep. 2015 December 1; 4(4): 234–239. doi:10.1007/s13669-015-0127-x.

The Impact of Diabetes on Gynecologic Cancer: Current Status and Future Directions

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Abstract

Diabetes mellitus has reached epidemic proportions in both the United States and worldwide with most authorities reporting a doubling in the prevalence of diabetes over the last 20–30 years. While this epidemic is closely tied to obesity, diabetes mellitus presents potential clinical challenges over and above that observed with obesity alone. From a women's health care prospective, this rise in diabetes may impact a woman's health across her lifespan. More specifically, diabetes impacts not only pregnancy as well as well as other medical conditions, but increases the risk for the development of various malignancies. From a gynecologic cancer standpoint, diabetes is most closely associated with endometrial adenocarcinomas, although increasing attention is being placed upon diabetes and ovarian cancer. Attention is also being placed on the potential role of metformin and its impact on outcomes in diabetics with cancer, as well as a potential preventative and/or adjunctive therapy for gynecologic cancer.

Keywords

Diabetes mellitus; Gynecologic cancer; Uterine cancer; Ovarian Cancer; Metformin; Review

Introduction

In 2014, the World Health Organization (WHO) estimated that the prevalence of diabetes is nearly 10% of the world's population over the age of 18 [1]. Most shocking, perhaps, is the apparent doubling in the worldwide rate of diabetes over the last two to three decades, fed by an increase in type II diabetes among children, adolescents and young adults [2, 3]. Moreover a direct link between the current obesity epidemic and diabetes is well appreciated. From a gynecologic cancer standpoint, endometrial cancer, the most common

Conflict of Interest

Brittany Lees declares no conflict of interest.

Charles A. Leath, III declares contracted research in Ovarian Cancer from Novartis and from Astra Zeneza, outside the submitted work.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

gynecologic malignancy with greater than 50,000 cases annually has steadily grown in incidence over the last decade [4]. While endometrial cancer was thought to be associated with diabetes, recent evidence suggests perhaps a more important biologic link in terms of outcomes. Traditionally, ovarian cancer was not thought to have a strong association with diabetes, although more recent evaluations have highlighted some of the complexities with this issue [5–7]. The purpose of this review is to highlight the current knowledge, with a specific emphasis on recent publications, regarding the potential impact of diabetes, in terms of incidence and outcomes in patients with both ovarian and endometrial cancer, with appropriate commentary on the role and potential impact of metformin in these patients.

Diabetes and Incidence of Endometrial Cancer

Diabetes Mellitus is a common condition in the United States, affecting 29.1 million Americans in 2012 [8]. Epidemiologic studies have shown that patients with diabetes are at increased risk of developing cancer [9]. Gynecologic cancers, including endometrial and ovarian have shown in epidemiologic studies to be more prevalent in diabetic individuals. In 2007, Friberg et al. performed a meta-analysis which showed a positive association; the summary relative risk 1.63 (95% CI 1.30–2.05) [10]. At that time they controlled for body mass index, a known risk factor of endometrial cancer, and found only two studies which had a combined summary relative risk 2.47 (95% CI 1.37–4.45), but these two studies had a high level of heterogeneity [10]. Since then, numerous studies have examined the link between diabetes and a higher risk of the development of endometrial cancer. One Swedish cohort study compared siblings, in an attempt to control for potential genetic or environmental confounders, and indeed demonstrated that individuals with diabetes mellitus had higher standardized incidence ratios of endometrial cancer compared to their siblings [11]. In 2014 Luo et al. examined the Women's Health Initiative (WHI) Database and found an increased hazard ratio of 1.44 of endometrial cancer in women with diabetes; however, when this link was controlled for BMI, the hazard ratio (HR) became non-significant 1.16 (95% CI 0.90–1.48)[12]. Certainly, epidemiologic data strongly suggests an association between endometrial cancer and diabetes mellitus, but it is not consistent the degree to which they are linked.

Diabetes and Metabolic Syndrome – Endometrial cancer

Given that endometrial cancer, more specifically type 1 endometrioid endometrial adenocarcinoma, is associated with prolonged estrogen exposure including obesity, the epidemiologic data has recently turned to perhaps an association with metabolic syndrome – abdominal obesity, low high density lipoprotein, elevated triglycerides and low density lipoprotein, hypertension and insulin resistance-as a risk factor for endometrial cancer. In 2015, Stocks et al. studied the metabolic risk score (MRS) of 7 European Cohorts and assessed the risk of endometrial cancer. They demonstrated that for each standard deviation rise in the MRS the risk of endometrial cancer rose by 56% [13].

Additional studies have looked at the overall metabolic syndrome and endometrial cancer risk, then further subdivided by the components of the metabolic syndrome. Results have been variable. Trabert et al. evaluated women over the age of 65 and noted a higher

endometrial cancer risk, HR 1.39, then when specifically assessing impaired fasting glucose when controlling for weight was 1.38 (95% CI 1.31–1.44][14]. Esposito et al. conducted a meta-analysis which showed a combined RR of endometrial cancer 1.89 [95% CI 1.31–1.48] for metabolic syndrome and specifically 1.81 for hyperglycemia[15]. These studies would support the data that some degree of insulin resistance or hyperglycemia and thus, diabetes mellitus is associated with an increased risk of endometrial cancer.

Diabetes and Prognosis

As rates of endometrial cancer continue to rise, researchers are constantly examining potential effects of co-morbidities on disease prognosis. It is often challenging to predict which patients will have higher overall survival rates, but it would be beneficial in counseling patients on treatment options if providers were aware of the relationship between potentially modifiable risk factors and disease prognosis. In 2007, Friberg et al. examined the known data and discovered conflicting evidence. Two cohort studies demonstrated a combined summary relative risk of mortality of 1.58, however, individually the studies showed opposite results and the heterogeneity was high[10]. In 2013, Zanders et al. showed a lower five-year overall survival rate of 68% compared to 84% in patients with diabetes and endometrial cancer. Even with adjustments for age, stage, comorbidities and treatment the difference persisted with a hazard ratio 2.3 (95% CI 1.4–3.7). However, the endometrial cancer specific mortality was only 1.4 (95% CI 0.7–2.6) when adjusted for stage [16]. Additional meta-analysis by Liao et al. in 2014 showed a similar pooled relative risk of disease specific mortality 1.32 (95% CI 1.1 to 1.6) although the results between studies were inconsistent. Examining all of these studies in combination, suggests a likely association of increased mortality for endometrial cancer patients with diabetes, however, the degree of risk and the actual effect on the disease status remain to be discovered.

Diabetes and Metformin

Metformin is a biguanide antihyperglycemic agent that has been used for over a decade in the United States. It is commonly prescribed as a first line agent for diabetes control and is often prescribed in women with infertility or polycystic ovarian syndrome. At less than one dollar per day, it is inexpensive, minimal side-effects; mainly gastrointestinal making it an optimal medication[17]. Recent epidemiologic data demonstrate a potential decreased incidence of cancer in diabetic patients taking metformin that has led to a recent investigation of the potential role for metformin in gynecologic cancer treatment and prevention.

The theorized effects of metformin on endometrial cancer are many. Overall, studies show that metformin decreases the overall circulating insulin levels leading to decreased growth factor stimulation of endometrial cancer cells. Additionally, metformin inhibits the mTOR pathway which has been implicated in a large percentage of endometrial cancers [9, 18]. *In vitro* and *in vivo* studies have showed preliminary success, but larger phase 2 studies are still underway.

Impact of Metformin Treatment in Diabetics

After recognizing that diabetes or hyperinsulinemia can increase a women's risk of developing endometrial cancer, investigators searched for possible protective factors. Metformin is a well-tolerated oral medication for diabetes and is typically the first-line therapy with early diabetics. In 2005, Evans et al. showed that the incidence of endometrial cancer was less in diabetics on metformin compared to those who were not [19]. In 2015, Soffer et al. showed similar incidence rates for diabetics taking and not-taking metformin 1.26 per 1000 women verses 1.29 per 1000 women [20]. Furthermore, Luo et al. utilized the WHI database focusing upon the potential impact of metformin and noted a hazard ratio of 1.00 (95%CI 0.62 to 1.62) for endometrial cancer risk for diabetics using and not using metformin [12].

In regards to outcomes, metformin does seem to be protective. Currie et al. showed a hazard ratio 0.47 for endometrial cancer patient diabetics taking metformin [21]. Additionally, studies have shown an increased overall survival rate [22, 23]. However, no study to date has shown an increase in the progression free survival. Further, it is uncertain if the patient chosen to take metformin verses other diabetic drugs such as insulin perhaps have other characteristics or hormonal balances that make them either more susceptible to the effects of metformin or perhaps put them at lower inherent risk of endometrial cancer development. No randomized control trial (RCT) has been performed on diabetic patients with metformin use, thus any causal relationship should await an RCT.

Use of Metformin to Treat Non-diabetics

If metformin can be of potential benefit to diabetics, its use in non-diabetics is uncertain. Nonetheless, based on a favorable side effect profile as well as its low cost, metformin use warrants additional evaluation as a re-purposed medication. There have been a couple of studies that have used metformin therapy in endometrial cancer patients, assessing a variety of outcomes.

Tabrizi et al. compared Metformin and Megesterol acetate therapy in patients with endometrial hyperplasia. In comparing pre-treatment and post-treatment endometrial biopsies. The majority, 95.5%, on metformin therapy had endometrial atrophy at time of post-treatment biopsy, compared to 61.9% in the megestrol group [24]. However, larger studies and longer follow-up should be undertaken prior to using metformin as a primary therapy.

Given its potential benefit on endometrial atrophy, many in vitro studies have looked at metformin's potential effect on endometrial cancer cell lines. Studies have been promising demonstrating a decrease in Ki67, increasing AMPK by inhibiting the mTOR pathway leading to increased cell apoptosis [25]. Mitsuhashi et al. studied these findings in vivo with 40 non-diabetic patients with endometrial cancer. They were randomized to preoperative treatment with or without metformin. Individuals with metformin pretreatment showed decreased rates of cell proliferation in endometrial cell lines at time of hysterectomy or endometrial curettage for diagnoses [26].

Combination Treatments

Advanced stage endometrial cancers often warrant chemotherapy treatment instead of, or in addition to, surgical management. Given promising results of metformin therapy alone on endometrial hyperplasia and theoretical effects at the intracellular level has led researchers to investigate its potential benefit in combination with current chemotherapy regimens including cisplatin or paclitaxel. In vivo studies have shown a “synergestic anti-proliferative effect” when metformin is combined with either chemotherapy agent [27, 28].

While these studies have shown promising results of combination treatments, phase 2 studies are still being undertaken. There are five current studies noted at clinicaltrials.gov investigating Metformin and its effects on endometrial hyperplasia or endometrial cancer. They include: (1) NCT01685762 Endometrial Hyperplasia and Metformin (2) NCT016975 Chemoprevention study In Obese Women (3) NCT01797523 Phase 2 Metformin with letrozole/RAD001 with advanced or recurrent endometrial cancer (4) NCT02035787 Metformin in combination with levonorgesterol with cancer or Complex atypical endometrial hyperplasia (5) GOG NCT02065687 Paclitaxel/Carboplatin/Metformin versus Paclitaxel/Carboplatin/Placebo for Stage III or IVA stage IVB or recurrent endometrial cancer. The majority of these studies are still open for enrollment and no preliminary data has been published.

Ovarian Cancer – Is Obesity or Diabetes more important?

While not as common as endometrial cancer, ovarian cancer is the second leading cause of gynecologic malignancy, with nearly 22,000 cases annually, and remains the fifth leading cause of cancer death in US women with 14,180 deaths predicted in 2015 [4]. The majority of women present with advanced stage disease at the time of diagnosis, and while the combination of surgery and chemotherapy results in remission for most, the majority of patients will ultimately experience recurrence of their disease [29]. Traditionally, prognostic outcome variables have included tumor characteristics, such as histology and grade, patient characteristics, including age and performance status, as well as treatment variables to include the completeness of surgical cytoreduction, and the use of intraperitoneal chemotherapy [29–31]. More recently, however, attention is being placed upon other medical conditions such as obesity, as well as diabetes, in terms of the impact on both the incidence, as well as outcomes in patients with epithelial ovarian cancer [6, 9, 32–34].

Obesity appears to increase the risk of a woman developing ovarian cancer [35, 36]. Mechanistically, insulin-like growth factor 1 appears to be the key drive secondary to increases in cytokine, androgen and estrogen levels, decrease in progesterone as well as hyperinsulinemia among other processes [37–40]. Most recently, Nagle and colleagues on behalf of the Ovarian Cancer Association Consortium, evaluated data from 21 prior case-control studies to determine if the survival for ovarian cancer patients is negative impacted by obesity [41]. Their data did demonstrate inferior survival outcomes in obese women when stratified by BMI, although the associations were relatively small as the pooled hazard ratios (pHR) for this data was 1.10 (95% CI 0.99–1.23) for women with a BMI of 30–34.9 and 1.12 (95% CI, 1.01–1.25) for women whose BMI was greater than 35.

Not surprisingly, secondary to the close association of obesity with diabetes, it remains a challenge to tease out exactly the contribution of either and or both of these medical co-morbidities. Difficulties with this exact question are illustrated by work from Nagle and colleagues utilizing data from the Australian Ovarian Cancer Study [42]. In this case-control study, the authors evaluated several surrogate endpoints to include: glycemic index, glycemic load and carbohydrate intake in addition to fiber intake. Although diabetes itself was not specifically evaluated, glycemic load was noted to have a higher RR for the development of ovarian cancer, RR 1.24 (95% CI1.00–1.55) when comparing the highest versus lowest quartile patients. Lee and colleagues performed a meta analyses on data from 19 case-control or cohort studies, including nested case-control studies, and found that the RR for ovarian cancer was higher for patients with diabetes, RR1.17 (95% CI, 1.02–1.33) [43]. The RR were higher for the case-control studies, RR 1.55 (95% CI, 1.11–2.19) than for either the cohort or nested case-control studies RR 1.16 (95% CI, 1.01–1.33).

Diabetes and Clinical Outcomes

Clinical outcomes for ovarian cancer patients with diabetes are increasingly being reported [5–7]. Bakhru and colleagues reported clinical outcomes over a ten-year period from the University of Michigan in a cohort of 642 ovarian, fallopian or primary peritoneal carcinoma patients, 72 (11.2%) of which were type II diabetic[7]. In this series, diabetics were older (59.9 versus 54.7 years of age, p=0.01) and not surprisingly more likely to be in menopause, had a higher mean BMI (33.4 kg/m^2 versus 27.8 kg/m^2, p<0.01), had more co-morbid conditions and were three-times less likely (9.7 versus 3.2%, p<0.01) to undergo surgical staging when compared to non-diabetics. When considering clinical variables known to predict outcomes, final stage, tumor grade and the proportion of patients undergoing an optimal cytorduection were similar; however, the diabetics were noted to have differential survival when compared to non-diabetics. Although differences in disease free survival were noted, with superior survival for the non-diabetics, this did not reach statistical significance; however, diabetics had inferior median overall survival (4.12 years) when compared to non-diabetics (6.75) (p=0.02). Additionally, in an exploratory subset of 46 diabetic patients with known hemoglobin A1c values, patients with hemoglobin A1c greater than 7.4% had inferior overall survival, 2.34 versus 3.11 years (p=0.24)

A smaller series of 341 ovarian cancer patients, including 44 diabetics (12.9%), were reported from Romero and colleagues from the University of Chicago over nearly a twenty-year period [5]. In this cohort of patients with Stage I–IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma, with a median follow-up of 63 months, 44 patients had type II diabetes, of which the minority, 16 (36.4%) used metformin. In terms of outcomes, both progression-free and overall survival (OS) appeared to be superior in the diabetics receiving metformin when compared to diabetics not receiving metformin as well as the non-diabetics. Specifically, 51% of diabetics on metformin were free of progression at five-years compared to 23% for non-diabetics and only 8% for diabetics not receiving metformin, which was statistically different (p=0.03). Likewise, diabetics receiving metformin had a 63% OS at five-years, compared to 37% for non-diabetics and 23% for diabetics not using metformin, again a statistically significant difference (p=0.03).

More recently, Shah and colleagues from the University of Alabama at Birmingham reported their observed outcomes in 367 patients with Stage I–IV epithelial ovarian cancer, including 62 diabetic women compared to a comparison group of 305 women [6]. The two groups of patients were similar in terms of age, tumor histology, use of intraperitoneal chemotherapy and cytoreductive status, although the diabetic group had a higher mean BMI, 30.7 vs. 27.5 kg/m^2 ($p < 0.001$) and more advanced stage disease (p=0.04). In this series, both progression-free survival (PFS), 10.3 vs. 16.3 months (p=0.024) and overall survival (OS), 26.1 vs. 42.2 months (p=0.005) were inferior for the diabetic patients. The proportion of patients utilizing metformin was less than 50% in this cohort and was not associated with any differences in either PFS or OS in their series. In contrast, Romero and colleagues reported on a 44 patients with type II diabetes, 16 of whom used metformin, and noted a superior proportion of patients both progression-free 51% versus 8% (p =0.03) and alive 63% versus 23% (p=0.03) at five years[5]. Additional clinical evaluations are indicated to determine the true implications of metformin and its impact on outcomes in ovarian cancer patients.

Pre-clinical work with Metformin in Ovarian Cancer

Recently Febbraro and colleagues completed a succinct review that evaluated the potential of repurposing metformin for use in gynecologic cancers [44]. In addition to reviewing the mechanisms of action, the authors also summarized preclinical as well as the limited, primarily retrospective studies, evaluating metformin's potential efficacy in primarily endometrial and ovarian cancer. While this review summarized available information regarding the potential rationale for such use, the potential challenges of utilizing supra-physiologic doses as well as the potential of a drug in diabetics to be successful in non-diabetics as a therapeutic were discussed. Most recently, the same institution reported preclinical work with metformin in terms of ovarian cancer growth inhibition and potential increased sensitivity to chemotherapy [45]. Specifically, both cell lines and mouse models were utilized to answer these important questions. *In vitro* experiments demonstrated a decrease in ovarian cancer proliferation without an increase in apoptosis. More importantly, however, was the fact that both pre-treatment with metformin prior to tumor cell implantation and the combined use of metformin with paclitaxel resulted in both 60% fewer tumor implants ($p<0.005$) and a 60% reduction in tumor growth (p=0.02) respectively.

Clinical Impact of Metformin in Ovarian Cancer

Bodmer and colleague from Switzerland provided some of the first suggestions that metformin may have a protective effect in terms of the future development of ovarian cancer[46]. In their case control study that utilized 1611 ovarian cancer patients as cases, a suggestion that long-term use of metformin, based on number of prescriptions filled, decreased ovarian cancer risk was noted (OR 0.61, 95% CI 0.30–1.25). Kumar and colleagues from the Mayo Clinic performed a case-control study to further evaluate the potential impact of metformin on overall survival in patients with ovarian cancer [47]. In their analyses, two cohorts of matched patients with ovarian cancer were compared based on the use or non-use of metformin. The initial comparison included 72 patients with ovarian cancer that used metformin compared to a control group of 143 controls. A second analysis

that included 61 ovarian cancer cases and 178 controls noted that in specific of similar pathologic and clinical parameters including, age, histology, use of platinum chemotherapy, stage and optimal cytoreduction, cases had superior overall survival than controls, 67% versus 47% (p=0.007). In addition, following multivariable analysis, metformin use was an independent predictor of superior survival, HR 2.2 (95% CI 1.2–3.8; p=0.007), when controlling for the previous covariates as well as BMI.

Conclusions

Diabetes appears to have detrimental impacts on potentially both the development and the outcomes of patients with endometrial and ovarian cancer. As noted, challenges remain in determining the impact of diabetes per se, versus obesity that is closely linked to the development of diabetes. Importantly, based on preclinical data and primarily observational data, metformin may have beneficial therapeutic effects in both diabetics as well as non-diabetics with either endometrial or ovarian cancer. Ultimately, clinical trials will be necessary to determine the exact role of metformin combined with chemotherapy or other therapies, and as noted several trials are currently accruing patients in various clinical scenarios.

Acknowledgments

Support: Funding support was provided in part by (NIH) to CAL 5K12HD0012580-15.

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•• Of major importance

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