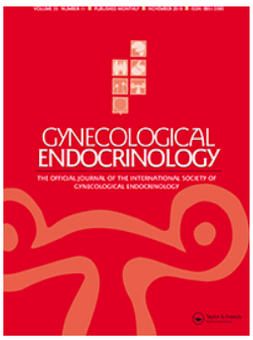

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CONSERVATIVE TREATMENT IN DIABETES MELLITUS ENDOMETRIAL HYPERPLASIA AND EARLY ENDOMETRIAL CANCER

Diabetes mellitus and responsiveness of endometrial hyperplasia and early endometrial cancer to conservative treatment

Antonio Raffone[a], Antonio Travaglino[b], Gabriele Saccone[a], Anna Di Maio[c], Antonio Mollo[a], Massimo Mascolo[b], Rossella De Rosa[a], Giuseppe De Placido[a], Luigi Insabato[b] and Fulvio Zullo[a]

[a]Obstetrics and Gynecology Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; [b]Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy; [c]RSA Oasi San Francesco, Castellammare di Stabia, Italy

ABSTRACT

Objective: The conservative treatment of endometrial hyperplasia without atypia (HWA), atypical endometrial hyperplasia (AH/EIN) and early endometrioid carcinoma (EEC) is based on progestins. We aimed to assess whether diabetes mellitus affects the responsiveness of HWA, AH/EIN and EEC to conservative treatment, through a systematic review and meta-analysis.

Study design: Electronic databases were searched for studies assessing the outcome of conservative treatment in HWA, AH/EIN and EEC, stratified based on the diagnosis of diabetes mellitus. The association of diabetes mellitus with treatment failure was assessed by using odds ratio (OR). A *p*-value $< .05$ was considered significant. The risk of publication bias was assessed by using a funnel plot. A subgroups analyses was performed based on histologic diagnosis of benignity (HWA) or premalignancy/malignancy (AH/EIN or EEC).

Results: Six studies with 876 patients (383 HWA, 365 AH/EIN and 128 EEC) were included. Overall, diabetes mellitus was not associated with outcome of treatment (OR = 1.20; $p = .62$). The association was not significant in both the HWA subgroup (OR = 0.95; $p = .93$) and in AH/EIN and EEC subgroup (OR = 1.43; $p = .46$). There was no significant risk of publication bias.

Conclusions: Diabetes mellitus does not affect the outcome of conservative treatment in HWA, AH/EIN and EEC.

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Endometrial hyperplasia; endometrial intraepithelial neoplasia; diabetes; endometrioid carcinoma; fertility-sparing

Introduction

Endometrial hyperplasia is an irregular proliferation of endometrial glands, which can be either a benign proliferation, or a neoplastic lesion that may evolve into endometrioid carcinoma. In the 2014 World Health Organization (WHO) classification, benign endometrial hyperplasia is termed 'hyperplasia without atypia' (HWA), while premalignant hyperplasia is termed 'atypical hyperplasia/endometrioid intraepithelial neoplasia' (AH/EIN). The diagnosis of HWA or AH/EIN, is based on the presence of cytologic atypia at histologic examination [1–3].

Patients with HWA may be followed without treatment when asymptomatic; otherwise, progestins are advisable. On the other hand, total hysterectomy is recommended for AH/EIN. A conservative treatment based on progestins can be used in patients with AH/EIN who desire pregnancy or who are contraindicated for surgery [4,5]. Such approach may still be chosen in case of low grade early endometrioid carcinoma limited to the endometrium (EEC) [5,6].

Several meta-analyses have suggested that levonorgestrel-releasing intrauterine device (LNG-IUD) is safer and more effective than oral progestins [7–9]. Recently, hysteroscopic resection followed by progestins has been proposed as an even more effective conservative treatment [10,11].

Despite the wide use of conservative treatments, a variable percentage of patients does not respond to progestins, and bear a considerable risk of progression to myoinvasive disease [12].

Several studies searched for predictive markers of response to progestins, including clinical, pathologic and immunohistochemical factors [5,12–15]. However, to date no clinically useful predictive markers have been identified.

In this review, we focused on diabetes mellitus. Diabetes mellitus has been proposed as a risk factor for endometrial cancer both in the general population and in patients diagnosed with endometrial hyperplasia [16,17].

The aim of our study was to assess whether diabetes mellitus affects the responsiveness to conservative treatment in women with endometrial hyperplasia or EEC.

Materials and methods

Study protocol

Methods for search strategy, study selection, data extraction, risk of bias assessment and data analysis were designed *a priori*. All review stages were conducted independently by two reviewers (AR, AT). Disagreements were resolved by discussion

CONTACT Antonio Travaglino antonio.travaglino.ap@gmail.com Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy

Supplemental data for this article can be accessed here.

among authors. This study was reported according to the PRISMA statement [18].

Search strategy

MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library as electronic databases were searched from the inception of each database to June 2018 by using several different combinations of the following text words: endometrial hyperplasia; endometrial cancer; endometrioid adenocarcinoma; endometrial intraepithelial neoplasia; EIN; therapy; treatment; conservative; fertility sparing; progestogen; progestin; oral; medroxyprogesterone; MPA; intrauterine; levonorgestrel; LNG; mirena; response; regression; resistance; persistence; outcome. Relevant references of the included articles were also reviewed, and their abstract were screened.

Study selection

All studies assessing the response to conservative treatment in women diagnosed with HWA, AH/EIN or EEC were included. Exclusion criteria were: patients not stratified according to the diagnosis of diabetes mellitus; case reports; reviews. Language restrictions were not applied. Studies analyzing data overlapping with other studies were excluded from the meta-analysis.

Data extraction

Data were extracted from each study without modification and reported in 2×2 contingency tables. Data extraction was performed according to the PICO. P (Patient, Population, or Problem) were women diagnosed with HWA, AH/EIN or EEC and diabetes mellitus, treated conservatively with progestins; I (Intervention, Prognostic Factor, or Exposure) was the diagnosis of diabetes mellitus; C (Comparator) were women diagnosed with HWA, AH/EIN or EEC without diabetes mellitus, treated conservatively with progestins; O (Outcome) was the response to conservative treatment.

Diabetes mellitus was defined as a hemoglobin A1c level $\geq$6.5%, a fasting plasma glucose level $\geq$126 mg/dL, or a 2-h plasma glucose level $\geq$200 mg/dL [19].

The response to conservative treatment was considered "good" if the lesion regressed completely, or "poor" if the lesion persisted or progressed.

Data were also subdivided according to the histologic diagnosis into benign (HWA) or premalignant/malignant (AH/EIN or EEC).

Secondary data extracted were country, period of enrollment, administration route of progestins (oral vs intrauterine) and follow-up duration.

Risk of bias within studies assessment

The Methodological Index for Non-Randomized Studies (MINORS) [20] was used to assess the risk of bias within studies. For each study, quality criteria were evaluated with regard to seven domains: (1) Aim (i.e. clearly stated aim); (2) Patients (i.e. all patients meeting inclusion criteria were included in the study during the study period); (3) Data (i.e. data were collected according to a previously established protocol); (4) Endpoint (i.e. endpoints adequate to the study aim); (5) Bias (i.e. the study endpoint was assessed without bias); (6) Follow-up (i.e. the follow-up was sufficiently long to allow the assessment of the main endpoint), (7) Loss (i.e. no more than 5% of patients were lost to follow-up). For each domain, authors' judgment was 'low risk' of bias if the criterion was met, 'high risk' if the criterion was not met, or 'unclear risk' if an adequate evaluation of the criterion was impossible.

Data analysis

The association between diabetes mellitus and responsiveness to treatment was calculated as odds ratio (OR) for failure of treatment, with 95% confidence interval (CI). OR was calculated for each study and as pooled estimate, and reported graphically on a forest plot. A p value $< .05$ was considered significant.

The inconsistency index (I^2) was used to quantify statistical heterogeneity among studies: heterogeneity was considered minimal for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$ and high for $I^2 \geq 75\%$. A fixed effect model was adopted in the case of $I^2 < 50\%$; otherwise, a random effect model was preferred.

The risk of bias across studies (publication bias) was assessed by reporting the results on a funnel plot. Asymmetry of funnel plot indicated a significant risk of publication bias if stronger association was present in less accurate studies.

Data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014).

Results

Study selection and characteristics

Six studies with a total of 876 patients were included in the systematic review [21–26]. The whole process of study selection is reported in Supplementary Figure 1.

The sample assessed included 383 HWA, 365 AH/EIN and 128 EEC. Out of these, 120 AH/EIN were excluded due to the risk of overlapping data between two studies [25,26], and 3 EEC were excluded for lack of data in the primary study [26].

Sampling methods included endometrial curettage and hysteroscopic biopsy. Regarding administration route of progestins, 640 patients received oral progestins, while 262 patients were treated by LNG-IUD. The follow-up duration ranged from 1 to 148 months. Characteristics of each included studies are reported in Table 1.

Risk of bias within studies assessment

All studies were considered at low risk of bias for the 'Aim', 'Endpoint' and 'Loss' domains, and at unclear risk for the 'Data' domain.

For the 'Patient' domain, 3 studies were considered at low risk and 4 at unclear risk.

For the 'Bias' domain, one study was considered at unclear risk, because the presence of simple hyperplasia on follow-up was considered as a good response of complex hyperplasia to treatment; all other studies were considered at low risk instead, because they considered only a complete absence of hyperplasia or cancer as a good response to treatment.

For the 'Follow-up' domain, 2 studies were considered at unclear risk, because an unspecified number of patients were followed for less than 3 months, which should be the minimal time to ascertain the outcome of treatment [4].

Table 1. Characteristics of the included studies.

Study	Country	Study design	Period of enrollment	Sample size	Diagnosis			Age	Bmi	Sampling method	Treatment*			Follow-up
					EH	AEH	EC				Oral	IUD		
2012 Upson	USA	Nested case control	1985–2005	114	73	41	0	>18	52 obese	Biopsy	114	0		4
2013 Gallos	UK	Retrospective/ prospective	1998–2010	310	310	0	0	Reported as age groups	Reported as BMI groups	unclear	81	229		59 (12–148)
2015 Yang	China	retrospective	2001–2010	88	0	37	51	33 (24–39)	27 (17-45)	Biopsy, curettage	85	17		61 (15–96)
2016 Chen	China	retrospective	2000–2011	53	0	16	37	32 (21–41)	12 obese	Biopsy, D&C	53	2		54 (4–148)
2018 Yang	China	retrospective	2011–2016	151	0	151	0	33 (21–44)	24 (17-38)	D&C	151	0		12 (1–55)
2019 Yang	China	retrospective	2013–2017	160	0	120	40	32 (22–47)	24 (16-44)	D&C	156	4		13 (1–53)
Total			1985–2017	876	383	365	128	–	–	–	640	262		(1–148)

Authors' judgments on the risks of bias within studies are summarized in Supplementary Figure 2.

Meta-analysis

The overall estimate showed an OR of 1.20 (95% CI, 0.58–2.48), without statistical significance ($p = .62$); statistical heterogeneity among studies was minimal (I^2=9%).

In the subgroup of AH/EIN and EC, pooled OR was 1.43 (95% CI, 0.55–3.69), without statistical significance ($p = .46$), and with low heterogeneity among studies (I^2=33%).

In the subgroup of HWA, pooled OR was 0.95 (95% CI, 0.30–2.97), without statistical significance ($p = .93$), and without heterogeneity among studies (I^2=0%) (Figure 1). The difference between the subgroups was not statistically significant ($p = .59$) (Figure 1). The funnel plot showed a symmetrical distribution of the included studies, hence excluding a significant publication bias (Figure 2).

Discussion

Main findings and interpretation

Our study showed that diabetes mellitus did not affect the response to conservative treatment in women with HWA, AH/EIN or EEC.

The importance of diabetes mellitus in the cancer risk has long since been subject of debate [27].

In diabetes mellitus type II, insulin-resistance leads to an increase in the levels of circulating insulin. As a consequence, the available circulating levels of insulin like growth factor 1 (IGF-1) also increase. This promotes the activation of pro-proliferative kinase pathways. Such a mechanism has been proposed as the cause of the presumed association between diabetes mellitus and cancer [17,28,29].

With specific regard to endometrial cancer, there have been several reports of diabetes mellitus as a significant risk factor [16,30]. However, some authors suggested that the association between diabetes mellitus and endometrial cancer might be dependent on BMI. In fact, it is known that increased body fat correlates to insulin-resistance [31]. By contrast, other studies suggested that, in diabetic patients, the risk of endometrial cancer was constant, independently from BMI [32]. According to a recent review, while evidence regarding the role of obesity in the risk of cancer appears robust, the role of diabetes mellitus is less clear [27].

Other studies have also supported the relevance of diabetes mellitus as a risk factor for occult cancer in women diagnosed with endometrial hyperplasia, highlighting its independence form BMI and proposing its integration in a prognostic algorithm [17,33,34]. Consistently, a recent meta-analysis showed that diabetes mellitus was a risk factor for occult malignancy in women with endometrial polyps [35].

All these findings call into question whether a diagnosis of diabetes mellitus may have practical consequences in the management of patients with endometrial hyperplasia and cancer.

In this meta-analysis, we focused on the conservative treatment based on progestins, which is widely used for endometrial hyperplasia and cancer, as well as for other endometrial lesions [36–39]. We found that diabetes mellitus did not significantly affect the outcome of conservative treatment of endometrial hyperplasia and EEC.

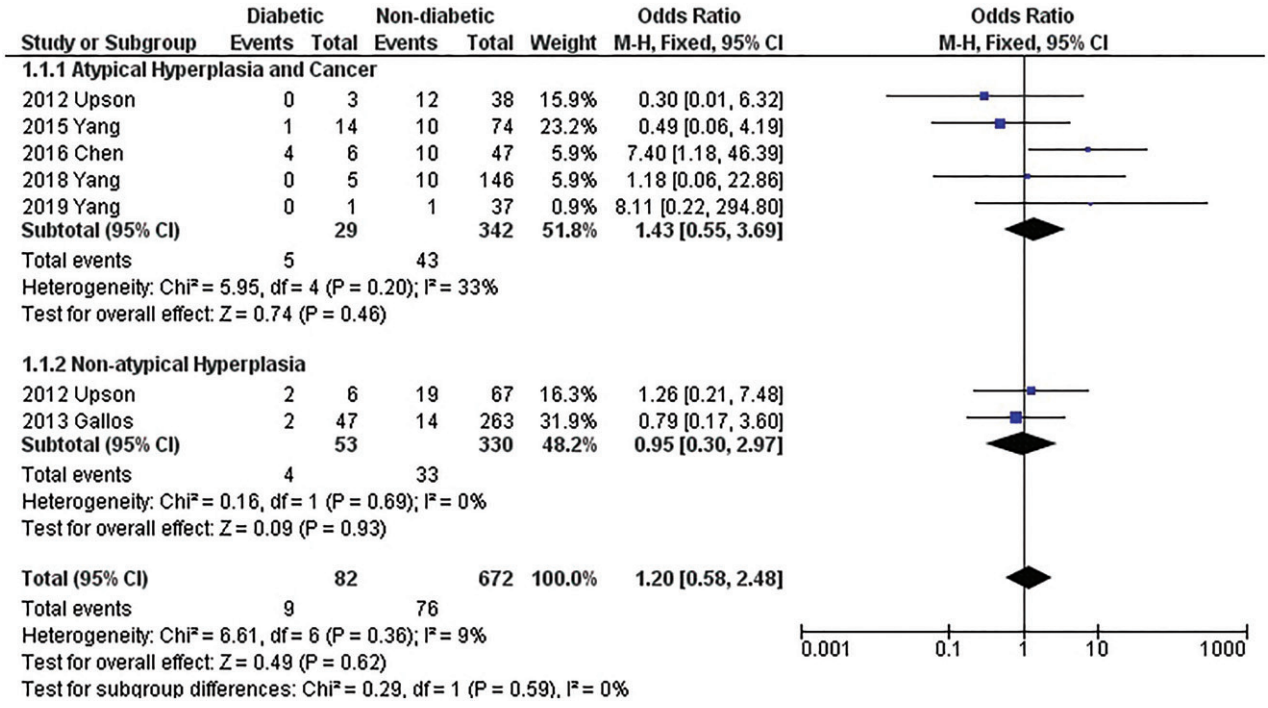

Figure 1. Forest plots reporting odds ratio (OR) for the association between diabetes mellitus and failure of conservative therapy in patients with endometrial hyperplasia without atypia (HWA), atypical hyperplasia (AH/EIN) and early endometrioid carcinoma (EC).

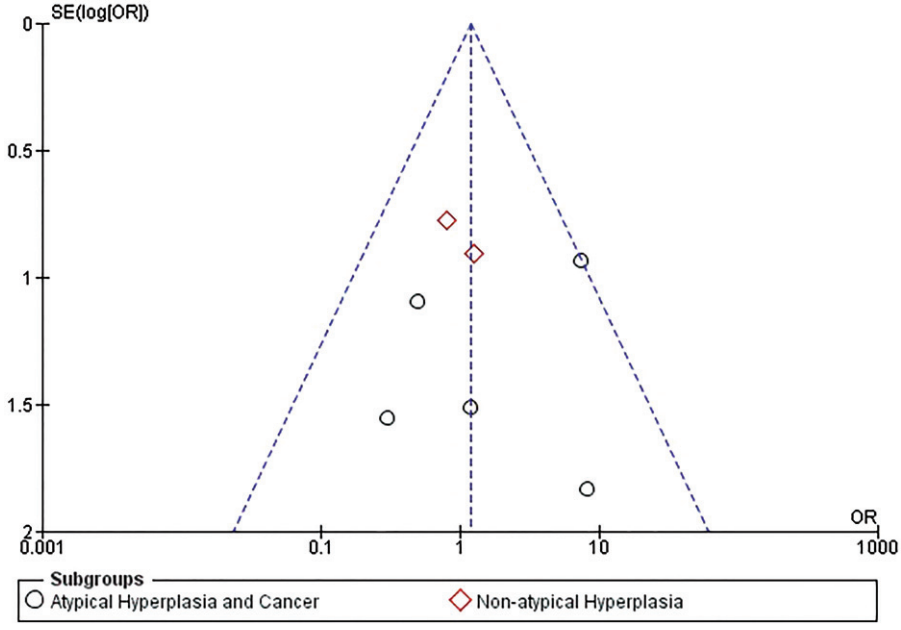

Figure 2. Funnel plot reporting odds ratio (OR) and standard error (SE) for the assessment of the risk of bias across studies.

We further investigated this association by performing a subgroup analysis based on histologic diagnosis. In fact, HWA is a benign condition, while AH/EIN and EEC are neoplastic lesions. The pathogenetic process of HWA is dysfunctional, hormone-driven, and caused by an unopposed action of estrogens; on the other hand, AH/EIN and EEC harbor several mutations that promote survival and proliferations [40–43].

Although diabetes seemed to have a slightly more negative effect on AH/EIN and EEC (OR = 1.43) than on HWA (OR = 0.95), the results were non-significant in both subgroup; furthermore, also the difference between subgroups was non-significant.

These findings support that diabetic women with endometrial hyperplasia and cancer are not at higher risk of failure of conservative treatment. Thus, no differences in management and follow-up timing appear to be advisable for diabetic woman with endometrial hyperplasia and/or cancer conservatively treated.

Such result appears of clinical value, since glycemic control has been proposed as a possible relevant target in the management of women with endometrial hyperplasia and cancer [17,44]. In this regard, a major antidiabetic drug such as metformin has been considered as a valuable option for the conservative treatment of endometrial hyperplasia and cancer. There is evidence

that the addition of metformin to progestin may improve the effectiveness of the conservative treatment; such evidence is also strengthened by a meta-analysis [45]. However, a further meta-analysis in this field concluded that scientific evidence did not support nor contrast with the usefulness of metformin [46].

In this background, we think that our study may provide a new element to investigate the actual clinical significance of diabetes mellitus in women with endometrial hyperplasia and EEC. Our findings seem to exclude the relevance of diabetes mellitus in a predictive algorithm of response to conservative treatment in endometrial hyperplasia and EEC. Further studies are necessary to confirm these results.

Strengths and limitations

To the best of our knowledge, this is the first review and meta-analysis evaluating the relevance of diabetes mellitus in the conservative treatment of endometrial hyperplasia and cancer. We could assess a quite large sample, analyzing the results separately for benign functional conditions (HWA) and premalignant/malignant lesions (AH/EIN and EEC). The low-to-absent statistical heterogeneity among studies and the absence of a significant risk of publication bias give solidity to our results.

A limitation to our results may be the retrospective design of the included studies. Another limitation may be the small number of patients diagnosed with diabetes mellitus, mainly due to the fact that most patients were premenopausal; in fact, while young women are more likely to undergo conservative treatment, they also are less likely to have diabetes.

Finally, it was impossible to assess the results separately for oral and intrauterine administration of progestins.

Conclusion

Diabetes mellitus does not seem to affect the responsiveness of HWA, AH/EIN or EEC to progestin-based conservative treatment. Therefore, diabetic patients might be considered for conservative treatment without particular concerns and without the need for a different management or follow-up timing. Further studies are necessary to confirm these results.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Gabriele Saccone http://orcid.org/0000-0003-0078-2113

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