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The Prevalence of Abnormal Cervical Pap Smears in Women with Morbid Obesity in Dubai, United Arab Emirates

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Abstract

Background and Objectives: The prevalence of abnormal cervical cytology in morbidly obese women using ThinPrep® liquid-based Pap Test™ and HPV DNA Test™ is unknown. We aimed to investigate whether women with morbid obesity have a higher frequency of abnormal Pap smears compared with nonobese women, and to explore the rate of Pap smear screening in morbidly obese women.

Design and Setting: We conducted a retrospective study over five years in two general government hospitals in Dubai.

Patients and Methods: We screened ThinPrep slides and HPV DNA of morbidly obese women and nonobese women. The age, ethnicity, demographic and socioeconomic backgrounds of the two groups were matched. We studied hypertension (HTN), diabetes (DM), infertility, sexually transmitted diseases (STD), connective tissue disease (CTD), immunosuppression and oral contraceptive pills (OCP) as potential risk cofactors.

Results: Only 90 (29%) out of 310 morbidly obese women had had Pap tests. They showed more prevalence ($P<0.05$) of ASC-US, high-risk HPV DNA and LSIL [16 positive (18%) (95% CI: 7.0-26.2)], and of endometrial AGCs [4 positive (4.5%) (95% CI: 0.3-13.5)] than the nonobese women (n=8175), [279 positive (3%) (95% CI: 3.0-3.8] , and [2 positive (0.024%) (CI:0.01-0.09)]. There were no endocervical AGCs, HSIL or squamous cancer in morbidly obese women. DM, HTN, OCPs, CTD and STD were more common in morbidly obese women having abnormal Pap smears.

Conclusions: Low-grade squamous abnormalities, high-risk HPV, and endometrial AGCs are more frequent in morbidly obese women than in nonobese women. Women with morbid obesity have a low rate of cervical screening. This, among other factors, could increase the risk of these women to abnormal cervical cytology. This vulnerable group should benefit from more frequent cervical cytology screening. Appropriate clinical and educational measures should be implemented to encourage compliance to Pap smears. Weight reduction might help.

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Introduction

Human papillomavirus (HPV) is a crucial etiologic factor in the pathogenesis of cervical dysplasia and carcinoma.[1] Other cofactors like smoking, oral contraceptive pills (OCP), sexually transmitted diseases (STD) like herpes simplex virus (HSV) and Chlamydia trachomatis infections, prolonged immunosuppression and infertility hormonal treatment, chronic connective tissue diseases such as systemic lupus erythematosus, may play a role in the persistence of high-risk HPV infection and subsequent risk to cervical cancer.[2-5] A systematic review showed that an inadequate screening and poor compliance to cervical cancer screening program in women with morbid obesity to be an important risk factor for abnormal cervical Pap smears.[6] Women with morbid obesity are commonly hypertensive, diabetic, could be exposed to prolonged medical and hormone manipulations for dieting or infertility treatment, and have increased estrogen levels.[6-13] These obesity-associated conditions are potential risk factors for endometrial and cervical neoplasia.[6-13] Therefore, in theory, women with morbid obesity could be vulnerable to abnormal endometrial proliferation, as well as persistent cervical HPV infection. They could be at a higher risk of developing endometrial hyperplasia and carcinoma, and cervical epithelial abnormalities.[6-13] However, whether morbid obesity is an independent risk factor for cervical and endometrial abnormalities, or if other additional cofactors contribute to this risk is still a controversial topic.

Even though morbid obesity is a growing problem in our region, studies to investigate the prevalence and spectrum of abnormal Pap smears in women with morbid obesity are relatively scarce. To bridge the gap, we conducted a retrospective study to demonstrate whether women with morbid obesity have a higher frequency of abnormal Pap smears and therefore are at a higher risk of developing cervical and endometrial epithelial abnormalities compared with women without morbid obesity. We also attempted to assess the relationship between certain morbidity and non-morbidity associated cofactors and the risk to cervical and endometrial abnormalities in morbidly obese women.

Patients and Methods

We have conducted a retrospective study over five years from January 2009 to November 2013. All of the Pap tests that were reported in the cytology unit in Dubai hospital within this period were retrieved.

A computer-based retrieval system was used to retrieve and review the data. Women who were registered with the clinical diagnosis of morbid obesity based on body mass index (BMI) were selected. Morbidly obese women comprised women with a BMI ≥ 35 kg/m^2 with or without obesity-related health conditions like diabetes mellitus, hypertension or obstructive sleep apnea. Women who were clinically diagnosed with morbid obesity and who had ThinPrep (TP) Pap tests (Cytyc Corp., Boxborough, MA) during this period or records of previous Pap smears were included in the study. Morbidly obese women who stated that they had not performed Pap Tests during the study period or had no previous records of Pap tests in our instituion were excluded. The other group included women without morbid obesity who had Pap tests during the same period of the study. We have excluded non-local women of non-Arabic ethnic origin from both groups. Both groups were recruited from the same local community and were demographically similar and of comparable socioeconomic status. The ages were matched. The age range for both groups was limited between 23 and 56 years. The youngest patient with

morbid obesity was 23-year-old and therefore the age of 23 was chosen as the lower limit. We took the upper limit of 56 years for both the cases and the controls because the eldest patient with morbid obesity in our study was 56-year-old. Abnormal Pap tests included atypical squamous cells of undetermined significance (ASC-US) and above, that is all cervical TP tests with abnormal squamous and/or glandular epithelial abnormalities. Two pathologists had retrospectively screened and reviewed the TP slides of the positive Pap tests to confirm the cytology reports. We used the 2001 Bethesda system to classify the epithelial abnormalities.[14]

We could not perform HPV DNA Tests on all of the Pap tests. This is because of financial limitations to perform this expensive test on a large number of Pap smears. In addition, since our study was retrospective, we were not able to retrieve the cytology vial materials. This is because the vials are routinely discarded 3 months after signing the reports in our institution. The policy of our laboratory is to perform Digene Hybrid Capture 2 High-Risk HPV DNA Test™ on ASC-US Pap tests only. Therefore, the HPV DNA results for women with

ASC-US were available for comparison. Clinical data with regards hypertension, diabetes, smoking, alcohol drinking, OCPs, marital status, nulliparity, infertility, sexual habits, history of STDs and connective tissue disease (CTD), and blood estrogen levels, when available and accessible, were collected for the women with morbid obesity.

Statistical analysis included Pearson Chi-Square (χ^2) test and Fisher exact test. The χ^2-test was used to test for significant differences between the cases and the controls using two by two tables and Fisher's exact test in linear by linear association. The odds ratio (OR) and 95% confidence interval (95% CI) were used to estimate the relative risk between negative and positive Pap tests of the cases and the controls. The univariate relationships between hypertension, diabetes, OCPs, infertility, nulliparity, CTDs and STDs and risk of abnormal cervical cytology in the women with morbid obesity were assessed using $\chi 2$ tests. A multivariable logistic regression was performed to investigate whether the increased risk was a reflection of the relationships between morbid obesity and these risk factors. Variables that were significant in univariate analysis were considered for inclusion in the multiple logistic regression model, which was used to identify the set of variables that independently contributed to the risk of abnormal Pap smears. Test results with a probability value (P) of <0.05 were considered statistically significant. We utilized the Statistical Package for Social Sciences (SPSS, Chicago, IL) version 16.0 software to perform the statistical analysis.

Results

We identified 90 (29%) out of 310 morbidly obese women between the age of 23 and 56 who had performed Pap Tests during the study period or had records of previous Pap smears. Twenty (22%) of the 90 morbidly obese women with Pap smears showed abnormal Pap tests (Table 1). Four patients had abnormal glandular cells (AGCs) of endometrial origin. Histology showed atypical complex endometrial hyperplasia in three cases and endometrial adenocarcinoma in one case. The nonobese group revealed 285 (3.5%) out of 8175 women with abnormal Pap tests (Table 1). Six had abnormal glandular lesions (three had endocervical adenocarcinoma in-situ (AIS), one endocervical adenocarcinoma and two had endometrial adenocarcinoma). The histology of LSIL and higher-grade squamous lesions, and glandular lesions was confirmed by tissue biopsy in both groups. The percentage of abnormal cervical TP Pap tests for the cases was significantly different from the controls (P=0.002). The nonobese women had more normal i.e. negative Pap tests (96.5%) than the morbidly obese women (78%). The estimated relative risk for the cases [OR 9.45 (95% CI: 5.1-17.4); RR 9.06 (95% CI: 5.1-16.2] was significantly raised more than the relative risk for the controls [OR 0.1 (95% CI: 0.05-0.2); RR 0.1 (95% CI: 0.9-0.1]. The frequency of abnormal cervical cytology in the morbidly obese women was 22% (95% CI: 8.3-28.5), while the frequency of abnormal cervical cytology in women without morbid obesity was 3.5% (95% CI: 3.1-3.9).

Morbidly obese women with abnormal Pap smears showed more prevalence of hypertension, diabetes, CTDs, STDs and use of OCPs compared with the morbidly obese women with negative Pap smears (Table 2). Four women with ASC-US had hypertension and six had diabetes diagnosed and treated on average

Table 1: Numbers and percentages of the findings in ThinPrep® cervical cytology in women with morbid obesity and in women without morbid obesity

ThinPrep® Cytology	Obese n= 90 (%) / (95% CI) Age range (23-56) mean=37	Nonobese n= 8175 (%) / (95% CI)
Negative	70 (78%) / (95% CI: 7.1-9.2) (23 -56) 36	7890 (96%) / (95% CI: 9.6-9.7) (23-56) 38
Positive	20 (22%) / (95% CI: 8.3-28.5) (28-49) 37	285 (3.5%) / (95% CI: 3.1-3.9) (24-56) 39
ASC-US	9 (10%) / (95% CI: 3.2-18.8) (31-49) 38 7 HPV +ve (78%) 2 HPV –ve (22%)	173 (2%) / (95% CI: 1.8-2.4) (25-53) 36 113 HPV +ve (65%) 60 HPV –ve (35%)
LSIL	7 (8%) / (95% CI: 2.1-16.2) (30-45) 36	69 (0.8%) / (95% CI: 0.67-1.1) (24-50) 34
HSIL	0	32 (0.4%) / (95% CI: 0.03-0.05) (26-52) 39
SCC	0	5 (0.06%) / (95% CI: 0.03-0.14) (34-56) 48
Total Squamous lesions	16 (18%) / (95% CI: 7.0-26.2) (30-49) 38	279 (3%) / (95% CI: 3.0-3.8) (24-56) 38
Endocervical AGCs	0	4 (0.05%) / (95% CI: 0.02-0.13) (34-50) 44
Endometrial AGCs	4 (4.4%) / (0.35-13.5.0) (42-51) 47	2 (0.024%) / (95% CI: 0.01-0.09) (52, 55) 53
Total glandular lesions	4 (4.4%) / (0.35-11.0) (42-51) 47	6 (0.07%) / (95% CI: 0.03-0.20) (34-55) 49

n: number, (%): percentage, CI: confidence interval, ASC-US: atypical squamous cells of undetermined significance, HPV: Human Papilloma Virus DNA Test™, +ve: positive, -ve: negative, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, SCC: squamous cell carcinoma, AGCs: abnormal glandular cells.

seven years ago. Four women had CTDs of which, two had rheumatoid arthritis, one systemic lupus erythematosus, and one Sjogren disease. All of the women with CTDs received immunosuppressant treatment from one year to four years. Three morbidly obese women with abnormal cervical cytology had STDs, of which one had Trichomonas vaginalis and two had genital HSV infection. Three obese women had a history of prolonged OCPs intake for more than five years, two of which had LSIL and one had AGCs. Six morbidly obese women with abnormal cervical cytology had a history of primary infertility and had a hormonal treatment from two years to five years. Three had ASC-US and three had LSIL. No statistically significant differences were observed between the morbidly obese women with hypertension, infertility, nulliparity and OCPs, and the morbidly obese women without these associations (P=0.573) (Table 3). However, the logistic regression for women with morbid obesity who had these conditions showed χ^2 value of 0.317. Morbidly obese women with abnormal cervical cytology who had diabetes, CTDs and STDs showed more significant differences in Pap test results ($P< 0.05$) than morbidly obese women with negative cytology (Table 3). All of the women with endometrial AGCs had diabetes, one had HTN and one had STD.

Both groups had no reported history of smoking or alcohol drinking. The majority of women with morbid obesity were married (98%) with at least one child. Five nulliparous women were found, four of which were married and had primary infertility and only one was unmarried. Of the twenty morbidly obese women who had their blood estrogen levels measured, 14 had raised estrogen levels ranging from 220 to 998 pmol/L (normal range: 28-156). Two women (14%) out of the fourteen women with raised estrogen had abnormal Pap smears. One patient had ASC-US and another patient had AGCs. The remaining twelve obese women with raised estrogen levels had negative Pap tests.

Discussion

The United Arab Emirates (UAE) ranks 18th in obesity worldwide with 42% of its female citizens are obese. Morbid obesity is almost epidemic in the rich rapidly developing Gulf States including the UAE.[15-18] Women have a higher obesity rate than males due to social and cultural factors. Women with morbid obesity are exposed at least to some of the risk factors of cervical and endometrial neoplasia, such as increased estrogen levels.[5-13] Patients may be at higher risk of developing and sustaining squamous and glandular pre-neoplastic lesions compared to nonobese women. Because morbid obesity is a common health problem in our country, this provides an opportunity to study the risk of women with morbid obesity to cervical and endometrial neoplastic lesions and the frequency of abnormal squamous and endometrial abnormalities in Pap smears.

In our study, abnormal cervical TP Pap tests were observed more often in women with morbid obesity (22%) than in women without morbid obesity (3.5%) of comparable age and similar socioeconomic status and ethnic background. Lower-grade squamous lesions were higher in women with morbid obesity (18%) than in controls (3%). Other studies had suggested OCP use and other STDs as possible cofactors.[2,3] Prolonged hormonal exposure with OCP use for more than 5 years, prolonged immunosuppression to treat CTDs and hormonal manipulation to treat infertility were also suggested to promote progression of cervical low-grade lesions to high-grade lesions.[3-5] These factors increase the risk of persistent high-risk HPV infections. Therefore, OCPs, STDs, high estrogen levels, diabetes and CTDs are potential risk factors that might have some contributory role to the increased risk of abnormal Pap smears associated with morbid obesity in our study. This might suggest that, even though it is not statistically significant, these conditions might independently have some minor contribution to the relative risk of women with morbid obesity having abnormal cervical cytology. In our study, morbid obesity - unrelated STDs and CTDs, and obesity-related diabetes were significantly associated with abnormal Pap smears in morbidly obese women. Morbid obesity is probably not an independent risk factor. The relationships of hypertension, infertility, nulliparity and OCPs and abnormal Pap smears in the morbidly obese women were not statistically significant, however.

Several studies had previously demonstrated an increased incidence and a higher risk of cervical squamous intraepithelial abnormalities in women with morbid obesity.[6-13] This is in concordance with our study and supports the notion that women with morbid obesity are at a higher risk of cervical and endometrial epithelial

Table 2. ThinPrep® cervical cytology of women with morbid obesity correlated with obesity-related co-morbidities and other potential risk factors and cofactors of cervical and endometrial lesions.

Risk Factor ThinPrep Cytology	HTN n (%)	DM n (%)	Infert. n (%)	Nul-liparn (%)	OCP n (%)	CTD n (%)	STD n (%)
Negative (n=70) Age range (23-56) mean= 36	13 (18)	19 (27)	15 (21)	4 (6)	2 (3)	5 (7)	3 (4)
Positive (n=20) Age range (28-49) mean=37	5 (25)	11 (55)	6 (30)	1 (5)	3 (15)	4 (20)	3 (15)
ASC-US (n=9) Age range (31-49) mean=38	4 (44)	6 (66)	3 (33)	0	0	4 (44)	1 (11)
LSIL (n=7) Age range (30-45) mean=36	0	2 (28)	3 (42)	1 (14)	2 (28)	0	1 (14)
AGC (n=4) Age range (42-49) mean=46	2 (50)	4 (100)	0	0	1 (33)	0	1 (33)

HTN: hypertension, DM: diabetes, Infert: infertility, Nulllipar: nulliparity, OCP: oral contraceptive pill, CTD: connective tissue disease, STD: sexually transmitted disease, n: number, (%): percentage.

Table 3: Multivariate logistic regression results for morbidly obese women with positive Pap smears.

Risk factor	Odd ratio	95% CI	P
Hypertension	1.27	0.65-2.50	0.49
Diabetes	2.84	1.12-7.22	0.028
Infertility	2.1	0.49-8.97	0.31
Nulliparity	1.09	0.87-1.36	0.47
OCP	1.02	0.82-1.28	0.84
CTD	4.31	1.10-16.8	0.03
STD	2.26	1.08-4.87	0.038

abnormalities than the general population. The question to be addressed is whether morbid obesity is an independent risk factor or that the increased risk is related to other associated factors. Some authors suggest that morbid obesity could be an independent risk factor for abnormal Pap smears regardless of other factors.[6,7] Others, however, conclude that the increased risk of endometrial abnormalities in morbid obesity is mainly related to exposure to obesity-associated factors like hypertension, diabetes, low fertility and hormonal alterations.[6,7,11] Still others suggest that the risk of cervical and endometrial epithelial abnormalities could be influenced by factors unrelated to morbid obesity, for example smoking, alcohol, STDs, infertility and OCPs.[2-6] The prolonged immunosuppression as part of CTDs treatment and high estrogen levels might have increased the risk in certain morbidly obese patients. Some authors point to the fact that a lack of Pap smears , missed or delayed Pap tests in women with morbid obesity might partly explain the higher risk of cervical cancer mortality in obese women.[6,8-10] Morbidly obese women have poor adherence to physicians' recommendation and might delay or skip screening.[6,8-10] Therefore, less screening might explain the higher frequency of cervical abnormalities and cervical cancer mortality in morbidly obese women.[6,8-10] Our study and other studies' findings of a low Pap smear rate among obese women might justify a recommendation that women with morbid obesity should have annual screening. Educational and clinical tools are warranted to remove the barriers and encourage more compliance to regular Pap smears among obese women.

Our study is not without limitations. Two thirds of the women with morbid obesity did not perform Pap smears and had no past records of Pap tests. This reduced the sample size of the cases, the power of our study and the representativeness of this small group of women for the population of morbidly obese women in our community. It might also have caused biased results regarding the true prevalence of higher-grade squamous lesions and glandular lesions in women with morbid obesity compared with the controls. However, it seems that this trend of low rates of Pap smears in women with morbid obesity is a global problem and not unique to our population since it has been reported in the USA and some Asian countries, as well.[6,8-10] One reason is that morbidly obese women do not adhere to the routine mass screening program. Obese women may be reluctant to undergo Pap tests because they find it painful, uncomfortable or embarrassing than normal weight women.[8,10] Another confounding problem in our study, is that mass screening is not mandatory in the UAE. The lack of a screening program in our local community results in opportunistic screening, the rate of which is already low (0.4%) in our region.[19,20] This lack of mass screening could have contributed to the low number of women with morbid obesity who had Pap smears. In addition, the high SCC/HSIL ratio in the control group shows a population not without risk, but is consistent with a relatively low rate of regular screening. Most of the women with morbid obesity did not have follow up Pap tests after bariatric surgery or other measures to reduce weight. We could not compare the prevalence of abnormal Pap smears in these women after weight reduction. Therefore, whether the risk of epithelial abnormalities is reduced after weight reduction and whether this is related to a reduction in certain risk factors like hypertension, diabetes and high estrogen levels, which are known to improve after weight loss, could not be validated. Despite of these limitations, one of the strengths of our study compared to previous studies is that the control group was of adequate size. The control group has a similar and comparable socioeconomic, ethnic and demographic background to the age-matched cases. Finally, our findings were based on Pap tests and HPV DNA tests. They were not based on self-reporting questionnaires, which raise the issue of bias and inaccuracy in the previous studies.[6,8-10]

In conclusion, our study showed an increased prevalence of low-grade squamous lesions, high-risk HPV infections and endometrial glandular abnormalities in women with morbid obesity compared with nonobese women in an opportunistic screening population. Several obesity-related and non-obesity-related conditions are possible contributory risk factors. Whether morbid obesity is an independent risk factor needs further validation by future studies. Morbidly obese women are more likely to avoid or delay Pap tests, which increased their risk to abnormal Pap smears, as well. Several factors contribute to the poor adherence of morbidly obese women to cervical screening. Our data implies that morbidly obese women should benefit from more frequent Pap smears by modification of life-style factors that prevent adequate screening. This is possible

through implementing certain educational and clinical measures. The worldwide rise in morbid obesity should alert health professionals to the increased risk of abnormal Pap smears in this vulnerable population. Weight reduction could be a preventive measure.

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