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The Philippine Journal of GYNECOLOGIC ONCOLOGY

Official Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 19 Number 2 December 2024

ORIGINAL PAPERS

CASE REPORTS

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Offcial Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 19 Number 2 December 2024

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The Philippine Journal of Gynecologic Oncology (ISSN 2704-3045) is the peer-reviewed journal produced as a program of the Society of Gynecologic Oncologists of the Philippines (SGOP). It is published biannually by the SGOP with business and production offices at Unit 404, Manila Astral Towers, 1330 Taft Ave. cor. Padre Faura Sts., Ermita, Manila, Philippines. Copyright © 2012 by the Society of Gynecologic Oncologists of the Philippines, Inc.

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Impact of the Type of Hysterectomy on Prognosis in Patients with Stage II Endometrial Cancer: A Retrospective Cohort Analysis

Marilou S. Yu, MD[1] and Jonalyn G. Bagadiong, MD[1], MMHoA, FPOGS, FSGOP, FPSCPC

ABSTRACT

Background: Treatment of endometrial cancer with cervical involvement is either total abdominal hysterectomy or radical hysterectomy. Nevertheless, studies have different and contradictory results. The current study sought to determine the impact of hysterectomy type on prognosis and pattern of relapse in patients with stage II endometrial cancer.

Methods: Outpatient charts of the endometrial cancer patients from the outpatient department of Jose R. Reyes Memorial Medical Center Section of Gynecologic Oncology were retrospectively reviewed.

Results: Only 40 patients with stage II endometrial cancer were included in the analysis. The overall recurrence free survival for any type of hysterectomy was at 91.92% (95% CI 71.21-97.93) at 12 months, 87.54% (95% CI 66.02-95.83) at 24 months and 54.03% (95% CI 20.04-78.99%) at 36 months. The overall survival estimates were at 100% up to 24 months and at 90.91% (95% CI 50.81-98.67) at 36 to 42 months.

Conclusion: Patients with stage II endometrial cancer who underwent radical hysterectomy had fewer recurrence as compared to the extrafascial hysterectomy, however has no significant difference in the overall survival.

Keywords: *endometrial cancer, stage II, simple hysterectomy, extrafascial hysterectomy, radical hysterectomy*

INTRODUCTION

The 5-year overall survival decreases from 88% to 75% for patients with endometrial cancer FIGO stage II as compared to stage I. Radical hysterectomy can eradicate parametrial metastasis in patients with cervical involvement. Fourteen percent of the cases with cervical involvement had parametrial invasion. Thus, in patients with stage II endometrial cancer, the recommended surgery is radical hysterectomy. [1,2]

The aim of radical hysterectomy is to achieve optimum cytoreduction, to detect parametrial invasion and to guide for additional adjuvant treatment. Nevertheless, it is associated with complications such as longer operative time, greater blood loss and post-operative urinary retention. Cervical involvement can also be linked with other poor prognostic factors, such as lymphovascular invasion, deep myometrial invasion, lymph node involvement and unfavorable histologies.[2]

Diabetes and obesity, as risk factors of endometrial cancer, are also risk for surgical adverse events. Thus, a simpler hysterectomy can be done with adjuvant treatment to reduce local recurrence and with a lesser postoperative morbidity. The aim of this study is to determine the impact of hysterectomy type on prognosis and the pattern of relapse in patients with stage II endometrial cancer.

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OBJECTIVES

The retrospective study aimed to determine the impact of the type of hysterectomy done in patients with stage II endometrial cancer in terms of prognosis and pattern of relapse.

Specific Objectives

1. To compare the overall survival and recurrence free survival of patients with stage II endometrial cancer who underwent intrafascial, extrafascial and radical hysterectomy.
2. To determine the pattern of relapse in patients with stage II endometrial cancer who underwent intrafascial, extrafascial and radical hysterectomy.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board; patient's charts from the outpatient of Jose R. Reyes Memorial Medical Center, Section of Gynecologic Oncology and Trophoblastic Disease of endometrial cancer patients with stage II disease from January 1, 2011 to December 31, 2020 were reviewed. Inclusion criteria included the following: (a) patients with biopsy proven endometrial cancer, (b) with cervical involvement either by imaging or biopsy, (c) without extrauterine spread identified in the imaging, either by whole abdominal ultrasound, computed tomography scan or magnetic resonance imaging, (d) who underwent surgery, either intrafascial, extrafascial, or radical hysterectomy as the initial treatment, (e) with pelvic and/or para-aortic lymphadenectomy (f) no residual tumor and, (g) performance status of 0 to 2. Patients with (a) tumor histology of leiomyosarcoma, carcinosarcoma

and endometrial stromal sarcoma, (b) those who underwent neoadjuvant radiotherapy or chemotherapy, (c) incomplete records were excluded from the study.

Clinical data extracted from the chart comprised of age, body mass index, menstrual status, co-morbidity of diabetes mellitus, pre-operative imaging and/or cervical punch biopsy, type of hysterectomy performed, adjuvant treatment received, site of recurrence and status on the last follow up visit. Pathological data that were analyzed include histologic type, tumor grade, size of endometrial mass, myometrial invasion, lymphovascular space involvement, lymph node involvement and peritoneal fluid cytology.

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RESULTS

Forty patients with endometrial carcinoma met the inclusion criteria and were included in the study. Demographic profile of the patients was summarized in Table 1. The average age of the patients was 56.15 ± 9.83, there was no significant differences in the average age of total, extrafascial and radical hysterectomy groups (p=0.171). However, the distribution of age showed significant differences. Extrafascial hysterectomy group was statistically older than the intrafascial and radical hysterectomy groups; 40% of the extrafascial hysterectomy group was more than 60-year-old. The distribution of body mass index (BMI) was statistically similar with the 3 groups with p-value of 0.192. The menstrual status was significant (p=0.029), the table showed that a large percentage of extrafascial and radical hysterectomy were post-menopausal. The differences in percentage of patients with diabetes mellitus among the three groups were not enough to conclude significance (p=0.307).

No pre-operative evidence of cervical involvement, clinically or via ultrasound imaging, was documented in 80% (12 of 15) and 75% (3 of 4) of patients with data in the extrafascial hysterectomy group and intrafascial hysterectomy group, respectively. In contrast, 80% (3 of 5) in the radical hysterectomy group has an imaging evidence of cervical involvement pre-operatively. Eighty percent (4 of 5) in the radical hysterectomy group was diagnosed with cervical involvement histologically pre-operatively, as compared to the 33% (3 of 9) of the extrafascial hysterectomy group.

The most frequent histology was endometrioid adenocarcinoma: 96% (24 of 25) in extrafascial hysterectomy, 88% (8 of 9) in intrafascial hysterectomy group, and 100% (6 of 6) in the radical hysterectomy group. There were only 2 patients with mixed histology; 1 from the intrafascial and 1 from the extrafascial hysterectomy group. Grade 2 tumor grade was in majority of the patients. Sixty percent (15 of 25) in extrafascial hysterectomy group, 50% (4 of 8) in intrafascial hysterectomy group and 66% (4 of 6) in radical hysterectomy group. Of the 37 patients, the maximum endometrial tumor size was statistically higher (p=0.038) in the intrafascial hysterectomy group (7.0 cm) and in the radical hysterectomy group (6.0 cm) than the extrafascial group (4.3 cm). Involvement of more than half of the myometrium was reported in more than half of the patients in the extrafascial hysterectomy group (66%) and intrafascial hysterectomy group (55%) and in 50% of the radical hysterectomy group. No notable differences were observed in the parametrial invasion, lymphovascular space involvement (LVSI) and lymph node involvement among the intrafascial, extrafascial and radical hysterectomy group.

Bilateral pelvic lymph node dissection was done in 92% of extrafascial hysterectomy group and 78% of intrafascial hysterectomy group. Among women who underwent radical hysterectomy, half had para-aortic lymph node sampling done as well. Incomplete adjuvant treatment was more prevalent in the intrafascial hysterectomy group (55%) than extrafascial hysterectomy group (8%) and radical hysterectomy group (16%). Thirty-six percent of patients who underwent extrafascial hysterectomy received vaginal brachytherapy as compared to those who underwent intrafascial hysterectomy (22%) and radical hysterectomy (33%). Twenty percent of patients who underwent extrafascial hysterectomy received pelvic external beam radiotherapy with vaginal brachytherapy.

Six patients had recorded cancer recurrence: 4 (17%) in the extrafascial hysterectomy group, 1 (11%) in the intrafascial hysterectomy group, and 1 (17%) in the radical hysterectomy group (Table 3). Recurrences in the intrafascial and radical hysterectomy group occurred in the vagina, while those in the extrafascial hysterectomy group occurred in the lymph nodes (supraclavicular and para-aortic), bone and pelvis (1 each). Most of the patients of each group had no evidence of disease: 72% in the extrafascial hysterectomy group, 44% in the intrafascial hysterectomy group and 50% in the radical hysterectomy group. There was one patient who died due to sepsis secondary to incarcerated hernia, and our mortality rate was at 2.5% (95% CI 0.33 to 16.59%). Only 15% was lost to follow up.

At the end of this study, 62.5% (25 of 40) had no evidence of disease; 7.5% (3 of 40) needed to received adjuvant chemotherapy; 12.5% (5 of 40) needed to have adjuvant radiotherapy. Hence, there was no noted statistically significant difference among the intrafascial, extrafascial and radical hysterectomy group. There was 15% (6 of 40) of patients that were lost to follow up and 2.5% (1 of 40) mortality rate.

The K-M plot for RFS of the three groups are shown in Figure 1 (recurrence free survival) and Figure 2 (overall survival).

Table 1. Demographic profile of women with stage II endometrial cancer

	Total (n=40)	Extrafascial (n=25)	Intrafascial (n=9)	Radical (n=6)	*p*-value
	Mean ± SD; Frequency (%)				
Age, years	56.15 ± 9.83	58 ± 7.77	55.33 ± 13.53	49.67 ± 10.13	.171*
<40	3 (7.5)	0	2 (22.22)	1 (16.67)	.041†
40–60	21 (52.5)	15 (60)	2 (22.22)	4 (66.67)	
>60	16 (40)	10 (40)	5 (55.56)	1 (16.67)	
BMI, kg/m^2					
<18.5	2 (5.56)	0	2 (22.22)	0	.192†
18.5 to <23	4 (11.11)	3 (13.64)	0	1 (20)	
23 to 27.5	19 (52.78)	13 (59.09)	3 (33.33)	3 (60)	
>27.5	11 (30.56)	6 (27.27)	4 (44.44)	1 (20)	
Menstrual stage					
Pre-menopausal	4 (10)	0	3 (33.33)	1 (16.67)	.029†
Peri-menopausal	7 (17.5)	4 (16)	2 (22.22)	1 (16.67)	
Post-menopausal	29 (72.5)	21 (84)	4 (44.44)	4 (66.67)	
Diabetes	4 (10)	2 (8)	2 (22.22)	0	.307†

*Statistical test used: * - One-way ANOVA; † - Fisher's Exact test.*

Table 2. Clinical and operative profile of women with stage II endometrial cancer

	Total (n=40)	Extrafascial (n=25)	Intrafascial (n=9)	Radical (n=6)	*p*-value
	Frequency (%); Median (Range)				
Pre-operative cervical involvement [n=24]	56.15 ± 9.83	58 ± 7.77	55.33 ± 13.53	49.67 ± 10.13	.171*
None	3 (7.5)	0	2 (22.22)	1 (16.67)	.041†
Clinical	21 (52.5)	15 (60)	2 (22.22)	4 (66.67)	
Ultrasound imaging	16 (40)	10 (40)	5 (55.56)	1 (16.67)	
Histologically proven [n=16]					
Lymphadenectomy	2 (5.56)	0	2 (22.22)	0	.192†
None	4 (11.11)	3 (13.64)	0	1 (20)	
BLND	19 (52.78)	13 (59.09)	3 (33.33)	3 (60)	
BLND + PAL	11 (30.56)	6 (27.27)	4 (44.44)	1 (20)	
Adjuvant therapy					
None	1 (2.5)	1 (4)	0	0	.142†
Vaginal brachytherapy	13 (32.5)	9 (36)	2 (22.22)	2 (33.33)	
PEBRT	3 (7.5)	2 (8)	0	1 (16.67)	
PEBRT + vaginal brachytherapy	5 (12.5)	5 (20)	0	0	
PEBRT + vaginal brachytherapy + chemotherapy	0	0	0	0	
Vaginal brachytherapy + chemotherapy	3 (7.5)	1 (4)	2 (22.22)	0	
PEBRT + chemotherapy	3 (7.5)	2 (8)	0	1 (16.67)	
Chemotherapy	4 (10)	3 (12)	0	1 (16.67)	
Incomplete treatment	8 (20)	2 (8)	5 (55.56)	1 (16.67)	
Histology					.615†
Endometrioid	38 (95)	24 (96)	8 (88.89)	6 (100)	
Mixed	2 (5)	1 (4)	1 (11.11)	0	
Grade [n=39]					.889†
1	12 (30.77)	8 (32)	3 (37.5)	1 (16.67)	
2	23 (58.97)	15 (60)	4 (50)	4 (66.67)	
3	4 (10.26)	2 (8)	1 (12.5)	1 (16.67)	
Max. endometrium diameter, cm [n=37]	5.5 (2–13)	4.25 (2–11) ; n=22	7 (4.5–13) ; n=9	6 (5–11) ; n=6	.038‡
Parametrial invasion [n=37]	1 (2.7)	1 (4.35); n=23	0; n=8	0; n=6	
Myometrial invasion [n=39]					.038‡
None	0	0	0	0	

Table 3. Clinical and operative profile of women with stage II endometrial cancer

	Total (n=40)	Extrafascial (n=25)	Intrafascial (n=9)	Radical (n=6)	*p*-value
	Frequency (%); Median (Range)				
<½	15 (38.46)	8 (33.33)	4 (44.44)	3 (50)	
>½	24 (61.54)	16 (66.67)	5 (55.56)	3 (50)	
LVSI [n=37]	11 (29.73)	5 (21.74); n=23	3 (37.5); n=8	3 (50)	.311†
LN involvement [n=39]	0	0; n=24	0; n=9	0; n=6	-
Peritoneal fluid cytology	0	0	0	0	-

BLND, bilateral pelvic lymph node dissection; LN, lymph node; LVSI, lymphovascular space invasion; PAL, paraaortic lymphadenectomy; PEBRT, pelvic external beam radiotherapy.
*Statistical test used: * - One-way ANOVA; † - Fisher's Exact test.*

The overall recurrence free survival for any type of hysterectomy at 12-months was 91.92% (95% CI 71.21-97.93); at 24 months, this was estimated at 87.54% (95% CI 66.02-95.83), and drops to 54.03% by 36 months, with 95% CI of 20.04% to 78.99%. (Tables 4 and 4a)

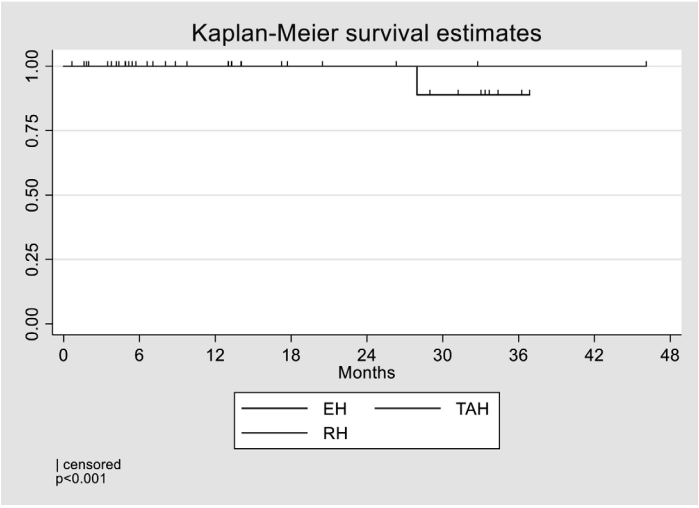

Figure 1. Kaplan-Meier plot of recurrence-free survival, by type of hysterectomy

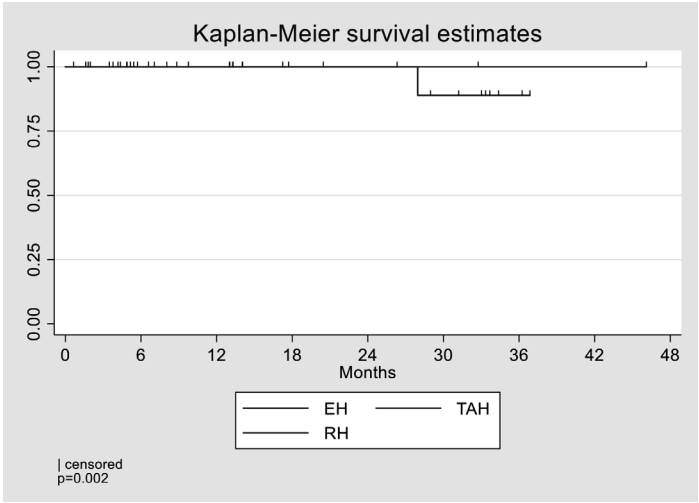

Figure 2. Kaplan-Meier plot of overall survival, by type of hysterectomy

We only have 9 patients who underwent intrafascial hysterectomy. The recurrence free survival at 12 and 24 months was 75% (95% CI 12.79-96.05). There was insufficient data to calculate for the 36 months' recurrence free survival. In the extrafascial hysterectomy group, at 12 months and 24 months, the recurrence free survival was at 94.74% (95% CI 68.12-99.24). At 36 months, the recurrence free survival was 51.81%, with 95% CI at 13.73% to 80.43%. There were only 6 patients who underwent radical hysterectomy. From 12 months to 36 months, the recurrence free survival was estimated at 66.67% (95% CI 5.41-96.05). Given the small sample size, the recurrence free survival was higher among patients who underwent intrafascial and extrafascial hysterectomy at 12- and 24 months as compared to those who underwent radical hysterectomy. However, at 36 months, those under the radical hysterectomy group has better recurrence free survival (66%) as compared to the extrafascial hysterectomy group.

Table 4. Recurrence-free survival of Stage II endometrial cancer

Month	Beginning total	Fail	Survivor function (95% CI)
All			
6	27	1	96.3 (76.49–99.47)
12	22	1	91.92 (71.21–97.93)
18	14	1	87.54 (66.02–95.83)
24	13	0	87.54 (66.02–95.83)
30	10	1	78.79 (49.75–92.18)
36	4	2	54.03 (20.04–78.99)
42	2	0	54.03 (20.04–78.99)
48	1	0	-
EH			
6	19	1	94.74 (68.12–99.24)
12	16	0	94.74 (68.12–99.24)
18	11	0	94.74 (68.12–99.24)
24	10	0	94.74 (68.12–99.24)
30	8	1	82.89 (42.92–95.92)
36	3	2	51.81 (13.73–80.43)
42	1	0	-
48	1	0	-
TAH			
6	6	0	100
12	5	0	100
18	2	1	75 (12.79–96.05)
24	2	0	75 (12.79–96.05)
30	1	0	-
36	1	0	-
42	1	0	-
48	1	0	-
RH			
6	4	0	100
12	3	1	66.67 (5.41–94.52)
18	3	0	66.67 (5.41–94.52)
24	3	0	66.67 (5.41–94.52)
30	3	0	66.67 (5.41–94.52)
36	2	0	66.67 (5.41–94.52)
42	2	0	66.67 (5.41–94.52)

Table 4a. Overall survival

Month	Beginning total	Fail	Survivor function (95% CI)
All			
6	27	0	100
12	22	0	100
18	14	0	100
24	13	0	100
30	10	1	90.91 (50.81–98.67)
36	4	0	90.91 (50.81–98.67)
42	2	0	90.91 (50.81–98.67)
48	1	0	-
EH			
6	19	0	100
12	16	0	100
18	11	0	100
24	10	0	100
30	8	1	88.89 (43.3–98.36)
36	3	0	88.89 (43.3–98.36)
42	1	0	-
48	1	0	-
TAH			
6	6	0	100
12	5	0	100
18	2	0	100
24	2	0	100
30	1	0	-
36	1	0	-
42	1	0	-
48	1	0	-
RH			
6	4	0	100
12	3	0	100
18	3	0	100
24	3	0	100
30	3	0	100
36	2	0	100
42	2	0	100
48	1	0	-

DISCUSSION

Corpus uteri carcinoma ranks number 11 in the Philippines with 4,374 new cases and 1,306 deaths based on the Globocan 2020 with a prevalence of 22.76/100,000. The lifetime risk for developing this disease is approximately 1.01 in Filipino women.[3] According to the American Cancer Society, the 5-year relative survival rates for endometrial cancer based on people diagnosed with endometrial cancer between 2011 to 2017 are the following: for localized tumor (96%), for regional disease (71%) and for distant metastasis (20%).[4] In a retrospective study done by Sartori, E., et. al., on clinical behavior of 203 stage II endometrial cancer cases showed that the survival rate of stage IIA and IIB decreases to 86% and 74%, respectively, at 5 years.[5] There are various factors that may alter the prognosis of stage II patients such as cervical stromal invasion, lymphovascular invasion and high grade histology. However, it is still uncertain what type of hysterectomy should be done in patients with suspected cervical involvement pre-operatively. In the present study, patients with stage II endometrial cancer who underwent radical hysterectomy had fewer recurrence at 36-months as compared to the extrafascial hysterectomy group; radical hysterectomy group has also better overall survival at 36-months as compared to the extrafascial hysterectomy group. However, there was insufficient data to calculate for the recurrence free and overall survival of the intrafascial hysterectomy group.

Endometrial carcinoma may occur during the reproductive or menopausal years. The mean age is 63 years; majority of the patients are between 50 to 59 years of age.[6] A retrospective analysis done by Simons, E. et. al., on foreign versus US born Asians and the association of type 1 uterine cancer showed median age was 56 years (range of 19-96 years). Sixty-one percent had type 1 uterine cancer mainly include endometrioid adenocarcinomas of low grade (grade 1 and 2) and this was linked with unopposed estrogen stimulation and are affected by diet and environmental exposures. Patients are usually younger with a higher body mass index. Japanese women followed by Chinese and Filipino women has the lowest type 1 cancer of all the immigrants.[7] These findings were in congruent to the present study. The average age of the patients was 56.15 ± 9.83, 72.5% were post-menopausal. Fifty-two percent of the patients was overweight based on the WHO Asian BMI classifications. Ninety-five percent of the patients had tumor histology of endometrioid carcinoma with 58.97% of which has tumor grade of 2. There were only 2 patients with mixed histology; 1 from the intrafascial and 1 from the extrafascial hysterectomy group.

Several factors have been linked to endometrial adenocarcinoma that has prognostic significance. It may be divided to clinical, surgical and pathologic factors. Clinical factors include age and race. While pathologic factors include histologic subtype, stage, tumor grade and lymphovascular space invasion.[6,8] In a study done by Sato, R. et. al. on 269 patients with endometrial cancer who underwent radical or modified hysterectomy with pelvic lymph node dissection showed 16 patients (5.9%) had parametrial spread. No parametrial invasion was seen in FIGO stage I, 6.3% (2 of 32) in stage II, 16.9% (12 of 71) in stage III and 100% (2 of 2) in stage IV. Parametrial involvement was associated with the depth of myometrial invasion, involvement of the cervix and metastasis to the lymph nodes and adnexa.[9] The result of the study done by Lee, T., et. al., on the necessity of radical hysterectomy for endometrial cancer patients with cervical invasion showed 14.1% parametrial involvement in stage II, III, or IVA endometrial cancer with cervical involvement. Also, depth of myometrial invasion and positive for tumor involvement of pelvic and/or para-aortic lymph nodes were considerably linked with parametrial invasion.[10] In the present study, only 2.7% (1 of 40) had positive parametrial invasion. All of the patients included in the study had FIGO stage 2, with maximum endometrial tumor size of 2 to 13 cm, 58.97% had tumor grade of 2, 61.54% had more than 50% myometrial invasion, and none had metastasis to the lymph nodes.

In the current NCCN guidelines for endometrial carcinoma version 1.2022 (Figure 3), for patients with cervical involvement and suitable for primary surgery total hysterectomy or radical hysterectomy with bilateral salpingo-oophorectomy and surgical staging is recommended.[11] Some clinical studies have validated the advantage of radical hysterectomy in patients with stage II endometrial cancer as compare to simple hysterectomy in terms of overall survival. Nonetheless, other studies have shown contradictory outcomes, and revealed simple hysterectomy has comparable survival benefit to radical hysterectomy. The need for a more radical surgery for stage II endometrial cancer remains a topic of debate. Sartori, E., et. al, retrospectively reviewed 203 records of patients with stage II endometrial cancer showed significant difference in survival rate in terms of surgical procedure; the radical hysterectomy group has better survival rate at 5-years (94%) and 10-years (94%) as compared to simple hysterectomy, 79% and 74%, at 5- and 10-years, respectively.[5] This result was similar with the present study, the overall recurrence free survival for any type of hysterectomy was 91.92% (95% CI 71.21-97.93) at 12-months, 87.54% (95% CI 66.02-95.83) at 24-months and 54.03% (95% CI 20.04-78.99%) at 36-months.

Figure 3. FIGO Staging of Carcinoma of the Endometrium (2009)

FIGO stage	
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
II[a]	Tumor invades cervical stroma, but does not extend beyond the uterus[b]
III[a]	Local and/or regional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexa[c]
IIIB[a]	Vaginal involvement and/or parametrial involvement[c]
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

[a]Either G1, G2, or G3.
[b]Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
[c]Positive cytology has to be reported separately without changing the stage.

The radical hysterectomy group has fewer recurrences, 66.67% (95% CI 5.41-96.05) at 36-monhts as compared to those who underwent extrafascial hysterectomy 51.81% (95% CI 13.73-80.43%) at 36-months. Of the 6 patients recorded with cancer recurrence, 17% occurred in the extrafascial hysterectomy group. There was only 1 recurrence in the radical hysterectomy group in the vagina. The overall survival estimates were 100% at 24-months and 90.91% (95% CI 50.81-98.67) at 36-42 months. The survival probabilities over time were not able to estimate since there was only one mortality. Nevertheless, the radical hysterectomy group has better overall survival at 100% at 36 months as compared to the extrascial group of 88%.

In a retrospective, multi-institutional done by Takano, M., et. al., showed that the types of hysterectomy has no significant difference on local recurrence free survival, progression free survival and overall survival. Moreover, radical hysterectomy was associated with longer operative time, greater blood loss and urinary tract dysfunction.[1] In the single-institution, matched-pair analysis done by Jiang, Y., et. al, on comparison of survival and perioperative outcomes following simple hysterectomy and radical hysterectomy for stage II endometrial cancer showed that simple hysterectomy has similar survival outcomes. The 5-year survival rates were 92.40% and 90.03% in the simple hysterectomy and radical hysterectomy groups respectively. The radical hysterectomy has significantly greater intra-operative blood loss and longer indwelling catheterization than the simple hysterectomy group.[12] The retrospective cohort study of Barquet-Muñoz, et. al., on the impact of radical hysterectomy on endometrial cancer with cervical involvement also showed consistent results to the preceding studies. Radical hysterectomy does not improve overall survival and disease free survival or change adjuvant treatment in patients with stage II endometrial cancer.[2]

Another retrospective study by Wang, M., et. al., that evaluated the survival between radical hysterectomy versus simple hysterectomy combined with vaginal brachytherapy in patients with stage II endometrial cancer. Both groups received adjuvant external beam radiotherapy post-operative. The study showed both the 5-year overall survival and 5-year cause specific survival were shorter in radical than in simply hysterectomy group with vaginal brachytherapy.[13] In the present study, 20% of the patients had an incomplete treatment. Mostly, 32.5% received adjuvant vaginal brachytherapy; 36% from the extrafascial hysterectomy group, 33.3% from the radical hysterectomy group, and 22.2% from the simple hysterectomy group. Only 12.5% received adjuvant pelvic external beam radiotherapy with vaginal brachytherapy; all under the extrafascial hysterectomy group. There was no statistically significant difference in the adjuvant between the 3 groups (p=0.142).

In a retrospective comparative analysis done by Yin, H., et. al, on postoperative complications and prognosis of different surgical procedures in stage II endometrial carcinoma showed overall early complication rate of 24.1%; with 14.3% for the subradical group versus 42.1% for the radical group, which was statistically significant p=0.043. Early complications include urinary retention, urinary tract infection, pelvic lymphocyst formation, deep vein thrombosis, subcutaneous hematoma, site dehiscence and neuropathy. While the overall late complication rate was 24.1%; 20.0% for the subradical group and 31.5% for the radical group, and it was not statistically significant. Late complications include pelvic lymphocyst formation, lower extremity weakness and vaginal dryness. There was also no survival and relapse rate difference between the subradical group and radical group.[14] In the present study, postoperative complications and long term outcome were not included.

CONCLUSION

The result of the retrospective study proposes that in patients with stage II endometrial cancer who underwent radical hysterectomy had fewer recurrence as compared to the extrafascial hysterectomy group. Radical hysterectomy group has also better overall survival as compared to the extrafascial hysterectomy group. Recurrences in the intrafascial and radical hysterectomy group occurred in the vagina, while those in the extrafascial hysterectomy group occurred in the lymph nodes (supraclavicular and para-aortic), bone and pelvis.

LIMITATIONS

The limitation of this study included a retrospective analysis with a small population and with six patients that were to lost to follow up. The surgical margins were not also included in the analysis. Post-operative and long term complications of each hysterectomy type were not in the scope of the present study.

RECOMMENDATIONS

Although the results were compatible with previous studies of radical hysterectomy provided better outcome in terms of recurrence free and overall survival for patients with stage II endometrial cancer, further clinical prospective clinical research with a larger population size is needed. ■

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The Association of Ultrasound Features of Various Endometrial Pathologies Using the International Endometrial Tumor Analysis (IETA) Group Terminology with the Histopathology Diagnosis for Women with Abnormal Uterine Bleedingy

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ABSTRACT

Background: Abnormal Uterine Bleeding (AUB) is a common problem observed among women, and poses a physical, emotional, and economic burden. Among the established etiologies of AUB, endometrial lesions are common findings noted upon investigation. Sonography is a simple and cost-effective initial step in the diagnosis. However, complete and final diagnosis of the etiology of AUB needs confirmation by histopathology. Currently, the International Endometrial Tumor Analysis (IETA) features are used in further describing endometrial lesions, but whether it correlates with the presence or absence of pathology is not established..

Objective: To determine if there is an association between a combination of sonographic IETA features with the final histopathology diagnosis.

Methods: Biopsy results of endometrial samples from women with abnormal uterine bleeding were collected and their respective ultrasound IETA features were reviewed. Data analysis was done using Binary Logistic Regression, one-way ANOVA, and Chi square test.

Results. The combination of IETA features from a total of 234 subjects were analyzed. With all p-values greater than the significance level (0.05), there was no significant association between Echogenicity, Endometrial midline, Endometrial-Myometrial junction, Color score, Vascular pattern, and fluid with the combination of IETA sonographic features of the above-mentioned endometrial pathologies

Conclusion: In the studied population, no combination of IETA features were significantly associated of any of the 5 histopathologic diagnoses. However, analysis of the individual features revealed that color score and endometrial thickness were significantly associated with endometrial cancer.

Keywords: *Endometrial Cancer, Endometrial Pathology, International Endometrial Tumor Analysis*

INTRODUCTION

A. Background of the Study

Abnormal Uterine Bleeding (AUB) is a common problem observed among women, with a prevalence of approximately 3 – 30% among reproductive aged women[1], with 9 to 14% having complaints of heavy menstrual bleeding[2]. Among the established etiologies of AUB, endometrial lesions are common findings noted upon investigation. Several imaging modalities are currently available to identify the cause of AUB, and sonography is known to be a simple and cost-effective initial step in the diagnosis. The standard procedure for complete and final diagnosis of the etiology of AUB is histopathology, but the process of collecting samples for biopsy are invasive and costly for the patient.

In the year 2008, the International Endometrial Tumor Analysis (IETA) Group was formed to come up with an agreement on the terms and definitions on the description of ultrasound findings, and to standardize measurement technique of the uterine cavity. A consensus statement was then formed to describe the sonographic features of the endometrium at gray-scale sonography, color flow imaging, and sonohysterography[3]. However, it is unknown at that time if the ultrasound features described on the consensus correlates with the presence or absence of pathology. The use of IETA terms and definitions are still confined as a form of basis for prospective studies in predicting the risk of presence of different endometrial pathologies[3]. At present, studies involving the use of IETA features gain more significance in identifying patients at risk for endometrial malignancy, but the use of these descriptors in diagnosing benign endometrial lesions needs further evaluation.

B. Significance of the study

This study aims to determine an association between a combination of sonographic features as described by IETA features to each endometrial pathology diagnosed by biopsy.

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Although histopathology remains to be the definitive measure in the diagnosis, the observed association as the outcome of this study may increase confidence in the interpretation of benign results, and help identify sonographic features which are predictive for malignancy. This in turn would increase the reliability of using IETA features in ultrasonography as part of pre-operative work-up for abnormal uterine bleeding. Thus, avoid subjecting patients whose IETA features correlate with a benign description to avoidable endometrial sampling which are invasive and costly. Moreover, this would identify patients warranted for immediate biopsy to confirm or rule out malignancy if their IETA feature is associated with a malignant description.

C. Research Question:

Among women with abnormal uterine bleeding, is there a characteristic combination of sonographic features as described by IETA that can be associated with each of the common endometrial lesions?

D. Objectives

General Objective:

To determine the association of a characteristic combination of sonographic description of common endometrial lesions using IETA features to a particular endometrial pathology.

Specific Objectives:

Specifically, this study aimed to:

1. Determine the various general histopathologic diagnoses of patients with abnormal uterine bleeding;
2. Determine the distribution of histopathologic diagnosis according to age in years;
3. Determine which combination of sonographic IETA features of endometrial lesions are significant predictors of the following:
   - 3.1 Endometrial Hyperplasia;
   - 3.2 Endometrial Polyp;
   - 3.3 Submucous Myoma;
   - 3.4 Proliferative and Secretory Endometrium; and
   - 3.5 Endometrial Malignancies.

E. Definition of Terms

1. Abnormal Uterine Bleeding – a change in the duration and amount of menstrual bleeding in women, with observable change in the quality of life.
2. International Endometrial Tumor Analysis (IETA) Features – terminologies used to describe the endometrium in ultrasonography as established by the International Endometrial Tumor Analysis group, pertaining to the endometrial echogenicity, endometrial midline, endometrial-myometrial junction, intracavitary fluid, vascular pattern, and color score.

RESEARCH METHODOLOGY

A. Design

This is a descriptive, analytical study.

B. Setting

The study was done by gathering data from January 2022 to December 2022 from two tertiary hospitals located in Cebu City and Mandaue City.

C. Participants

Post-menarchal women with abnormal uterine bleeding who fulfilled the inclusion criteria were included in the study.

Inclusion Criteria:

1. Transvaginal sonography done by an ObGyn sonologist in the participating institutions, who subsequently underwent endometrial sampling.
2. Samples taken for histopathology should be processed in the participating institutions.

Exclusion Criteria

1. Women with uterine bleeding but diagnosed to be pregnant.
2. Women previously diagnosed with malignancy of the reproductive tract.

D. Population and Sampling:

This study employed complete enumeration. All records of patients with abnormal uterine bleeding from January 2022 to December 2022 were pooled. Further selection of patient records was done based on the specified inclusion criteria, e.g., complete sonographic features of endometrial lesions. This stringent process of selection trimmed down the number further. From the pooled qualifying records, a final number of 234 were considered for analysis.

Describing the endometrium in sonography using the IETA features were only applied by the studied tertiary hospitals starting on the year 2022. To increase the pool of records for sampling, all patients who fulfill the inclusion criteria are taken into account.

E. Data Analysis and Statistical Considerations

Specific statistical tests for the treatment of data are specified below.

Descriptive statistics such as Mean, Standard Deviation, are reported to describe the patients' age.

Frequency distribution and percentage is used to present the data for categorical variables with frequency counts such as sonographic features of endometrial lesions as described by a specific combination of IETA features, and the general histopathologic diagnoses of patients.

Binary Logistic Regression was employed to describe the relationship between IETA features as predictors of each of the histopathologic diagnoses (Yes/No; a binary response), with 5% margin error. Aside from the p-value indicating whether or not there is significant association between the response variable and the predictors, coefficients were also noted. These indicate whether or not a factor associated with a histopathologic diagnosis becomes more likely as the predictor changes from one kind to another.

In cases of regression models not fitting properly, i.e.,

failure in the convergence of maximum likelihood estimates due to quasi-complete separation, problematic variables were combined provided the combination is sensible. An example of this is echogenicity—various categories were combined to form either of the two major categories "uniform" and "non-uniform". Doing so provides better and reliable results.

For all tests, confidence interval was set at 95%, relationship significant at <0.05, all hypotheses tested at 0.05 level of significance. Minitab, a statistical software package, was used in the statistical computations and analysis of data. Data were entered with Microsoft Excel Spreadsheet and then analyzed with Minitab version 19.0 for Mac Mojave OS.

REVIEW OF RELATED LITERATURE

A MEDLINE search revealed 23 studies on the use of IETA terminology in the evaluation of women with abnormal uterine bleeding.

The consensus statement formed by the International Endometrial Tumor Analysis group last 2008 encompasses sonographic qualitative assessment of the endometrial morphology. This includes describing the endometrial echogenicity as "Uniform" or "Non-uniform"; the endometrial midline as "linear", "non-linear", "irregular" or as "not defined"; the endometrial-myometrial junction as "regular", "irregular", "interrupted", or "not-defined"; and the intracavitary fluid as "anechogenic", "ground glass", or of "mixed" echonegicity. Color and power doppler assessment were also included in the consensus statement, and the endometrium is graded according to the amount of blood flow present, from a score of 1, when no color flow can be found, to a score of 4 when there is abundant color detected. Lastly, the vascular pattern of the endometrium is also described according to the dominant pattern of vessels, and recorded accordingly as a single vessel with or without branching, multiple dominant vessels with focal or multifocal origin, scattered vessels, or there is circular flow of vessels3.

In 2013, Kucur et. al. evaluated the terms and description contributed by the IETA group focusing on doppler imaging of endometrial lesions in 97 patients presenting with abnormal uterine bleeding. Findings of a single dominant artery with or without branching correlated with endometrial polyps, multiple vessels with focal origin pattern were significantly higher in endometrial cancer, and a relationship was found between findings of scattered vessel pattern with endometrial hyperplasia. Submucous fibroids were exclusively correlated with findings of a circular color flow. However, there were no statistical difference with the color score among the endometrial pathologies[4].

In 2015, Abdelrhman used IETA features in describing the different endometrial lesions causing AUB in 60 patients, and in this study, each of the lesions were differentiated by each parameter of the IETA features. Based on vascular pattern, Abdelrhman observed that majority of the samples with multiple vessel pattern were diagnosed with endometrial carcinoma; for those cases with a single vessel pattern, most were diagnosed with endometrial polyp; and for a scattered vessel pattern majority were diagnosed as endometrial hyperplasia[5], with findings of the vessel pattern similar to the study done by Kucur et. al. However, the parameter for endometrial-myometrial junction and echogenicity of the endometrium in this study was only useful in differentiating a benign from a malignant endometrial lesion, and no significant correlation was found among the different types of benign endometrial lesions.

In 2017, Alcazar et. al. studied the reproducibility of using the IETA color score for flow within the endometrium by having 8 different examiners study the same set of 68 anonymized three-dimensional volumes of the uterus from a nonconsecutive series of 68 corresponding women presenting with abnormal uterine bleeding. As a result, 77% of malignant lesions were assigned a color score of 3 or 4, as were all cases of myoma. Endometrial polyps were assigned a color score of 1 or 2 in 80.3%, as were proliferative and atrophic endometrium. Endometrial hyperplasia was more frequently assigned a color score of 2, and 50% of the secretory endometrium were assigned a color score of 3 or 4. Although this study suggests that the reproducibility of assigning the IETA color score for endometrial vascularization is high, this study was not designed to evaluate the diagnostic performance of the IETA color score6.

A study done by Epstein et. al. published on the year 2017 focused on patients diagnosed with endometrial cancer and correlated the tumor grade and stage by IETA features, and found out that there was a morphological difference between well, moderately, and poorly differentiated tumors, with higher grade tumors concurrently have bigger volume and endometrial thickness, less frequently regular endometrial/myometrial junction, less frequently uniform echogenicity, and higher color score, but further noted that tumor size was the single strongest predictor of high-risk disease[7].

A more extensive study done by Van den Bosch et. al. on the year 2020 recorded the most common feature of each histological outcome as described by IETA features. In cases of proliferative or secretory endometrium, Echogenicity was generally uniform hyperechogenic, the endometrial–myometrial junction was mostly regular, and the color score was often 1. In endometrial hyperplasia, the endometrium was often uniform hyperechogenic, the midline was usually undefined, particularly after menopause, and the endometrial–myometrial junction was usually regular. The color score was usually 1 or 2, and the most common vessel morphology was multiple vessels with multifocal origin or a scattered pattern. In women with endometrial polyps, Echogenicity was usually uniform hyperechogenic, the endometrial midline was often undefined, a bright edge was present in 48% of women, and the endometrial–myometrial junction was usually regular. On color-Doppler imaging, there was a single vessel with or without branching in 69% of cases with detectable color-Doppler signals, and the most common color score was 2 or 3. In the presence of an intracavitary leiomyoma, the endometrium often appeared uniform hyperechogenic or non-uniform heterogeneous without cysts, the endometrial midline undefined and the endometrial–myometrial junction interrupted. On color Doppler, there was circular flow in 52% of cases, and the most common color score was 2–4. In endometrial cancer, echogenicity was non-uniform heterogeneous without cysts or heterogeneous with irregular cysts in 73% of cases. In the most of the cases, the endometrial midline was undefined, and the endometrial–myometrial junction was interrupted in 42% of women. A high color score of 3 or 4 was common and, if color-

Doppler signals were detectable, the most common vessel pattern was multiple vessels of focal or multifocal origin[8]. The results agree with the findings revealed in the study done by Alcazar and Kucur in terms of color score and vascular pattern.

Furau et. al. compared Endometrial Cancer vs Benign endometrial lesions using IETA features in the year 2021, and they found out that the samples with endometrial cancer have an inhomogenous echogenicity, with an undefined or irregular endometrial-myometrial junction, and has vessels with multifocal origin and with color score of 3 or 4, as compared to benign pathology that usually has a homogenous echogenicity, regular endometrial-myometrial junction, and a vascular flow that has no subsequent branching[9].

All of the mentioned articles studied the association of each feature in relation to a certain endometrial lesion. Of all the IETA features, color score was predictive of cancer. However, the other description included in the IETA features remain to have questionable predictive significance.

RESULTS

An important objective of this study was to determine the general histopathologic diagnoses of patients with abnormal uterine bleeding. Results are presented in Table 1. About one third of the patients or around 35.90% (no=84) were diagnosed with proliferative and secretory EM. Twenty seven percent (no=64) were diagnosed with endometrial polyps; while 14.10% (no=33) of the cases were found out to be various endometrial malignancies. In the studied population, 12.39% (no=29) were diagnosed with endometrial hyperplasia and the remaining 10.26% (no=24) of the patients had submucous myoma.

Table 1. General histopathologic diagnoses of patients with abnormal uterine bleeding

Histopathologic Diagnoses	N=234	
	No	%
Endometrial Hyperplasia	29	12.39
Endometrial Polyp	64	27.35
Submucous Myoma	24	10.26
Proliferative and Secretory	84	35.90
Endometrial Malignancies	33	14.10

Patients varied in age across the five conditions. In general, patients with cancer were the oldest on average, while those with hyperplasia were the youngest in the data. A one-way ANOVA revealed that these differences were significant across the five categories ($F(4,229) = 9.37$, $p<0.001$). Results are presented in Table 2.

Table 2. Age

Condition	Participants (SD)
Cancer	52.45 (12.74)
Hyperplasia	39.00 (9.41)
Myoma	45.67 (5.73)
Polyp	42.69 (12.17)
Proliferative/Secretory	42.24 (6.65)

On tables 3.1 – 3.5, the results when testing for the association between IETA features and each of the histopathologic diagnoses are presented. With regression analyses, this study will be able to determine which of these IETA features and their combination are associated with a specific group of histopathologic diagnosis. With all p-values greater than the significance level (0.05), there is no significant association between Endometrial Hyperplasia and the following: echogenicity, EM midline, EM junction, color score, vascular pattern and fluid. The same can be said for the other four histopathologic diagnoses: Endometrial Polyp; Submucous Myoma; Proliferative and Secretory; and Endometrial Malignancies. This means that in the studied population, the aforementioned combination of IETA features that characterize

Table 3.1 IETA sonographic features and Endometrial Hyperplasia

Variables	Computed Values[a]	p-value[b]	Interpretation
Echogenicity			No association Significant
Uniform	-1.885	1.000	
EM Midline			No association Significant
Irregular	12	0.972	
Linear	14	0.967	
Non-linear	13	0.969	
Not defined	12	0.970	
EM Junction			No association Significant
Irregular	-10.7	0.910	
Not defined	-11	0.950	
Regular	12	0.374	
Color Score			No association Significant
2	1.30	0.391	
3	-1.05	0.582	
4	-12	0.925	
Vascular Pattern			No association Significant
Circular flow	0.90	0.676	
Multiple vessels: focal origin	-0.78	0.696	
Multiple vessels: multi-focal origin	-0.23	0.886	
Scattered vessels	-3.23	0.080	
Single vessel: with branching	-12	0.956	
Single vessel: without branching	-1.43	0.359	
Color Score			No association Significant
Ground glass echoes	-10	0.949	
Mixed echoes	1.159	0.084	

a values refer to coefficients computed using Binary Logistic Regression;
b significant at <0.05;

Table 3.2 IETA sonographic features and Endometrial Polyp

Variables	Computed Values[a]	p-value[b]	Interpretation
Echogenicity			No association Significant
Uniform	0.624	0.112	
EM Midline			No association Significant
Irregular	-14	0.970	
Linear	-14	0.969	
Non-linear	-14	0.969	
Not defined	-14	0.969	
EM Junction			No association Significant
Irregular	1.15	0.352	
Not defined	0.30	0.851	
Regular	2.02	0.063	
Color Score			No association Significant
2	-14	0.959	
3	-13	0.960	
4	-14	0.956	
Vascular Pattern			No association Significant
Circular flow	2	0.995	
Multiple vessels: focal origin	15	0.954	
Multiple vessels: multi-focal origin	14	0.958	
Scattered vessels	15	0.956	
Single vessel: with branching	15	0.955	
Single vessel: without branching	15	0.954	
Color Score			No association Significant
Ground glass echoes	-0.18	0.862	
Mixed echoes	-0.944	0.064	

a values refer to coefficients computed using Binary Logistic Regression;
b significant at <0.05;

Table 3.3 IETA sonographic features and Submucous Myoma

Variables	Computed Values[a]	p-value[b]	Interpretation
Echogenicity			No association Significant
Uniform	0.731	0.299	
EM Midline			No association Significant
Irregular	9	0.979	
Linear	9	0.980	
Non-linear	8	0.980	
Not defined	9	0.979	
EM Junction			No association Significant
Irregular	-2.89	1.000	
Not defined	-1.37	0.257	
Regular	-3.316	1.000	
Color Score			No association Significant
2	-10	0.961	
3	-21	0.924	
4	-21	0.928	
Vascular Pattern			No association Significant
Circular flow	0	0.967	
Multiple vessels: focal origin	-0	0.998	
Multiple vessels: multi-focal origin	9	0.966	
Scattered vessels	9	0.964	
Single vessel: with branching	-9	0.966	
Single vessel: without branching	9	0.964	
Color Score			No association Significant
Ground glass echoes	-10	0.949	
Mixed echoes	-0.245	0.805	

a values refer to coefficients computed using Binary Logistic Regression;
b significant at <0.05;

ultrasound results of patients are not significant predictors of any of the 5 histopathologic diagnoses. Thus, the investigator did further analysis in a manner similar to the previous studies where the individual IETA features were tested for association to the different endometrial pathologies. Color Scores varied significantly across conditions, as revealed by a one-way ANOVA ($F(4,229) = 12.13$, $p<0.001$) as shown in Table 4, and Endometrial thickness also varied significantly across the conditions, as revealed by a one-way ANOVA ($F(4,225) = 9.46$, $p<.001$) as shown in Table 5.

DISCUSSION

The purpose of this study is to be able to identify and differentiate the common benign endometrial lesions, and identify patients at risk for endometrial cancer with an attempt to use sonography with IETA features alone, aiming also to omit endometrial sampling for patients. However, as shown in the results, no combination of the IETA features is significantly predictive of an endometrial pathology.

In agreement with previous studies, Color score however varied significantly with endometrial malignancy as what was observed in this study, which was also in accordance to the study done by Alcazar. However, this still leaves the other features with unknown association to a particular diagnosis.

As endometrial cancer being known as the second most common gynecologic malignancy in women worlwide[10], it is then important to give emphasis of its timely diagnosis. Women with

Table 3.4 IETA sonographic features and Proliferative/Secretory Endometrium

Variables	Computed Values[a]	p-value[b]	Interpretation
Echogenicity			No association
Uniform	0.433	0.205	
EM Midline			No association
Irregular	11	0.962	
Linear	11	0.960	
Non-linear	12	0.959	
Not defined	12	0.960	
EM Junction			No association
Irregular	1.123	0.143	
Not defined	0.74	0.492	
Regular	0.974	0.119	
Color Score			No association
2	0.82	0.529	
3	0.85	0.536	
4	0.21	0.891	
Vascular Pattern			No association
Circular flow	-0.04	0.979	
Multiple vessels: focal origin	-2.43	0.150	
Multiple vessels: multi-focal origin	-1.17	0.393	
Scattered vessels	-0.86	0.529	
Single vessel: with branching	-0.83	0.586	
Single vessel: without branching	-1.56	0.242	
Color Score			No association
Ground glass echoes	0.424	0.639	
Mixed echoes	0.370	0.394	

a values refer to coefficients computed using Binary Logistic Regression;
b significant at <0.05;

Table 3.5 IETA sonographic features and Endometrial Malignancies

Variables	Computed Values[a]	p-value[b]	Interpretation	
Echogenicity			No association	Significant
Uniform	-0.466	0.382		
EM Midline			No association	Significant
Irregular	12	0.974		
Linear	11	0.976		
Non-linear	12	0.974		
Not defined	12	0.975		
EM Junction			No association	Significant
Irregular	1.420	0.144		
Not defined	1.48	0.228		
Regular	-0.325	0.689		
Color Score			No association	Significant
2	-10	0.960		
3	-8	0.967		
4	-6	0.975		
Vascular Pattern			No association	Significant
Circular flow	-5	0.987		
Multiple vessels: focal origin	9	0.963		
Multiple vessels: multi-focal origin	9	0.961		
Scattered vessels	10	0.961		
Single vessel: with branching	-9	0.963		
Single vessel: without branching	9	0.963		
Color Score			No association	Significant
Ground glass echoes	-0.40	0.757		
Mixed echoes	0.148	0.810		

a values refer to coefficients computed using Binary Logistic Regression;
b significant at <0.05;

Table 4. Color Score

Condition	Mean Color Score (SD)
Cancer	2.58 (1.15)
Hyperplasia	1.59 (0.57)
Myoma	1.25 (0.44)
Polyp	1.91 (0.75)
Proliferative/Secretory	1.65 (0.81)

Table 5. Endometrial Thickness

Condition	Mean EM Thickness (SD)
Cancer	2.28 (1.46)
Hyperplasia	1.60 (0.53)
Myoma	0.93 (0.47)
Polyp	1.41 (0.73)
Proliferative/Secretory	1.41 (0.73)

endometrial cancer present with abnormal uterine bleeding in 90% of instances[11], and transvaginal ultrasound is known to be a cost-effective initial step in the diagnosis. Although the IETA features were introduced to make a uniform description of the endometrium in sonography, it's clinical significance in identifying absence or presence of endometrial pathology is still not established, considering its use in the multiple studies done after the release of the consensus statement last 2008. Predicting risk of endometrial malignancy should still rely on other clinical parameters like Age, BMI, Parity, and Endometrial Thickness[12], with the last risk factor mentioned to also have a significance with endometrial cancer, as highlighted in the results.

The main outcome of this study did not show an association with any specific endometrial pathology, which then translates that sonography with the combination of IETA features cannot be solely used for diagnosis. Still, women with abnormal uterine bleeding should have endometrial sampling done to confirm histopathologic diagnosis[13], as what current guidelines suggest.

CONCLUSION

Results of this study show that there is no association between the combination of IETA features that characterize ultrasound results of patients with abnormal uterine bleeding, and with the diagnosis of Endometrial Hyperplasia; Endometrial Polyp; Submucous Myoma; Proliferative and Secretory Endometrium; and Endometrial Malignancies. However, analysis of the individual features revealed that color score and endometrial thickness were significantly associated with endometrial cancer.

STUDY LIMITATIONS

This study is conducted in two tertiary hospitals, one from Cebu City and one from Mandaue City. With each institution having multiple sonologists, the interpretation and use of IETA features may be subjective and results may be inconsistent, considering the new phase of the application of IETA features, and variability of the ultrasound interpretation among scanners. Furthermore, since the application of the use of IETA features was only started in these institutions a year prior to this study, the sample size is only limited to the ultrasound **results available within that time frame.**

RECOMMENDATIONS

Further research can be made with focus on the reproducibility of the ultrasound results using the IETA features in the institutions studied to identify inter-observer difference. Since the IETA features are now the adapted standard of description for the endometrium in ultrasonography, a multicenter study can also be considered to confirm if there is an association between the ultrasound features and endometrial pathology or not. A similar study can also be done covering a longer period to increase the sample size and reliability of the study. ■

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Diagnostic Accuracy of International Ovarian Tumor Analysis (IOTA) Assessment of Different Neoplasia in the Adnexa (ADNEX) Model in Detecting Ovarian Carcinoma in a Tertiary Hospital: A Retrospective Cross-Sectional Study

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ABSTRACT

Background: Ovarian Cancer ranks the 10th most common cancer in the Philippines. It is the 2nd most common cause of death from gynecologic neoplasm in the country. Possible reasons for its high death rate could be 1) due to its late diagnosis (most cases are usually detected after it has already metastasized), and 2) currently, there's no available effective screening methods for detection of early-stage ovarian carcinoma.

Objective: The study focuses on determining the accuracy of International Ovarian Tumor Analysis (IOTA) Assessment of Different Neoplasia in the Adnexa (ADNEX) Model in detecting Ovarian Carcinoma in patients admitted in tertiary hospital from January 2022 to October 2022.

Methods: A descriptive retrospective cross-sectional study was done through chart review of 42 patients. Demographic and clinical characteristics of the subjects, IOTA ADNEX score, and classification and histologic results were gathered. The histopathologic results were classified as to benign and malignant. Sensitivity and specificity were computed on a 10%-threshold risk. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy were used to assess the diagnostic performance of IOTA ADNEX model in predicting benign or malignant ovarian mass. The histopathological result was used as gold standard.

Results. IOTA ADNEX model is a good predictor in detecting malignant masses. Incorporating it in ultrasound reading and in clinical practice will aid gynecologists in the early distinction between a benign or malignant lesions and will aid in a timely management for surgical treatment.

Keywords: *Ovarian Mass, IOTA-ADNEX Model, Diagnostic Accuracy*

INTRODUCTION

According to the Globocan 2020, Ovarian Cancer ranks the 10th most common cancer in the Philippines and 18th worldwide. It is the 2nd most common cause of death from gynecologic neoplasm in the Philippines after Cervical Cancer. Possible reasons for its high death rate could be 1) due to its late diagnosis since most cases are usually detected after it has already metastasized and 2) currently, there are no available effective screening methods for detection of early-stage ovarian carcinoma.

Ultrasound plays a valuable tool for detecting the presence of ovarian masses. It can help discriminate between benign and malignant tumors, and help gynecologists plan the appropriate intervention for the patient. The International Ovarian Tumor Analysis (IOTA) developed a risk model, the Assessment of Different Neoplasia in the Adnexa (ADNEX) model, that could differentiate between benign and the four types of malignant ovarian tumors: borderline, stage I cancer, stage II-IV, and secondary metastatic cancer. It consists of three clinical predictors: 1) age, 2) serum CA-125 (U/mL), and 3) type of center (oncology referral center vs non-oncology center), and six ultrasound predictors: 1) maximum diameter of the lesion (mm), 2) maximum diameter of the largest solid part of the lesion (mm), 3) presence more than 10 cyst locules, 4) number of papillary projections, 5) presence of acoustic shadows, and 6) presence of ascites. The IOTA ADNEX model is utilized in patients admitted in tertiary hospital to aid in determining whether ovarian masses are most likely benign or malignant and in turn help determine whether patients should be managed conservatively or if a patient warrants surgical management.

OBJECTIVES

The authors determined the diagnostic performance of IOTA-ADNEX Model in detecting Ovarian Carcinoma in patients admitted in tertiary hospital from January 2022 to October 2022. The objectives of the study were as follows:

1) To determine the demographics and clinical characteristics of the subjects to include age, gravidity, parity, menopausal status, age at menopause, family history of cancer, and CA-

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125 level

2) To determine the following diagnostic performance properties of IOTA-ADNEX Model in detecting ovarian carcinoma:
   a. Sensitivity and specificity
   b. Positive and negative predictive values
   c. Likelihood ratios positive and negative
   d. Diagnostic accuracy

This study will aid gynecologists in differentiating ovarian masses whether it is benign or malignant thru the application of the IOTA ADNEX Model. Early distinction between benign or malignant lesion will lead to timely management. This will then lead to early referral to gynecologic oncologists for further management. This will also help gynecologists in determining the appropriate optimal treatment and pre-operative plan for patients.

MATERIALS AND METHODS

A. STUDY DESIGN

This is a retrospective descriptive cross-sectional study wherein a chart review was conducted to determine the diagnostic accuracy of the IOTA-ADNEX Model in detecting Ovarian Carcinoma in patients admitted in a tertiary hospital from January 2022 to October 2022.

B. STUDY POPULATION (INCLUSION/EXCLUSION CRITERIA)

The study population consisted of 42 patients who were admitted at the Obstetrics and Gynecology Department of tertiary hospital from January 2022 to October 2022 who presented with at least one (1) ovarian mass and underwent surgical management.

INCLUSION CRITERIA

1) Patients with at least one (1) ovarian mass based on ultrasound
2) Ovarian mass was assessed using the IOTA-ADNE Model
3) Patients underwent surgical treatment
4) Patients with histopathological results

EXCLUSION CRITERIA

1) Patients with adnexal mass with no indication for surgery
2) Patients who fail to undergo surgery within 120 days of the ultrasound examination
3) Patients with indefinite histopathological results

C. DATA COLLECTION, METHODS, AND TOOL

The sample size required for this study was computed using the equation by Haijan-Tilaki (2014). The sample size was computed to be a minimum of 168 patients. A list of qualified cases was produced from the census of hospital admissions from January 1, 2022 to October 31, 2022.

The following data such as the demographics and clinical characteristics of the subjects (including age, gravidity, parity, menopausal status, age at menarche and menopause, family history of cancer, and CA-125 level), IOTA ADNEX score, and classification and histopathologic results were collected from the patients' records in the hospital. Patients with ultrasound diagnosis of an ovarian mass who met the inclusion criteria were classified into benign or malignant tumor based on IOTA ADNEX model (borderline tumors were classified under malignant). Those who had no indication for surgery, and those who failed to undergo surgery within 120 days when ultrasound was taken were excluded from the study. After which, histopathologic results of these patients were gathered. Those with indefinite histopathological results was excluded from the study. Patients will then be classified whether they a benign, borderline, malignant histopathological findings (borderline histopathological results were classified as malignant). Figure 1 shows the process flow of the selection process.

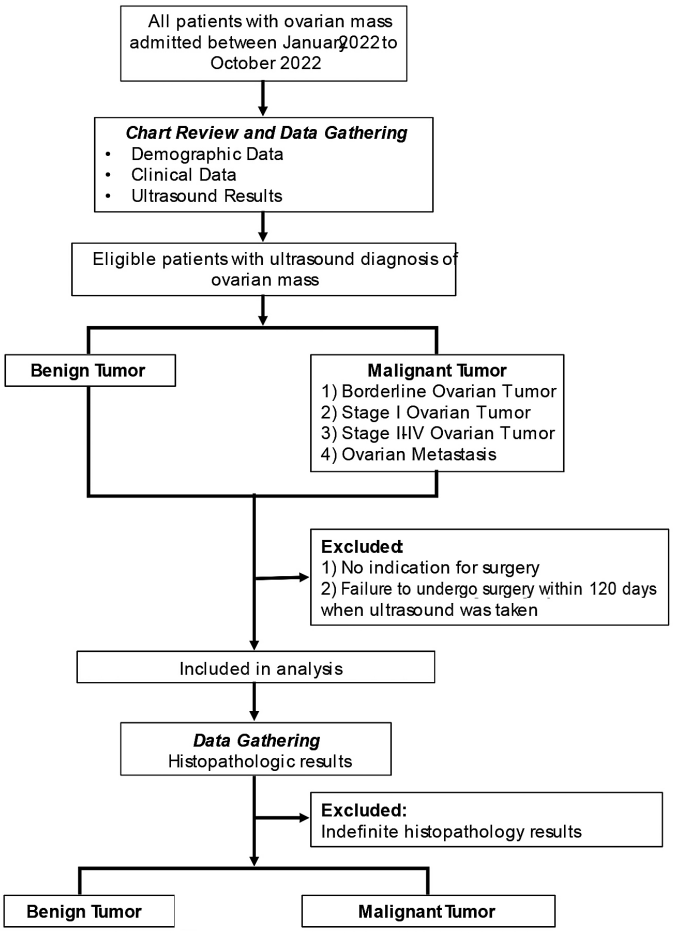

Figure 1. Process Flow of Selection Process

The general and clinical characteristics of the participants were analyzed by means of descriptive statistics. Frequency and proportion were used for categorical variables. Sensitivity, specificity was computed on a 10% threshold risk. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy was used to assess the diagnostic performance of IOTA ADNEX model in predicting benign or malignant ovarian mass. The histopathological result was used as gold standard. SPSS 25 was used for data analysis.

RESULTS

The study was not able to meet the sample size

recommended for this study. Out of the 168 patients needed, only 42 patients were gathered and included in the analysis. Out of the 140 patients who had an ultrasound diagnosis of ovarian mass from January to October 2022, only 42 patients underwent surgery and were eligible to be included in the study.

Presented in Table 1 is the demographic and clinical profile of the patients. The different variables are numerical in nature, thus the mean ± SD are computed. Based on the results, the mean ± SD for age is 47.48 ± 13.84, for gravidity is 2.98 ± 2.06, for parity is 2.58 ± 1.83. The mean ± SD age at menopause of these 11 patients with data is 50.19 ± 2.64 years. 7% of these patients have a history of cancer in the family. Lastly, the CA-125 (u/ml) is at 169.19 ± 204.19. The high SD of the CA-125 indicates scatteredness of in the levels among the 42 patients.

For the categorical variables of the clinical profile of the patients, Table 1.2 shows that majority of the patients are pre-menopause (71.43%) and the rest are already post-menopausal (28.57%), while in terms of family history, 92.86% do not have cancer and 7.14% have cancer.

Table 1. Demographic and Clinical Profile of Patients

Variable	n	Mean ± SD
Age	42	47.48 ± 13.84
Gravidity	42	2.98 ± 2.06
Parity	42	2.58 ± 1.83
Age at Menopause	12	50.19 ± 2.64
CA-125 (u/ml)	42	169.19 ± 204.19

Table 1.2. Clinical Profile of Patients (Categorical Data)

Menopausal Status (n = 42)	Frequency	Percentage
Post-menopausal	30	71.43
Pre-menopausal	12	28.57
Family History of Cancer (n = 42)	**Frequency**	**Percentage**
Yes	3	7.14
No	39	92.86

The histological type and distribution of benign and malignant is revealed in Table 2. Based on the results, for those with benign ovarian mass, the histological type are Mucinous Cystadenoma (53.33%), Serous Cystadenoma (20.00%), Endometriotic Cyst (13.33%) and both with 6.67% are Fibrothecoma and Seromucinous Cystadenoma. For those with borderline ovarian mass, Borderline Mucinous Tumor (Atypical Proliferative Mucinous Tumor) had a higher percentage (87.50%) as compared to Serous Borderline Tumor (Atypical Proliferative Serous Tumor), which is only 12.50%. Lastly, for those with malignant ovarian mass, Mucinous Cystadenocarcinoma accounts for 42.11%, and this was followed by Low Grade Serous Carcinoma (15.78%), Clear Cell Carcinoma and High-Grade Serous Carcinoma with 10.52% and tied at 5.26% are Carcinosarcoma (Malignant Mixed Mullerian Tumor), Dysgerminoma, High Grade Carcinoma with Seromucinous Features, and Squamous Cell Carcinoma Arising from a Mature Teratoma.

The diagnostic performance of IOTA-ADNEX in identifying benign and malignant ovarian masses with histopathology

Table 2. Histological Type and Distribution of Benign and Malignant

BENIGN (n=15)	Frequency	Percentage
Fibrothecoma	1	6.67
Seromucinous Cystadenoma	1	6.67
Endometriotic Cyst	2	13.33
Serous Cystadenoma	3	20.00
Mucinous Cystadenoma	8	53.33

BORDELINE (n=8)	Frequency	Percentage
Serous Borderline Tumor (Atypical Proliferative Serous Tumor	1	12.50
Borderline Mucinous Tumor (Atypical Proliferative Mucinous Tumor)	7	87.50

MALIGNANT (n=19)	Frequency	Percentage
Carcinosarcoma (Malignant Mixed Mullerian Tumor)	1	5.26
Dysgerminoma	1	5.26
High Grade Carcinoma with Seromucinous Features	1	5.26
Squamous Cell Carcinoma Arising from a Mature Teratoma	1	5.26
Clear Cell Carcinoma	2	10.52
High Grade Serous Carcinoma	2	10.52
Low Grade Serous Carcinoma	3	15.78
Mucinous Cystadenocarcinoma	8	42.11

results as the gold standard is presented in Table 3. Positive on test indicates that there is malignant risk based on IOTA ADNEX model, while negative on test indicates that it leaned toward a benign risk based on IOTA ADNEX model. Based on the results, the sensitivity value of 0.93 indicates 93% probability that the IOTA-ADNEX will yield a result of malignant risk based on IOTA ADNEX Model when the ovarian mass is malignant, while the specificity value of 0.47 shows 47% probability that the IOTA-ADNEX will yield a result of benign risk on IOTA ADNEX model when the ovarian mass is benign. This was based on a 10%-risk threshold. A 1.74 positive likelihood ratio indicates a 1.74-fold increase in the odds of patients having ovarian mass with a positive test (malignant risk based on IOTA ADNEX Model) result whereas 0.16 negative likelihood ratio shows that a 16-fold decrease in the odds of having an ovarian mass with a negative test result (benign risk based on IOTA ADNEX Model). The low negative likelihood ratio was expected since the IOTA ADNEX Model is used in ovarian masses that have features suspicious of malignancy rather than in ovarian masses who only have benign features.

On the other hand, the positive predictive value of 0.76 indicates that overall, 76% of those who have positive test (malignant risk based on IOTA ADNEX Model) result have malignant ovarian histopathological result while negative predictive value of 0.78 reveals that 78% of those who have negative test (benign risk based on IOTA ADNEX Model) result have benign histopathological result.

The accuracy, which is derived from sensitivity and specificity, has a value of 0.76 means that the IOTA-ADNEX is 76% correct in determining those with true positive (malignant IOTA ADNEX risk with malignant histopathological result) and true negative (benign IOTA ADNEX risk with benign histopathological result).

Table 3. Diagnostic Performance of IOTA-ADNEX in Identifying Benign and Malignant Ovarian Masses with Histopathology Results as the Gold Standard

	True Positive (Malignant Histopathological Result)	True Negative (Benign Histopathological Result)	Total
Frequency			
Positive on Test (Malignant IOTA Risk)	25	8	33
Negative on Test (Benign IOTA Risk)	2	7	9
Total	27	15	42
Sensitivity	0.93	Positive LR	1.74
Specificity	0.47	Negative LR	0.16
PPV	0.76	Accuracy	0.76
NPV	0.78		

The following IOTA ADNEX Risk for Malignancy was further classified in this paper into 4 tiers to better distinguish which risk of malignancy demonstrated accuracy in determining whether the ovarian mass is benign or malignant. The following tiers are as follows: Tier 1 – those with less than 25% risk of malignancy, Tier 2 - those with 25-50% risk of malignancy, Tier 3 - those with 51-75% risk of malignancy, and Tier 4 - those with more than 75% risk of malignancy. Table 4 shows the distribution of patients in the different tiers. Tables 4.1 to 4.4 demonstrate the diagnostic

Table 4. Distribution of Patients in the Different Tiers (n=42)

Tier	n
1	10
2	5
3	4
4	23

Table 4.1 Diagnostic Performance of IOTA-ADNEX in Identifying Benign and Malignant Ovarian Masses with Histopathology Results as the Gold Standard in Tier 1 – Less than 25% Risk of Malignancy (n=10)

	Malignant Histopathological Result	Benign Histopathological Result	Total
Frequency			
Malignant IOTA Risk	2	0	2
Benign IOTA Risk	4	4	8
Total	6	4	10
Sensitivity	0.33	Positive LR	0.00
Specificity	1.00	Negative LR	0.67
PPV	1.00	Accuracy	0.60
NPV	0.50		

Table 4.2 Diagnostic Performance of IOTA-ADNEX in Identifying Benign and Malignant Ovarian Masses with Histopathology Results as the Gold Standard in Tier 2 – 25-50% Risk of Malignancy (n=5)

	Malignant Histopathological Result	Benign Histopathological Result	Total
Frequency			
Malignant IOTA Risk	4	1	5
Benign IOTA Risk	0	0	0
Total	4	1	5
Sensitivity	1.00	Positive LR	1.00
Specificity	0.00	Negative LR	0.00
PPV	0.80	Accuracy	0.80
NPV	0.00		

performance of IOTA-ADNEX in identifying benign and malignant ovarian masses in the different tiers. The accuracy was computed for each tier and are as follows: Tier 1 – 60%, Tier 2 – 80%, Tier 3 – 75%, and Tier 4 – 61%. Among the different tier, Tier 2 (patients with 25-50% risk of malignancy in IOTA ADNEX) had the highest accuracy, meaning that it is 80% correct in determining those with true positive result (malignant risk in IOTA ADNEX with malignant histopathological result).

Table 4.3 Diagnostic Performance of IOTA-ADNEX in Identifying Benign and Malignant Ovarian Masses with Histopathology Results as the Gold Standard in Tier 3 – 51=75% Risk of Malignancy (n=4)

	Malignant Histopathological Result	Benign Histopathological Result	Total
		Frequency	
Malignant IOTA Risk	3	1	4
Benign IOTA Risk	0	0	0
Total	3	1	4
Sensitivity	1.00	Positive LR	1.00
Specificity	0.00	Negative LR	0.00
PPV	0.75	Accuracy	0.75
NPV	0.00		

Table 4.4 Diagnostic Performance of IOTA-ADNEX in Identifying Benign and Malignant Ovarian Masses with Histopathology Results as the Gold Standard in Tier 4 – More than 75% Risk of Malignancy (n=23)

	Malignant Histopathological Result	Benign Histopathological Result	Total
		Frequency	
Malignant IOTA Risk	14	9	23
Benign IOTA Risk	0	0	0
Total	14	9	23
Sensitivity	1.00	Positive LR	1.00
Specificity	0.00	Negative LR	0.00
PPV	0.61	Accuracy	0.61
NPV	0.00		

Area Under the Curve (AUC), also called as C statistic (Table 5), the concordance statistic or the C-index determines how well the model will be able to distinguish between positive and negative outcomes. The value of AUC can range from zero (0) to one (1). Higher AUC value indicates better model that correctly classify outcomes. For IOTA ADNEX Model, the AUC is 0.858, which means that the prediction is 85.8% correct, with standard error of 0.068 and p-value of 0.000 (<0.05), which indicates that the AUC is statistically significant. 95% confidence interval (C.I.) indicates that we are 95% confident that the true area will lie within the lower bound (0.725) and upper bound. (0.991) denoted as 95% C.I. [0.725, 0.991].

Table 5. Area Under the Curve of the IOTA ADNEX Model

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.858	0.068	0.000	0.725	0.991

In terms of Receiver Operator Characteristic (ROC) Curve, a model that has high sensitivity and specificity will have an ROC curve that meets the top left corner of the plot, while a model with low sensitivity and specificity will have a curve that is almost near the red diagonal line (45-degree). The ROC curve is a plot of values of sensitivity against 1-specificity as the value of the cut-off point moves from zero (0) to one (1). By visual inspection, we can see that the ROC Curve is somehow close to the top left corner of the plot. This only means that the model for IOTA-ADNEX is good in predicting whether patients will have malignant ovarian mass, which can be supported by AUC of 0.858 in Table 5.

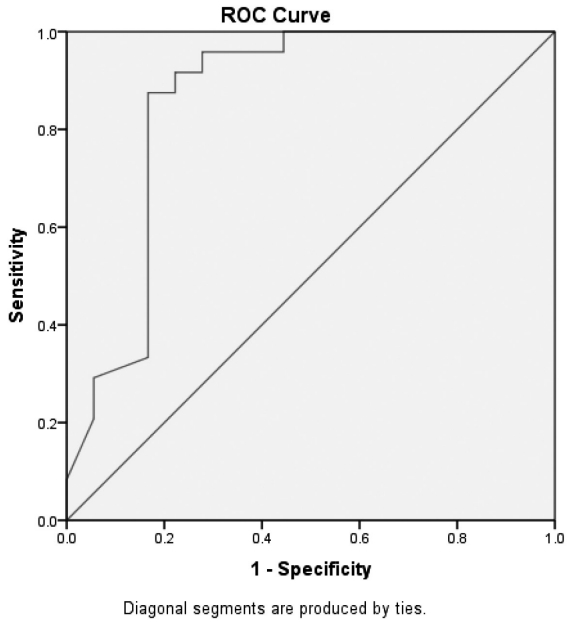

Figure 2. Receiver Operator Characteristic (ROC) Curve of IOTA-ADNEX in Predicting Benign and Malignant Ovarian Masses

The IOTA-ADNEX and histopathology results are tested for possible association using chi square test of independence, since the variables are categorical (nominal) in nature. Based on the results provided in Table 6, there exists significant relationship between the two variables since the computed p-value is less than the significance level of 0.05 (□2=13.090,□=0.011).

Table 6. Test of Association between IOTA-ADNEX and Histopathology Results

	Histopathological Result		
	Benign	**Borderline**	**Malignant**
	Frequency (Percentage %)		
IOTA-ADNEX			
Benign	7 (16.67%)	1 (2.39%)	1 (2.39%)
Borderline	2 (4.77%)	1 (2.39%)	0 (0.00%)
Malignant	Benign	6 (14.29%)	18 (42.86%)

Chi Square = 13.090, p = 0.011

DISCUSSION

Transvaginal ultrasound is among the first line for diagnosing gynecologic diseases since it can visualize the lesion and analyze some of the characteristics of the mass. However, the accuracy of the assessment depends greatly based on experience of the sonologist. The evaluation is also subjective and arbitrary to the sonologist. The diagnostic accuracy of the IOTA ADNEX model has been evaluated in different studies. In a study by Peng et al, the diagnostic accuracy of the ADNEX model with CA-125 was evaluated among different cut-off values for malignancy risk. Using the 10% cut-off, the model had a sensitivity of 94.3% and specificity of 74%, while when using the 46.7% cut-off, it had a sensitivity of 86.7% and specificity of 91.6%. In this study, the IOTA ADNEX Model had a sensitivity of 93% and a specificity of 47%, meaning that that it will provide positive test (malignant risk) when the ovarian mass is malignant, while the specificity value of 0.47 shows 47% probability that it will provide negative test (benign risk) when the ovarian mass is benign. However, the sensitivity and specificity of the IOTA ADNEX model was only computed based on a 10% risk threshold. In a study by Jeong et al in the validation of IOTA-ADNEX Model in Discriminating Characteristics of Adnexal Masses, the optimal cut-off values to discriminate ovarian malignancy using the IOTA ADNEX model using the Youden Index Method. The Youden index summarizes the performance of a diagnostic test. To get the Youden Index, the sensitivity of a diagnostic test is added to the specificity of the same diagnostic test, then subtract 100 from that value. The cut-off point for having an acceptable Youden Index is 50%. Any value below 50% denotes an overall lack of the diagnostic test to detect either disease or health. In our study, the Youden index is 40%. A possible reason for the low index score in this study could be secondary to the low sample size.

The diagnostic performance of IOTA ADNEX model was evaluated in the different tiers mentioned above to better analyze the results. Tier 2 (those with 25-50% IOTA ADNEX risk for malignancy) showed the highest accuracy in determining whether an ovarian mass is truly malignant. However, those in Tier 4 (those with >75% IOTA ADNEX risk for malignancy) showed the lowest accuracy, meaning that some patients interpreted with malignant IOTA ADNEX risk yielded a benign histopathologic result. The histopathological results of those patients were Serous Cystadenoma, Mucinous Cystadenoma and Endometriotic Cyst. Factors that could have affected the IOTA ADNEX Score are age of the patient (mean age of these patients are 44-46 years old), CA-125 level (CA-125 level of these patients range from 41-256 u/mL), and menopausal status of the patient (one of the patient is menopause).

Receiver-operating characteristic (ROC) curves were used to study the IOTA-ADNEX model in predicting benign and malignant ovarian mass and the areas under the curve (AUCs) were calculated. The IOTA ADNEX model had a high sensitivity in diagnosing malignant ovarian tumors. This was supported by the AUC of 0.858, indicating that the model is good in predicting whether patients will have malignant ovarian mass.

The results of this study are limited by the small sample size, since the participants were obtained during the time of a pandemic (COVID-19 Pandemic). During this time, there were restrictions that needed to be followed, and there were lesser patients who underwent surgery. The inadequate sample size may not be representative of the whole population. Another limiting factor is that the sonologists in the institution had their certification on IOTA Scoring last December 2021 and started officially using of the IOTA ADNEX Model afterwards. A third limitation of our study is that not all patients had their CA-125 prior to the ultrasound because most women usually undergo a transvaginal ultrasound first, and CA-125 is req ested a ter ards to further assess one's risk or for ovarian malignancy.

SUMMARY AND CONCLUSION, LIMITATION/S, RECOMMENDATION/S

The IOTA ADNEX model is a good predictor in detecting malignant masses. Therefore, incorporating it in ultrasound reading and in clinical practice will aid gynecologists in the early

distinction between a benign or malignant lesions. This will aid in timely management in determining whether a patient would be warranting surgical treatment. Recommendation for future research would be to include in the study the sensitivity and specificity of the IOTA ADNEX Model at different risk threshold values. Another recommendation would be to have a standardized way of relaying ultrasound results of IOTA ADNEX Model, with the clinical and ultrasound predictors enumerated and with the computed risk for a benign or malignant tumor also indicated. This could play a room in conducting a study to determine which of the clinical and ultrasound predictors has a strong correlation in the pathological stage of the mass. The diagnostic performance of the IOTA ADNEX model can also be compared with or without CA 125. ■

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Double Primary: Endometrial Endometrioid Carcinoma and Squamous Cell Carcinoma of the Cervix – A Case Report and Review of Literature

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ABSTRACT

This case report highlights the diagnostic strategies employed in unusual encounters of double primary malignancy involving the endometrium and the cervix. It explores the diagnostic challenges faced in differentiating between these malignancies through imaging modalities. In addition, this report presents the management dilemmas encountered when faced with these both malignancies.

Double primary malignancy of the cervix and endometrium is a rare case. We present a case of a 61 year-old, Gravida 3 Para 3 (3002) who consulted due to postmenopausal bleeding. She was managed as a case Squamous cell carcinoma of the cervix, stage IB1 and underwent Exploratory laparotomy, radical hysterectomy, bilateral salpingo-ophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling. Histopathologic result showed double primary: endometrial endometrioid carcinoma and squamous cell carcinoma of the cervix.

Patient underwent adjuvant systemic chemotherapy in the form of Carboplatin-Paclitaxel for 6 cycles and for pelvic external beam radiation.

Keywords: *Endometrial endemtrioid carcinoma, squamous cell carcinoma, double primary*

INTRODUCTION

Distinguishing between primary endometrial and primary endocervical malignancy, as well as determining the tumor origin of synchronous gynecologic malignancy is a common challenge in clinical practice. Integrating the clinical, radiologic and pathologic features plays a crucial role in achieving an accurate diagnosis and subsequent management. Ancillary studies such as immunohistochemistry, are commonly beneficial.

According to a retrospective study done last 2017, synchronous genital malignancy is rare with an incidence of 0.7%. Endometrial-ovarian malignancy was the most common type of coexisting cancer. The mean age of diagnosis of the first and second primary malignancy was 51.6 and 56.0, respectively. The cervix was found to be the most common site of the first primary cancer which was followed by the breast, ovaries, uterus and colon. On average, it takes about five years from the initial detection of a primary malignancy for a secondary gynecologic malignancy to be identified. The overall recurrence and mortality rate were reported to be as high as 76.9% and 8.5%, respectively. This highlights the role of timely diagnosis, management and long-term surveillance for these patients.

CLINICAL CASE PROTOCOL

A 61-year-old, G3P3 (3002) woman, ECOG 0, with hypertension, dyslipidemia and bronchial asthma presents with post-menopausal bleeding. She has no vices, had her first sexual contact at 20 years-old with one sexual partner, no history of oral contraceptive pill use, menarche at 15 years-old and menopause at 50 years-old. A year prior to consult, she had onset of post-menopausal bleeding fully soaking one pad per day prompting consult with a private physician. A transvaginal ultrasound was done which showed a uterine myoma wherein she was advised observation and surveillance. In the interim, there was persistence of the bleeding prompting consult with another physician wherein a repeat transvaginal ultrasound revealed an enlarged uterus with endometrial mass suggestive of endometrial pathology with features of malignancy with normal ovaries. These findings prompted referral to Gynecologic Oncology. Systemic physical examination was essentially normal. Internal examination revealed normal external genitalia, smooth vagina, cervix was noted to be smooth, measuring 3.0 x 3.0 cm, the corpus is enlarged at 10 weeks size, with no adnexal mass or tenderness and the bilateral parametria were smooth and pliable.

An endometrial biopsy was done which revealed poorly differentiated carcinoma. Immunohistochemistry showed the following results: CEA - focal moderate membranous staining; Vimentin – negative; P63 – positive patchy; and P16 – positive strong; findings that are consistent with Human Papilloma Virus-associated Squamous Cell Carcinoma. Other pertinent laboratories revealed a clear chest radiograph, normal hemoglobin, normal renal and liver function, and unremarkable electrolytes.

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In accordance with the 2019 Society of Gynecologic Oncologists of the Philippines Guidelines on Cervical Cancer, the patient was advised and underwent successfully underwent exploratory laparotomy, radical hysterectomy, bilateral salpingoophorectomy, bilateral lymph node dissection and para-aortic lymph node sampling. Grossly, the uterus had smooth, tan serosal surface with regular contour measuring 12.0 x 8.0 x 5.0 cm (Fig. 1). The cervix was smooth which measured 4.0 x 4.0 x 3.0 cm with note of posterior cervical nodularity measuring 1 x 0.5 x 0.5 cm (Fig. 2). Within the uterine cavity is a 7.0 x 6.0 x 3.5 cm friable necrotic mass that is posteriorly attached to the posterior midcorpus extending towards the uterine fundus with >50% myometrial invasion (Fig. 3). The most inferior portion of the mass was 4 cm away from the internal cervical os. The uterine cavity measured 10 cm, 4 cm of which was the endocervical canal. The anterior and posterior myometrium both measured 1 cm. The right parametria measured 5.0 x 5.0 x 0.5 cm, while the left measured 5.0 x 5.0 x 0.5 cm; both are grossly free of tumor. The right ovary and right fallopian tube were both grossly free of tumor measuring 3.0 x 1.0 x 0.5 cm and 7.0 x 0.5 cm, respectively. Likewise the left ovary and fallopian tube were both grossly normal measuring 3.0 x 1.0 x 1.0 cm and 8.0 x 0.5 cm, respectively (Fig. 4). The harvested bilateral pelvic and paraaortic lymph nodes were not suspicious for malignancy. No ascites was noted. In addition, the liver, subdiaphragmatic surfaces, gallbladder stomach, omentum, spleen, kidneys, appendix and bowels were all smooth and grossly normal. There were no palpable pelvic nor paraaortic lymph nodes. The vesicovaginal, paravesical, rectovaginal, pararectal spaces were free of tumor. There were no peri- and intraoperative complications. The patient was able to tolerate the procedure and discharged improved.

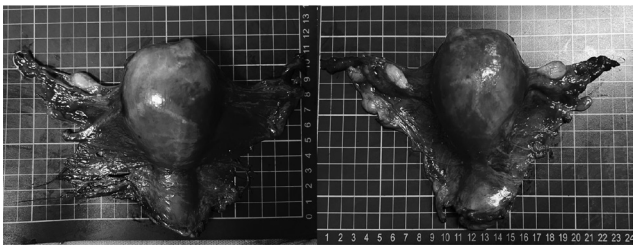

Figure 1. Gross pathology of the uterus: smooth, tan serosal surface with regular contour, measuring 12.0 x 8.0 x 5.0 cm.

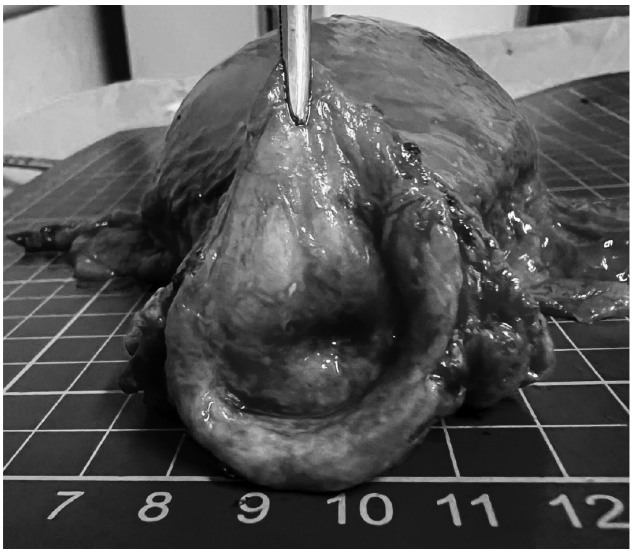

Figure 2. Gross pathology, cervix: smooth, measuring 4.0 x 4.0 x 3.0 cm. A posterior cervical nodularity measuring 1x 0.5x 0.5 cm was noted

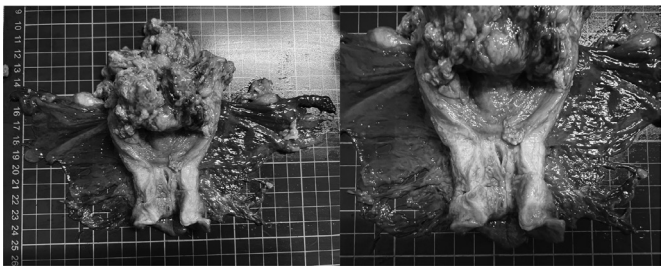

Figure 3. Cut section of the uterus (left) and endocervix (right). A 7.0 x 6.0 x 3.5 cm friable necrotic mass posteriorly attached to the posterior midcorpus extending towards the uterine fundus is noted

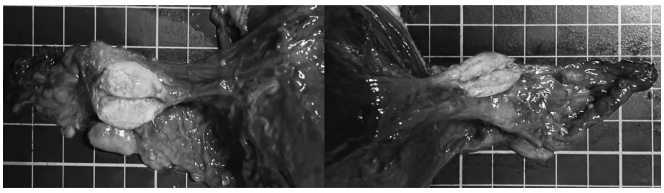

Figure 3. Left (left photograph) and right (right photograph) adnexae. Grossly normal bilateral ovaries and fallopian tubes

The final histopathologic findings revealed endometrial endometrioid carcinoma, FIGO grade 3, 7.5 centimeters in greatest tumor dimension; tumor invades more than fifty percent of the myometrium (0.6 centimeter of 1.1 centimeters myometrial thickness) with lymphovascular space invasion. The cervix was positive for residual squamous cell carcinoma, NOS, well-differentiated, 0.1 centimeter in greatest tumor dimension, left inferior (posterior) quadrant, cervix, with tumor invasion of the superficial one-third of cervical stroma (not more than 0.3 centimeter). Lymphovascular invasion was not identified. A diagnosis of double primary malignancy was then made: Endometrial, endometrioid carcinoma, FIGO grade 3, stage IB with lymphovascular space invasion and Squamous cell carcinoma, HPV-associated, cervix, stage IB1. Further test utilizing immunohistochemistry was done revealing abnormal expression (mutated P53) with intact nuclear expression of MLH1, MSH2, MSH6, PMS2, indicative of endometrial cancer with high-intermediate risk.

The subsequent plan of management would involve systemic chemotherapy with six cycles of Carboplatin (AUC 5-6) and Paclitaxel (175 mg/m2) followed by pelvic external beam radiotherapy. Surveillance imaging utilizing CT-scan is indicated after completion of adjuvant treatment. Regular follow-up is warranted every three months for the first two years, then biannually thereafter until the 5th year of diagnosis then annually thereafter.

CASE DISCUSSION

Distinguishing between endometrial and endocervical carcinomas can be challenging due to multiple factors such as shared cellular differentiation, similarity in growth patterns, involvement of both segments in biopsy specimens, absence

of precursor lesions, and the fact that the dominant tumor component may not necessarily indicate the primary site. Distinction between the two is crucial as it directly impacts the overall management and prognosis of patients. The integration of clinical, radiographic and pathologic features is essential to achieve an accurate diagnosis. Consideration should be given to the use of immunohistochemistry and molecular analysis which can add valuable information. Usually, synchronous tumors have lower grade, better prognosis, and survival rate when compared to a metastatic tumor.

A retrospective study was done in 3,863 patients with female genital malignancies, only 0.7% were identified and managed a s case of synchronous primaries. Multiple primary malignant tumors is diagnosed if there one or more tumors diagnosed as a cancer, if there are different histopathologic result or origins, metastasis or recurrence are already ruled out.

The prevalence of multiple primary gynecologic cancers is 1.9 to 4.3%. Of these, there were only 2 recorded cases of cervical- endometrial double primary cancers.

The recurrence rate of double primary cancers is 76.9 % and mortality rate of 8.5%.

The dilemma of diagnostic imaging is still yet to be resolved due to scarcity of data and case studies.

In cases of pa/ents diagnosed with single ovarian cancers that are usually asymptoma/c un/l it reached an advanced stage, double primary cases of endometrial and cervical cancers usually produce earlier signs and symptoms such as vaginal bleeding. Hence, leading to an earlier detec/on and diagnosis. The diagnosis of synchronous cancers is usually diagnosed and confirmed once with histopathologic results. ■

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A Case of Partial Mole Following a Gestational Trophoblastic Neoplasia from a Complete Mole: Traversing the Spectrum of Disease

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) occurs in 1 - 3 per 1000 pregnancy but is recorded to be higher in the Philippines at 7 in 1000. Eighty percent of which are complete hydatidiform moles and the remaining 20 percent occur to be partial moles. Out of the 80, 15 - 20% further develop into post molar neoplasia but the incidence of patients having another molar pregnancy from a GTN is not yet well recorded. Presented is a case of a 27- year - old Gravida 3 Para 1 (1-0-1-1) who had recurrent molar pregnancy after a gestational trophoblastic neoplasia with a different histopathologic type from her index molar pregnancy.

Treatment plans, possible reproductive outcomes, monitoring and future operative choices are important in this cases especially if the patient is still in the reproductive years and desirous of a normal viable pregnancy despite the strong possibility of a recurrent molar pregnancy.

Keywords: *Gestational trophoblastic neoplasia, Recurrent molar pregnancy, Reproductive outcomes after GTN*

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) comprises a spectrum of conditions arising from neoplastic proliferation of placental trophoblastic cells[1,2] that has aggressive and potential tissue invasion and metastasis. Its rarity occurs only in 1 : 40, 000 gestations worldwide[3]. One molar pregnancy has the risk of another hydatidiform mole in the subsequent pregnancy with only 1 % where 0.91% follows a complete molar pregnancy and 0.28 % from a partial hydatidiform mole[4]. Eight percent of the second hydatidiform mole are of the same histopathological type regardless of its outcome[5].

Surveillance by serial ß - HCG allows identification of patients who develop late GTN. Approximately 15 - 20% of patients develop postmolar GTN after evacuation of a complete mole and 1 - 5% of patients develop postmolar GTN after a partial mole[1]. Questions arise if these rates will still hold true for the subsequent pregnancies after post-molar GTN. Hammond et al. stated that after effective treatment for malignant GTN, molar pregnancies can still occur in about 1 - 2% of subsequent pregnancies[6]. However treatment plans, possible reproductive outcomes, monitoring and future operative choices are important especially if a patient is still in the reproductive years and desirous of a normal viable pregnancy despite the strong possibility of recurrent molar pregnancy.

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CLINICAL CASE PROTOCOL

This as a case of J.A. a 27-year-old Gravida 3 Para 1 (1-0-1-1) at 12 weeks and 1 day age of gestation. She is a non-smoker, non-alcoholic beverage drinker, single and unemployed. Patient's menstrual history is non-contributory. Coitus was at 18 years old with 1 monogamous partner and has no contraceptive use. Patient had her first pregnancy at the age of 19 to a live, term, baby boy via normal spontaneous delivery with no associated fetomaternal complications.

Two years prior to consult, on her second pregnancy, patient underwent suction followed by endometrial curettage for a complete molar pregnancy (Figure 2). She was given 5-day Methotrexate chemoprophylaxis and maintained on ethinyl estradiol 30 µg – levonorgestrel 150 µg combined contraceptive pill. Two months post curettage, increasing values of ß - HCG (Figure 3 and Table 1) were noted. She was diagnosed with post-molar GTN and chemotherapy was started with 2 consolidation therapies. She had no evidence of disease for 1 year. Patient was asymptomatic with resumption of regular menses.

4 months prior to consult, she had vaginal bleeding, followed by passage of vesicular tissues, with associated nausea and vomiting. She had her serum ß - HCG tested and baseline revealed 530,560 mIU / mL. Upon consult, abdomen was globular and non-tender. Speculum revealed a smooth cervix with vesicular materials per os. Vaginal walls were smooth. Upon internal examination, cervix was 2 x 2 cm, smooth, soft and dilated to ~1 cm. Corpus was enlarged to 18-20 weeks size hence adnexa cannot be assessed. Bilateral parametria was free.

Transvaginal ultrasound revealed an enlarged anteverted uterus ~11.0 x 10.6 x 9.9 cm with ill- defined endometrium and a heterogenous mass measuring 9.4 x 9.5 x 7.8 cm with bilateral theca lutein cysts (Figure 4) compatible with a molar pregnancy.

Patient underwent suction curettage followed by endometrial curettage. A total of 2000 cc of vesicular materials

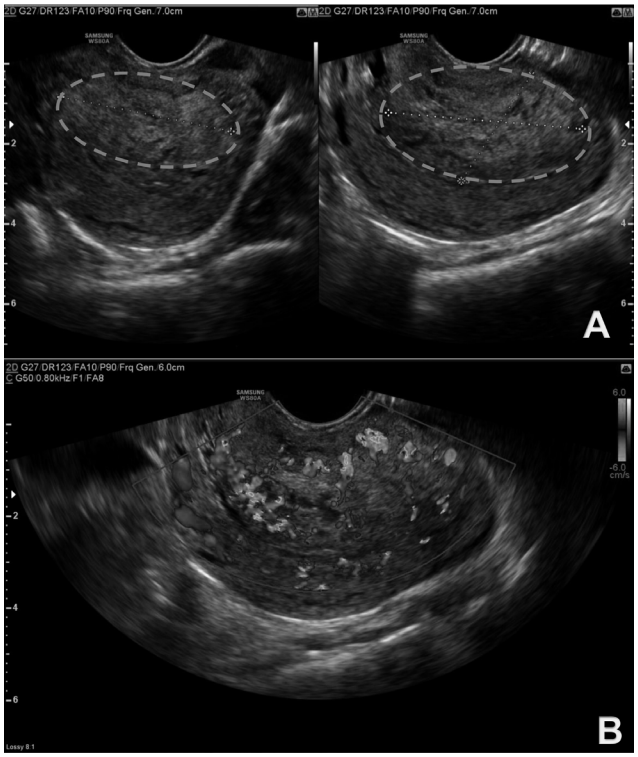

Figure 1. Transvaginal ultrasound of first molar pregnancy (2019)
A. Endometrial mass B. Color Score via doppler

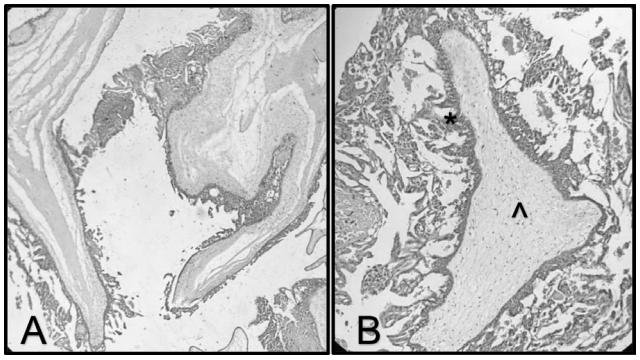

Figure 2. Complete Hydatidiform Mole: 2A showed the diffused, villous enlargement with marked hydropic changes of the chorionic villi. 2B showed the circumferential proliferation of the trophoblastic cells ^ core, *trophoblasts

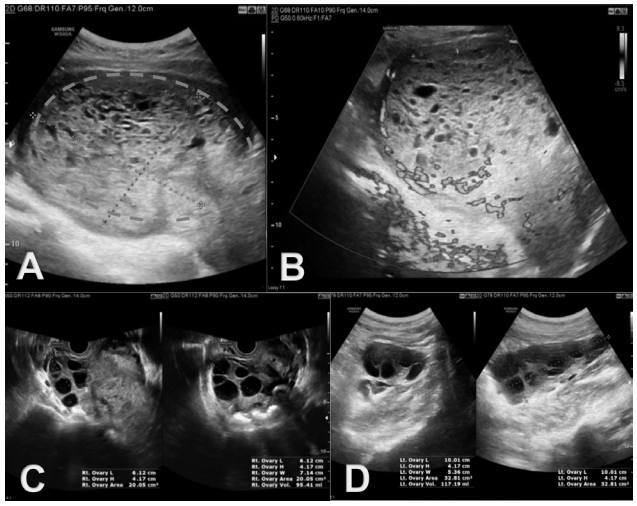

Figure 4. Transvaginal ultrasound of second molar pregnancy (2022)
A. Endometrial mass B. Color Score via doppler
C-D. Bilateral theca lutein cysts

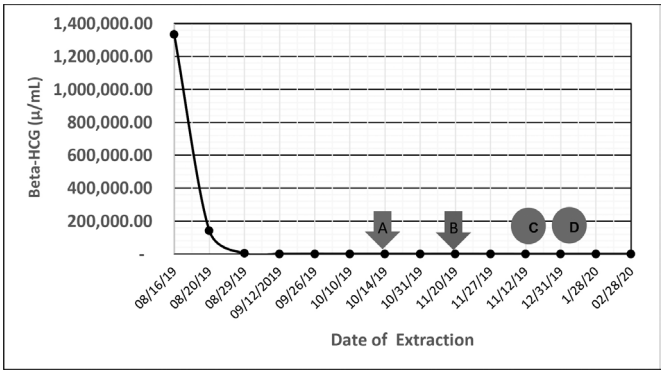

Figure 3. ß - HCG Trend (2019) 3A- First rise of B-HCG, 3B – 2nd rise of BHCG, 3C and 3D- 1st and 2nd consolidation courses

Table 1. ß - HCG Trend 2019

2019 ß - HCG Trend	Date	ß - HCG (µ/mL)
1	08/16/19	1,334,586.00
2	08/20/19	141,414.00
3	08/29/19	4,192.00
4	09/12/19	743.49
5	09/26/19	877.91
6	10/10/19	679.79
7	10/14/19	705.20*
8	10/31/19	457.42
9	11/20/19	606.11**
10	11/27/19	329.42
11	11/12/19	3.55
12	12/31/19	0.40
13	01/28/20	0.15
14	02/28/20	0.51

admixed with blood was evacuated with an estimated blood loss of 2100 cc. She was discharged stable and given 5-day Methotrexate chemoprophylaxis as out-patient basis. Figure 5 showed a partial hydatidiform mole on histopathology. At present, ß - HCG is serially monitored (Figure 6) and maintained at normal values.

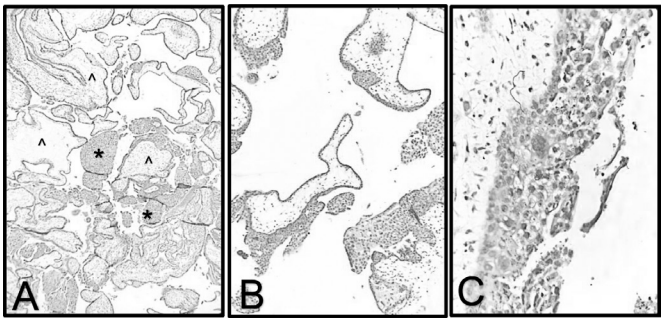

Figure 5. Partial Hydatidiform Mole
5A- Low magnification showing 2 populations of villi: Small fibrotic villi (*) and edematous hydropic villi (^), 5B- Intermediate magnification, 5C- High power magnification showing the focal hydropic swelling of the villi

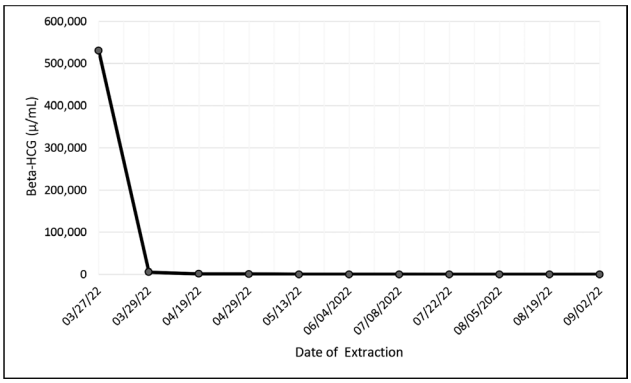

Figure 6. ß - HCG Trend (2022)

Table 2. ß - HCG Trend 2022

2019 ß - HCG Trend	Date	ß - HCG (µ/mL)
1	03/27/22	530,560.00
2	03/29/22	5,527.90
3	04/19/22	1,170.40
4	04/29/22	880.20
5	05/13/22	14.65
6	06/04/22	20.09
7	07/08/22	6.16
8	07/22/22	0.04
9	08/05/22	0.33
10	08/19/22	0.15
11	09/02/22	0.15

CASE DISCUSSION

Incidence and Origin

Hydatidiform mole (HM) is the most common form of gestational trophoblastic disease at 1.3 cases per 1,000 pregnancies and its rarity is one – tenth fold at 0.13 cases per 1,000 pregnancies. Sebire et. al. stated that complete and partial moles are associated with similar risk of recurrence and are likely to be of the same histology as the index pregnancy[5]. However another study[7] showed that different histologic type may be present in 25% of cases. Several researches showed that recurrent molar pregnancies may be familial despite a negative clinical history, yet our patient had a personal history of recurrent mole but has no family history of recurrent hydatidiform mole. Smagt et al, explained they may have androgenetic complete molar pregnancy origin[8] and Al Hussaini supported this due to the absence of Barr body in the molar tissues of a patient with 6 consecutive hydatidiform moles[9]. Ideally, our patient should have undergone molecular genetic testing (karyotyping) to specifically determine the type of histology she possess. The p57 immunochemistry, NLRP7 and KHDC3L should be done but, unfortunately these are unavailable in the country and requires a huge amount of monetary aid[10].

Resumption of menses

Resumption of normal menses happens in 95% of patients within 1 to 3 months[11], same in our patient who resumed her menses 3 months post curettage even when treated with chemotherapy[12]. Although menopause occurs approximately 3 years earlier, the difference compared with those who have not is statistically, but not clinically significant[13]. This high percentage of normal menstrual resumption lie on the following factors such as 1) young age, 2) type of chemotherapy drug used, 3) WHO risk score 4) use of assisted reproductive techniques and 5) strong desire of pregnancy. Our patient is young and is less than 30 years-old at diagnosis of GTN, hence her fertility resumed same as the general population.

The type of chemotherapy regimen used was another significant factor because methotrexate as single agent chemotherapy, do not have much detrimental effects on our patient's ovaries compared to EMACO. EMACO regimen contain alkylating agents that may hinder ovarian dysfunction[14]. WHO risk score of high versus low was also associated with higher rate of temporary amenorrhea - 67 % for high risk compared to 33 % of those with low risk. Our patient is classified in the low risk and found to have significantly shorter period of amenorrhea of 1.3 months compared with 6.8 months for those with high risk.[15]

Reproductive outcome

Five studies[11,16-19] including 2,168 pregnancies showed the same chances of having normal pregnancies whether after GTN or GTD regardless of histopathology or gestational weeks achieved with 75-86% and 77-84% respectively. Also, almost similar chances of becoming recurrent moles from GTN and GTD with 1.3-7.6% and 1.3-2.8% respectively. The optimal interval for another pregnancy has not been well established, though a standard recommendation was 12 months after disease remission with normal ß - HCG values[20].

Contraception use

Our index patient used artificial contraception and its use was advised for at least one year not only due to the high recurrence rate in the first year after treatment, but also because of some studied fetal abnormality and gene mutation-related long-term diseases on reproductive cells.[12]

CONCLUSION

Pre-treatment reproductive function, patient's desire, and counselling for future child bearing should be of top priority in dealing with couples with recurrent molar pregnancies especially after GTN. Effective contraception should be encouraged for the first 12 months. Though it contradicts the idea of possible pregnancy, it also helps decrease the possibility of fetal abnormalities post chemotherapy. Surgical options should also be individualized.

Our index patient is still young and desirous of pregnancy but if available and with access, karyotyping, albeit its expense, must be done to triage patients who are and who are not at risk. It must also be emphasized that reproductive outcomes after chemoprophylaxis of gestational trophoblastic neoplasia are same with the general population regardless of histopathologic type but with higher propensity of post molar GTN after a partial mole. Though there are still proportion of population developing normal viable pregnancies, it must be well discussed that she may still have another molar pregnancy and that a recurrence of post molar GTN cannot be preventable. ■

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Its HAIRstory: A Rare Case of Ovarian Setroid Cell Tumor (SCT) in a Young Filipino Female: A Case report

Innah Marriah V. Tolentino, MD[1] and Valerie P. Tiempo-Gunito, MD[1], MSc, FPOGS, FPSMFM

ABSTRACT

Excessive male-pattern hair growth or hirsutism is devastating for an adolescent female. It has varied causes both benign and malignant conditions with different prognosis and treatment, hence, warranting thorough work-up for hirsutism.

Androgen-secreting tumors, such as ovarian steroid cell tumors (SCT), represent a rare yet serious cause of hirsutism. It is a rare type of neoplasm arising from the sex cord, ovarian stroma or both. Ovarian steroid cell tumor (SCT) arising purely from ovarian stroma, is even one of its rarest subtypes accounting for only 0.1% of all ovarian neoplasms[1].

We present the case of a 17-year-old nulligravid presenting with hirsutism and was later diagnosed with an androgen-secreting ovarian tumor. She underwent oophorectomy with frozen section followed by complete surgical staging for a suspicion of malignancy. The final histopathological diagnosis was Ovarian Stroma Cell Tumor Stage 1A. The paper will discuss an approach on hirsutism and the management of SCTs..

Keywords: *Androgen-secreting ovarian tumor, Hirsutism, Sex cord stromal tumor, Steroid cell tumor, Unilateral salpingooophorectomy*

INTRODUCTION

Hirsutism, defined as appearance of dark, coarse hair or terminal hair in the upper lip, chin, chest, abdomen and back of females, where typically fine hair grow or no hair should grow at all[3]. It is caused by excess production of male hormones, particularly androgen, typically produced in the ovaries and adrenal cortex. Multiple causes of hirsutism include familial, idiopathic, excess androgen secretion by either the ovary (Polycystic Ovarian Syndrome (PCOS) or tumors) or adrenal glands, (congenital adrenal hyperplasia, tumor), or exogenous androgen intake. PCOS remains the most common cause of hirsutism, in a study by Sirmans, et. al, 80% of women with symptoms of hyperandrogenism have PCOS, of which 70% would present with hirsutism[4].

Hirsutism is the response of human hair follicle to increased circulating serum androgens and various local growth factors or increased conversion of testosterone to dihydrotestosterone (DHT)[3]. Androgen causes increase hair follicle size and diameter, and reduced duration in the anagen phase. As a result, there is increased growth of terminal hair in androgen-sensitive sites (upper lip, chin, upper back, abdomen and buttocks) while causing hair loss in the scalp due to shorter growth phase.

Hirsutism is a common symptom of many diseases, both benign and malignant. Polycystic Ovarian Syndrome (PCOS), a benign condition is still the most common cause of hirsutism[5]. Other causes include: non-classic congenital adrenal hyperplasia, severe hyperandrogenemia, androgen secreting tumors, ovarian hyperthecosis and idiopathic hirsutism[12]. In working up the cause of hirsutism, thorough history and physical examination is needed to exclude exogenous intake of steroids or medications that alter hormonal balance. Diagnostics differentiate conditions presenting with elevated androgen levels. Cushing syndrome, would present with elevated cortisol levels, in the background of chronic steroid use. PCOS presents with signs and symptoms of hyperandrogenism, oligo- or anovulation and polycystic ovaries on transvaginal ultrasound.

Androgen-secreting tumors, specifically produces increased levels of testosterone causing virilizing symptoms, which in females may manifest as hirsutism, voice deepening, acne and ambiguous genitalia. High blood testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels support the diagnosis[6]. Imaging studies like Abdominal ultrasound, Computed Tomography (CT) Scan, Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) Scan may help in tumor visualization.

These tumors are more common in the older population and usually progress rapidly. It only represents 5% of all ovarian tumors, and may be further differentiated histologically to Sertoli-Leydig cell tumors, Granulosa-theca cell tumor and Hilus cell tumors[1]. Diagnosis are clinically based supported with direct visualization of an ovarian mass via transvaginal or transrectal ultrasound. Its rarity may cause diagnostic dilemma causing delay in management. The approach requires a multidisciplinary team, which includes specialists from the disciplines of obstetrics and gynecology, anesthesiology, general pediatrics, pediatric endocrinology, adolescent medicine, dermatology, nutrition and reproductive endocrinology and infertility.

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Financial Disclosure:
The authors did not report any potential conflicts of interest.

CLINICAL CASE PROTOCOL

This is a case of a 17-year-old nulligravid complaining of hirsutism and amenorrhea. She has no known co-morbidities and no previous surgeries. Her family medical history was pertinent for hypertension and diabetes mellitus on both maternal and paternal side, no history of any malignancy. She is a Grade 11 student with no vices. She is born full term to a 30-year-old secundigravid via spontaneous vaginal delivery with no fetomaternal complications. At birth, she has normal appearance with no mention of ambiguous genitalia or dysmorphic features. She had no menarche and no coitarche.

Her history started 6 years prior when she noted hyperpigmentation starting at her nape area eventually appearing on her face and body with appearance of coarse hair on arms and legs, breast budding and pubic hair growth. Her hirsutism became more evident affecting her torso, back and extremities. There was noticeable thinning of hair on the crown, darkening of axilla, groin and nape with undocumented but significant weight gain. Because of worsening hirsutism and anxiety of parents over her condition and lack of menstruation, she was brought for consultation. Physical examination revealed: BMI of 37.3 kg/m2, thinning of hair in the vertex (Figure 1-A), breast mound (Tanner Stage 5) (Figure 1-B), facial hair on upper lip, chin (Figure 1-C), excessive hair growth on upper back (Figure 1-E), chest, abdomen and bilateral extremities, giving a Modified Ferriman-Gallwey score of 28, indicative of severe hirsutism. Noticeable were the hyperpigmentation and thicker skin on nape, axilla, groin area, and striae distensae on axilla and abdomen (Figure 1-D). On pelvic examination, she has coarse and sparse pubic hair (Tanner Stage 5) (Figure 1-F) with clitoromegaly measuring 2.0 x 3.0 cm. On digital rectal examination, she has good sphincter tone, intact rectal vault, however, there was difficulty in assessing cervix, uterus and adnexae due to obesity.

Pregnancy test was done to rule out the most common cause of amenorrhea. Initial considerations were primary amenorrhea from 1) Cushing syndrome, 2) Polycystic ovarian syndrome 3) HAIR-AN Syndrome 4) Late onset non-classical Congenital Adrenal Hyperplasia. Diagnostics showed high testosterone levels at 23.48 nmol/L, ACTH (adrenocorticotropic hormone) at 92.34 pg/mL (<40 pg/mL), 17-OHP (hydroxyprogesterone) at 4.06 ng/mL (<0.2 ng/mL) and elevated prolactin at 32.85 ng/mL (5.18-25 ng/mL). Her lipid profile were elevated indicating dyslipidemia. She had normal values for follicle stimulating hormone, thyroid stimulating hormone, 75g-OGTT and CA-125.

On transrectal ultrasound, a right adnexal mass was seen described as an irregular heterogenous solid mass measuring 5.5 x 4.5 x 4.5 cm (volume: 58.2 cc) with cystic areas (Figure 2-A). There is a rim of normal ovarian stroma measuring 2.3 x 2.3 x 0.9 cm at the inferior border of the mass. The impression was right adnexal mass consider ovarian new growth (consider functional or virilizing tumor), normal sized anteverted uterus, normal left ovary.

The consideration was a virilizing tumor (adrenal vs ovarian) versus nonclassical congenital adrenal hyperplasia. On abdominal computed tomography (CT) scan, a fairly-defined, predominantly hypodense, heterogeneously enhancing focus arising from right adnexal region measuring 5.5 x 4.9 x 5.5 cm likely ovarian in origin (Figure 2-B) with normal bilateral adrenal glands (Figure 2-C), which ruled out the possibility of a virilizing tumor arising from adrenal glands.

The case was co-managed by a multi-disciplinary team which consists of specialist and sub-specialists from different services. The plan was to send for intraoperative frozen section, given the patient is young and a consideration of malignancy would warrant complete surgical staging. The operation, its risks and benefits were explained particularly, the possibility of premature menopause, premature ovarian failure and possibility of advanced malignant stage and metastasis. They consented for completion surgery with staging.

She underwent exploratory laparotomy, unilateral, salpingo-oophorectomy, frozen section. The initial reading was stromal tumor component, admixed sex-cord component cannot be totally ruled out. The rest of the pelvic organs were inspected and no gross lesions appreciated. The surgical team proceeded with complete surgical staging including bilateral lymph node dissection, paraaortic lymph node sampling, random peritoneal biopsy and infracolic omentectomy. Intraoperatively, the right ovary was converted to a 6.0 x 5.0 x 3.0 cm solid lobulated mass (Figure 3-A) which on cut section contained a well-circumscribed, yellow, lobulated mass measuring 5.5 x 5.0 x 3.5 cm with no areas of hemorrhage or necrosis (Figure 3-B), surrounded by thin rim of ovarian parenchyma measuring 0.3 cm. The outer surface of the mass was smooth with no areas of rupture. Microscopically, there is a well-circumscribed mass with lobules separated by thin fibrous septa (Figure 3-C). The tumor cells were granular eosinophilic, vacuolated with lipid rich cytoplasm (Figure 3-D). The final histopathologic diagnosis was ovarian pure stromal tumor, primary consideration is a steroid cell tumor, not otherwise specified (NOS). The final surgical stage was IA, without extension or metastases to adjacent and distant organs. No adjuvant therapy was given.

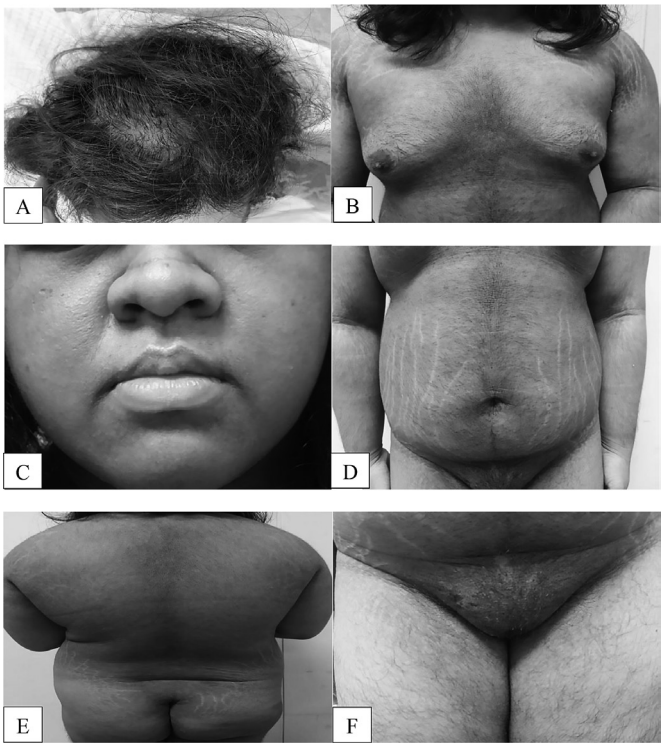

Figure 1. (A) Hair thinning on the vertex. (B) Breast (Tanner Stage 5). (C) Hair on upper lip and chin. (D) Hirsutism and striae distensae on the abdomen. (E) Hirsutism upper back. (F) Pubic hair (Tanner Stage 5)

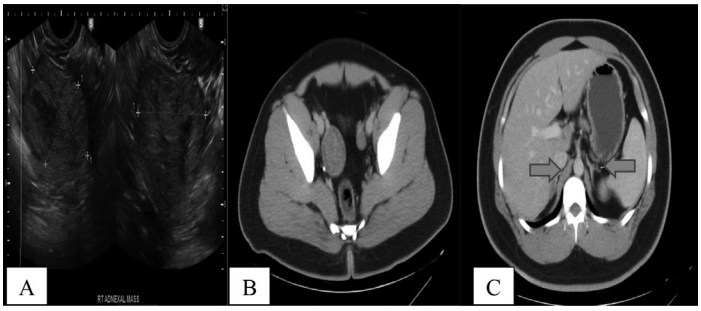

Figure 2. (A) Right adnexal mass on Transrectal ultrasound. (B) Abdominal mass likely ovarian in origin on CT Scan. (A) Normal bilateral adrenal glands on Abdominal CT Scan

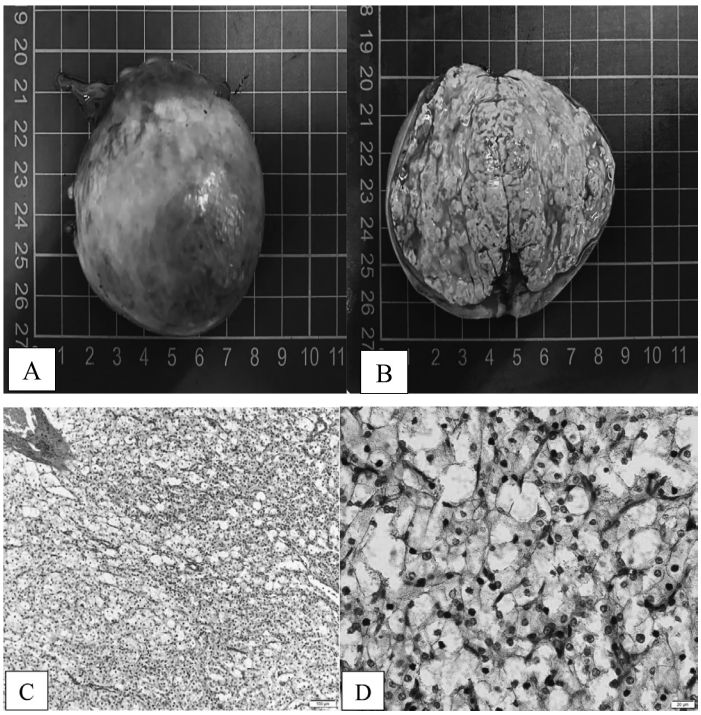

Figure 2. (A) Right ovary intact. (B) Right ovary on cut section. (C) Lobules separated by fibrous septa. (D) Tumor cells showing granular eosinophilic and vacuolated and lipid rich cytoplasm

The management warrants a holistic approach, addressing every concern of the patient, hence comprehensive skin care routine from the Dermatology service, and counselling from both Dietary service, Pediatrics and Adolescent medicine was given.

On follow up, the patient had noticeable changes: less hair on upper lip and chin (Figure 4-A), decreased hirsutism on abdomen and upper back (Figure 4-B and 4-C), chest and with lighter striae distensae on her bilateral shoulders and abdomen (Figure 4-B), her complexion became lighter (Figure 4-D). These improvements made the patient more confident and her parents less anxious.

DISCUSSION

Excessive male pattern hair growth, a physically altering symptom, is associated with serious psychological distress to adolescent females who have increased awareness of body image. To manage the problem, it is prudent to rule out the most common cause which is Polycystic Ovarian Syndrome (PCOS). The European Society for Human Reproduction and Embryology

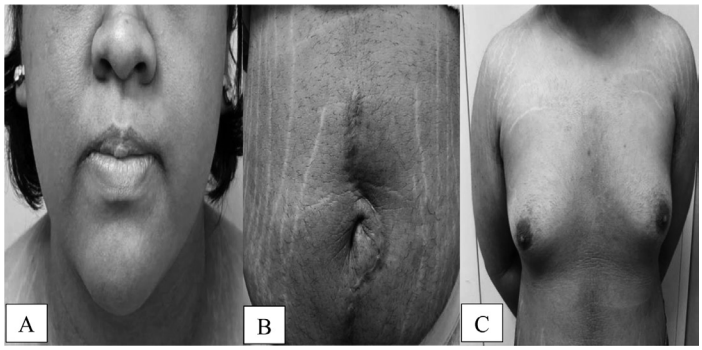

Figure 2. Post-operatively. (A) Less hair on upper chin and chin. (B) Less hirsutism on abdomen and (C) Less hirsutism on chest and lighter striae distensae on her shoulders

(ESHRE) listed the following as criteria for the diagnosis of PCOS: clinical or biochemical hyperandrogenism, oligo- or anovulation and polycystic ovarian morphology as seen on ultrasound[9]. The pathophysiology of PCOS is an intermarriage of genetic and environmental factors, associated with insulin resistance and hyperandrogenism. The current PCOS guidelines is based among adult population, hence the diagnosis of PCOS among adolescent age group remains controversial. Nonetheless, an increase in cases among adolescents is seen as a result of their immature and asynchronous hypothalamic-pituitary-ovarian axis[9].

Hirsutism can be a manifestation of both benign and malignant disease hence, emphasis is given to the prompt recognition and early work up of probable causes. PCOS, a common differential however, rare malignancies such as androgen secreting tumors also manifest as hirsutism at first. Missing the diagnosis of these rare tumors might be detrimental.

Thorough history and physical examination is done to exclude use of steroid or any medications that may cause increased levels of androgen manifesting as hirsutism or other virilizing symptoms. The index patient denied intake of any medications. In case of use, intake of medication is stopped and reassessment is done after six months. It is important to probe for other symptoms that are usually present in combination with hirsutism such as amenorrhea or menstrual pattern changes. In addition to hirsutism, the patient is amenorrheic. Multiple laboratory tests such as serum testosterone, serum 17-OHP, beta-HCG, prolactin, thyroid stimulating hormone, follicle stimulating hormone to evaluate oligomenorrhea and imaging modalities to visualize tumors help to clinch the diagnosis. The patient presented with elevated serum testosterone level, prompting additional imaging studies to visualize the ovaries and the adrenals for possible tumors. A right ovarian mass with normal left ovaries was seen on transrectal ultrasound with normal bilateral adrenal glands seen on abdominal CT scan thus, supporting the impression of an androgen producing ovarian tumor.

Androgen secreting tumors are extremely rare, comprising only 5% of all ovarian tumors. It is commonly seen in older population. It produces virilizing symptoms, although quite low has a malignant potential and may progress rapidly. Androgen secreting tumors may either be caused by an adrenal adenoma or primary ovarian tumor which is further differentiated histologically as Sertoli-Leydig cell tumors, Granulosa-theca cell tumor, Hilus cell tumors and Sex cord stromal tumors. Differentiating one from the other helps in the prognosis

and management of these tumors. Laboratory tests such as testosterone levels and dehydroepiandrosterone sulfate (DHEA-S) are good screening parameters for these tumors. Elevated testosterone and androstenedione levels with normal dehydroepiandrosterone sulfate (DHEA-S) levels will help rule out adrenal etiology of hyperandrogenism. A thorough pelvic exam coupled with imaging modalities help in the accurate diagnosis.

Many disease may manifest as hirsutism yet the management of one is entirely different from the other. The first line management in PCOS is lifestyle modification with emphasis to improve quality of life and weight reduction through well-balanced diet and moderate exercise[10]. In terms of pharmacotherapy, the first choice is combined oral contraceptives (COC) because it addresses most of its symptoms.

In comparison, the mainstay of treatment of ovarian tumors is never medical but rather surgical[2]. The rarity of these tumors, account for the limited documented and published cases hence, it continues to be a diagnostic and therapeutic dilemma. Unilateral oophorectomy is the surgery of choice particularly in cases where it is confined to only one ovary, however, studies have shown that the delay in diagnosing these tumors cause detecting them in an advanced stage, extending beyond the ovary hence, a more radical surgery is warranted. For patients who have completed childbearing, it is highly recommended they undergo total hysterectomy bilateral salpingoophorectomy with complete staging while those with malignant tumors diagnosed with advanced stage must undergo surgery plus adjuvant therapy in the form of Bleomycin, Etoposide and Cisplatin courses[2]. GnRH Agonist as an adjuvant therapy remains promising but studies supporting its efficacy is limited[2].

Appraising the diagnosis of an ovarian malignancy in a young patient is both a challenge and an opportunity. Good physician appraisal improves patient understanding of their condition, increasing their compliance to treatment. The challenge lies on breaking diagnosis and prognosis particularly to parents of these adolescents. As for the index case, the patient and her parents were appraised well on the risks and benefits of the plan. The patient underwent unilateral salpingo-oophorectomy with complete surgical staging which is the ideal treatment for the disease.

In terms of prognosis, these tumors rapidly progresses. The distress over the disease and its recurrence inconveniences both the patient and her family. Unlike other stromal tumors, recurrence after two decades have been reported on steroid cell tumor. The role of tumor markers in monitoring tumor recurrence still continues to be debatable. As for monitoring tumor recurrence, studies have identified the supposed role of testosterone levels in monitoring disease progression or recurrence. Close follow up with symptom monitoring is the practiced method in detecting possible tumor recurrence.

Ovarian tumors particularly its symptoms affects physical health, mental and social well-being of patient. She became less confident, more conscious about her physique, comparing herself to girls her age, which greatly affected how she carries herself. Her condition brought anxiety to her parents as they have poor understanding of her condition and they worry over their children's future fertility. The multidisciplinary team worked together in managing the case.

The problem is more than skin deep, it immensely affects an adolescent's mental and social well-being. Hirsutism is one of the many symptoms of PCOS, but it is also a feature of a life-threatening disease. Emphasis to the importance of a multidisciplinary approach to comprehensively diagnose and properly manage the case is warranted.

CONCLUSION

This is a rare case of Steroid Cell Tumor in a 17-year-old nulligravid presenting with hirsutism and amenorrhea. The successful outcome is attributed to timely diagnosis, good communication among subspecialities, and complete surgical management on the patient.

Hirsutism, a common symptom of benign and malignant disease, ultimately is a product of excess serum androgen. Polycystic Ovarian Syndrome (PCOS), a benign condition is still the most common etiology. Other causes include: non-classic congenital adrenal hyperplasia, severe hyperandrogenemia, androgen secreting tumors, ovarian hyperthecosis and idiopathic hirsutism. ■

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