ASSESMENT OF THE VALUE OF A MODIFIED RISK OF MALIGNANCY INDEX (RMI) IN PRE OPERATIVE DISCRIMINATION BETWEEN BENIGN AND MALIGNANT OVARIAN MASSES

Thesis

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First of all, I wish to express my sincere thanks to ALLAH for guidance and support in this work.

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INTRODUCTION

A pelvic mass is one of the most frequent indications for referral to specialist gynecologists. Often these pelvic masses are malignant and require surgical treatment ***(Yamamoto et al., 2009)***.

Up to 24% of ovarian tumors in premenopausal women are malignant and up to 60% are malignant in postmenopausal women ***(Yamamoto et al., 2009)***.

Despite advances in treatment, ovarian cancer has consistently had the highest case fatality ratio of all gynecologic malignancies, with a 5-year survival rate of 40-50% for all stages ***(Mazhar et al., 2008)***.

Approximately 70 % of all ovarian cancers are diagnosed in International Federation of Gynecology and Obstetrics (FIGO) stages III – IV, where the five year survival rate is 20 % compared to FIGO stage I, where the five year survival rate is 90 %. Diagnosis in late stages is one of the reasons for poor prognosis .One approach to improve survival is appropriate preoperative differentiation between ovarian cancer and benign pelvic masses in order to refer patients with cancer ovary to centers with gynecologic oncology specialists ***(Fanny et al., 2012)***.

Patients with malignant tumors should be referred to gynecologic oncologist as the quality of cytoreductive surgery and surgical staging / lymph node dissection are important prognostic factors in ovarian cancers ***(Sharon et al., 2009)***.

Before ultrasound was routinely available, the finding of a pelvic mass or a palpable ovary in a postmenopausal woman was considered to be an indication for surgery ***(RCOG, 2011)***.

However, the large numbers of ovarian cysts now being discovered by ultrasound and the low risk of malignancy of many of these cysts suggests that they need not all be managed surgically ***(RCOG, 2003)***.

The finding of an ovarian mass raises questions about the most appropriate management and the place where this management is to be carried out ***(RCOG, 2011)***.

The risk of malignancy index (RMI) is a simple scoring system based on menopausal status, ultrasound findings, and the serum CA125 level. This method has given significantly better results than the use of a single parameter ***(RCOG, 2011)***.

In ***Jacobs et al. 1990***originally developed the RMI, which they have termed: RMI I. Tingulstad et al. developed their version of the RMI in 1996 and it is known as RMI II.

In ***Tingulstad et al. 1999*** modified the RMI, which they have termed: RMI III. Yamamoto et al. modified the RMI, which they have termed: RMI IV

In the current study a modified RMI will be created by adding Doppler blood flow to the parameters of ultrasound criteria and this scoring system will be termed RMI V.

Doppler evaluation of adnexal masses was initially proposed as means of decreasing the false positive rates of sonography for ovarian carcinoma ***(Hill et al., 2003)***.

The role of color Doppler ultrasound in differentiating adnexal masses has been suggested in various published studies reporting diagnostic accuracies of 90% and higher ***(Mazhar et al., 2008)***.

Malignant tumors characteristically contain dilated saccular and randomly dispersed vessels ***(Hill, 2003)***.

92.59% of malignant tumors showed RI less than 0.6 in contrast to only 9.09 per cent of benign tumors ***(Taori et al., 2002)***.

AIM OF THE WORK

The purpose of this study is to asses the usefulness of a modified RMI in pre-operative discrimination between benign and malignant adnexal masses.

Research question:

Is RMI V a sensitive scoring system in diagnosis of ovarian cancer in women presenting with adnexal mass?

Research Hypothesis:

In the current study we hypothesize that assessment of blood flow of an ovarian mass by Doppler when added to calculation of RMI will increase sensitivity of pre-operative discrimination between benign and malignant adnexal masses.

Chapter 1

Ovarian Cancer: Incidence, Etiology, Screening, Genetic Testing, Prevention, Diagnosis, Referral, Treatment, Surveillance, Prognosis

Incidence:

Worldwide each year, 204,000 women are diagnosed, and 125,000 women die from this disease ***(Sankaranarayanan et al., 2009).*** Of these, epithelial ovarian carcinomas comprise 90 to 95 percent of all cases ***(Quirk et al., 2005).*** Overall, the average age at diagnosis is in the early 60s ***(Hoskins et al., 2011)***. Ovarian cancer remains the fifth leading cause of cancer-related death ***(Jemal et al., 2007)***.

Etiology*:*

Pathogenesis of ovarian tumors:

There are at least three distinct tumorigenic pathways to account for the heterogeneity of epithelial ovarian cancer. First, relatively few cases seem to arise from an accumulation of genetic alterations leading to malignant

transformation of benign cysts to invasive ovarian carcinoma ***(Makarla et al., 2005)***.

Typically, these invasive tumors are low grade and clinically indolent. In these tumors, K-*ras* oncogenic mutations occur early. The *ras* family of oncogenes includes K-*ras,* H-*ras,* and N-*ras*. Their protein products participate in cell cycle regulation and control of cell proliferation. As such, ras mutations have been implicated in carcinogenesis by their inhibition of cellular apoptosis and promotion of cellular proliferation ***(Mammas et al., 2005).*** In contrast, invasive cancers arising from LMP tumors have mutations in the *p53* tumor suppressor gene ***(Buller et al., 2001; Shcharge et al., 2000).***

Second, about 5 to 10 percent of epithelial ovarian carcinomas result from an inherited predisposition. Women born with a *BRCA* mutation only require one "hit" to the other normal copy (allele) to "knock out" the *BRCA* tumor suppressor gene product. As a result, *BRCA* -related cancers develop about 15 years before sporadic cases. Thereafter, *BRCA* -related ovarian and peritoneal cancers appear to have a unique molecular pathogenesis, requiring

p53 inactivation to progress ***(Buller et al., 2001; Shcharge et al., 2000).***

P53 is a tumor suppressor gene that has been mapped to chromosome 17. Its protein product prohibits cells from entering subsequent stages of cell division and thereby halts uncontrolled tumor cell replication. Mutations in *p53* are linked with a variety of cancers. In fact, loss of *BRCA* and *p53* function has been detected prior to invasion, further supporting their importance as an early triggering event ***(Werness et al., 2000).***

Third, the vast majority of carcinomas appear to originate de novo from ovarian surface epithelial cells that are sequestered in inclusion cysts within the ovarian stroma. Numerous inciting events and subsequent pathways have been proposed. For example, cyclic repair of the ovarian surface during long periods of repetitive ovulation requires abundant cellular proliferation. In these women, spontaneous *p53* mutations arising during the DNA synthesis that accompanies this proliferation appear to play a primary role in carcinogenesis ***(Schildkrau et al., 1997).***

Certainly, several developmental pathways are possible, stemming from early inactivation of innumerable genes ***(Schildkrau et al., 1997).***

Screening:

If ovarian cancer is detected in the earliest stage, when it localized to the ovary, the five-year survival rate is 92**%** ***(Aschengrau et al., 2008).*** However, only 19% of ovarian cancers are localized when first detected ***(Badgewell et al., 2007)***. Most women are diagnosed with either regional or distant disease and the five-year survival rate is 71% and 30%, respectively ***(Hoskins et al., 2011).***

The serum CA125 test is integral to management of epithelial ovarian cancer. CA125 is a glycoprotein that is not produced by normal ovarian epithelium but may be produced by both benign and malignant ovarian tumors. This tumor marker is synthesized within affected ovarian epithelial cells and often secreted into cysts ***(Verheijen et al., 1999).***

Serum CA125 is well established, being raised in over 80% of ovarian cancer cases and, if a cut-off of 30 u/ml is used, the test has a sensitivity of 81% and specificity of 75**%** ***(Jacobs et al., 1990).***

Current recommendations:

ACOG and the Society of Gynecologic Oncologists (SGO) recommend women get an annual gynecologic exam with an annual pelvic exam for routine preventive health care. It is important for patients to realize the importance of an annual well-woman visit. This visit is a yearly opportunity for examination and an appropriate time to discuss risk factors, prevention strategies and patient awareness regarding symptoms of ovarian cancer ***(Jekyll et al., 2007).***

Primary Prevention and Screening: the American Cancer Society (ACS), ACOG and the National Institutes of Health (NIH) Consensus panel all recommend against routine screening for ovarian cancer. The ACOG cited the low incidence of ovarian cancer, the low PPV of current screening methods, the high number of false positive tests generated, and the lack of evidence that screening reduces mortality from ovarian cancer as support for their recommendation ***(Menon et al., 2005).***

Genetic Testing:

The main purpose of genetic testing is to identify women with deleterious *BRCA1* and *BRCA2* mutations, to intervene with prophylactic surgery, and thereby to prevent ovarian cancer ***(Berry et al., 2009).***

Three distinct results are possible with this testing. The first is identifying a recognized BRCA mutation. A positive test suggests the presence of a deleterious mutation ***(Berry et al., 2009).***

The most common are the three "Jewish founder" mutations: 185delAG or 5382insC in *BRCA1* and 6174delT in *BRCA2*. Each of these frame shift mutations significantly alters the downstream amino acid sequence, resulting in alteration of the BRCA1 or BRCA2 tumor suppressor protein ***(Chen et al., 2006).*** As suggested, founder mutations are thought to have originated from within the Ashkenazi population thousands of years ago. As a result, Ashkenazi women with a single first-degree relative having either ovarian or premenopausal breast cancer also should be referred for genetic counseling ***(Claus et al., 2008).*** Although Jewish founder mutations are most common, any