INTRODUCTION

Breast cancer is the second leading cause of cancer mortality among women, after lung cancer. According to the American Cancer Society, approximately 1.3 million women worldwide are diagnosed with breast cancer annually, and >465,000 women die of this disease ***(Lee et al., 2018).***

Postoperative adjuvant systemic therapy prolongs survival in selected women with breast cancer and reduces the odds of death by 25% per year ***(Lee et al., 2018).***

Since the early 1980s, Tamoxifen has become the standard adjuvant therapy for patients with breast cancer, reducing the risk for a second case of contralateral primary breast cancer by 30% to 50% ***(Jindal et al., 2015).***

Tamoxifen is structurally related to diethylstilbestrol and clomiphene citrate. While acting as an estrogen antagonist in the breast, it has estrogen agonist activity in other tissues, increasing thickness of the vaginal epithelium, reducing serum cholesterol levels, and preserving bone density in postmenopausal women ***(Jindal et al., 2015).***

Laboratory studies have demonstrated estrogen-like effects on steroid hormone receptors in endometrium and growth-promoting effects on endometrial carcinoma cells. During the past decade, several reports have cited an increased

incidence of endometrial abnormality, ranging from polyps to cancer, in women receiving Tamoxifen ***(Jindal et al., 2015).***

Although Tamoxifen has been implicated in the development of endometrial cancer, many epidemiologic and genetic risk factors that predispose women to breast cancer can also increase the overall risk for developing gynecologic cancer ***(Jindal et al., 2015).***

Transvaginal ultrasound is a highly reliable method for detecting endometrial cancer in patients with postmenopausal bleeding. It may indicate the type of abnormality seen within the endometrium for example, endometrial hyperplasia, polyps, or carcinoma ***(Sahdev et al., 2007).***

Sampling of the endometrium must be performed if there is diffuse or focal thickening of the endometrium. Pathological confirmation of the histology is needed in all cases, as the ultrasound appearances overlap considerably ***(Sahdev et al., 2007).***

Transvaginal ultrasound also identify ovarian pathology that may occur with tamoxifen use, including polycystic ovaries in younger women and ovarian tumours secreting oestrogens, causing abnormal vaginal bleeding ***(Moradi et al., 2016).***

Thus, we undertook this study to evaluate the effect of Tamoxifen on endometrium in breast cancer patients and to know the correlation between ultrasonographic, and histopathological findings.

AIM OF THE WORK

The aim of the study is to detect endometrial changes in breast cancer patients under hormonal therapy, so we can diagnose endometrial changes in early stage, thus better prognosis, and to determine the role and efficacy of Trans vaginal ultrasound in the diagnosis of endometrial carcinoma as a leading cause of death.

Our aim also is to evaluate whether is there a correlation between period of tamoxifen therapy and presence of endometrial benign and malignant changes, and to correlate the findings seen in TVUS by the histopathology results of endometrial biopsies.

Anatomy of the Female Genital System

The female reproductive system consists of the lower genital tract vulva and vagina and the upper tract uterus and cervix with associated uterine Fallopian tubes and ovaries **(Figure 1)** ***(Standring, 2016).***

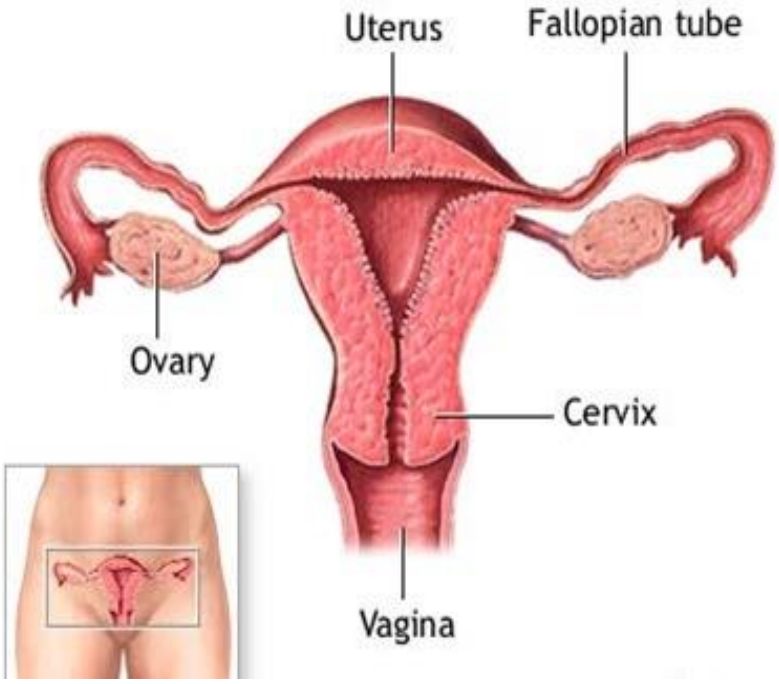

Figure (1): Anatomy of the female genital system ***(Standring, 2016).***

Uterus

The uterus is a pear-shaped organ made up of a fundus, body, isthmus and cervix which projects into the vagina. At each superolateral margin of the body is a uterine cornu, from which a fallopian tube emerges. Also in this area are the origins

of the round and uteroovarian ligaments. Between the points of fallopian tube insertion is the convex upper uterine segment termed the fundus ***(Cunningham et al., 2014).***

The uterus is divided structurally and functionally into t3wo main regions: the muscular body of the uterus (corpus uteri) forms the upper two-thirds, and the fibrous cervix (cervix uteri) forms the lower third ***(Standring, 2016).***

The cavity of the uterus is triangular in coronal section, and slit-like in sagittal section. It communicates with the cervical canal via the internal os. In the child, the cervix is twice the size of the uterine body, but at puberty the body enlarges to its adult proportions ***(Berek , 2012).***

A. Layers

The three layers of the uterus, from innermost to outermost, are as follows:

- ***Endometrium***

The uterine cavity is lined with endometrium, which is composed of an overlying epithelium, invaginating glands, and a supportive, vascular stroma, the endometrium varies greatly throughout the menstrual cycle and during pregnancy. This layer is divided into a functional layer, which is sloughed with menses, and a basal layer, which serves to regenerate the functional layer following each menses ***(Cunningham et al., 2014).***

- ***Myometrium***

Most of the uterus is composed of myometrium, which is smooth muscle bundles united by connective tissue containing many elastic fibers. Interlacing myometrial fibers surround myometrial vessels and contract to compress these. The innermost layer of myometrium is known as the junctional zone, which becomes thickened in adenomyosis ***(Cunningham et al., 2014).***

Serosa

The uterine body is covered by peritoneal serosa, which continues downwards posteriorly to cover the supravaginal cervix. The anteriorcervix and the lateral surfaces of the uterine body and cervix are not covered by peritoneum ***(Standring, 2016).***

B. Support

The uterus is primarily supported by the pelvic diaphragm, perineal body and the urogenital diaphragm. Secondarily, it is supported by ligaments and the peritoneum (broad ligament of uterus) ***(Cunningham et al., 2014)***.

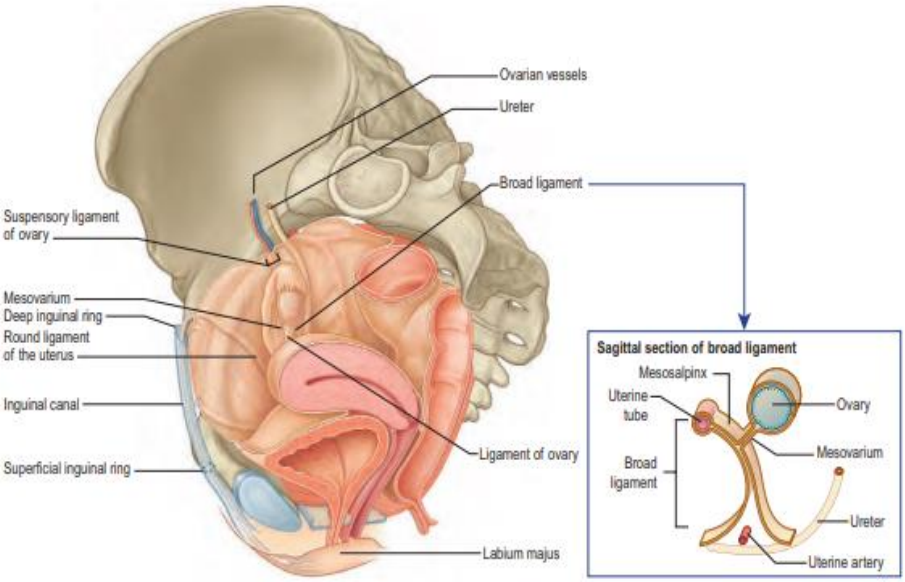

Figure (2): Broad ligament and its contents ***(Standring, 2016).***

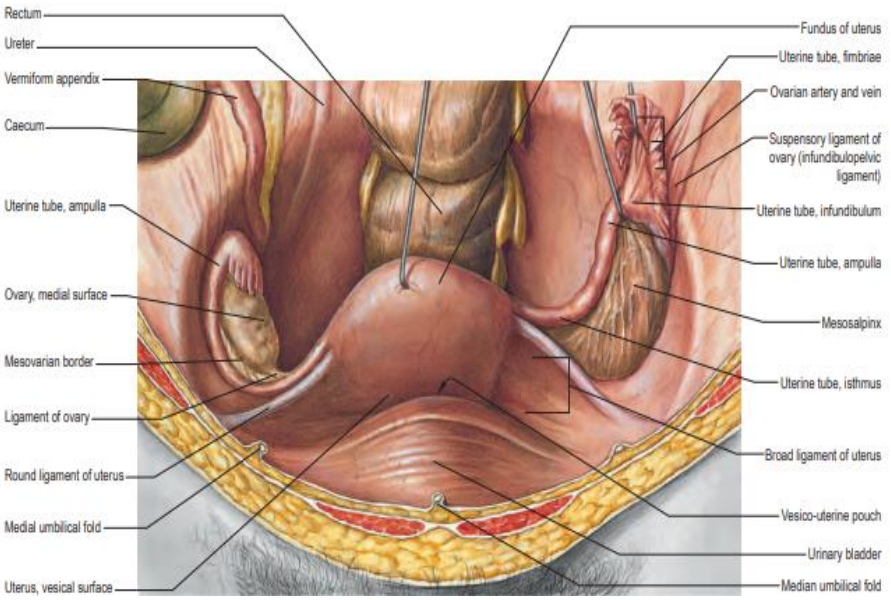

Figure (3): Ligaments of the uterus ***(Standring, 2016).***

- ***Major ligaments***

The uterus is held in position within the pelvis by condensations of endopelvic fascia, which are called ligaments, these ligaments include the pubocervical, transverse, cervical ligaments, cardinal ligaments, and the uterosacral ligaments. It is covered by a sheet-like fold of peritoneum***).*** **(Figure 2,3)**

C. Relations

Anteriorly the body of the uterus is related to the uterovesical pouch of peritoneum and lies either on the superior aspect of the bladder or on loops of small intestine. Posteriorly lies the recto-uterine pouch of Douglas, containing loops of intestine **(Figure 4)** ***(Berek, 2012).***

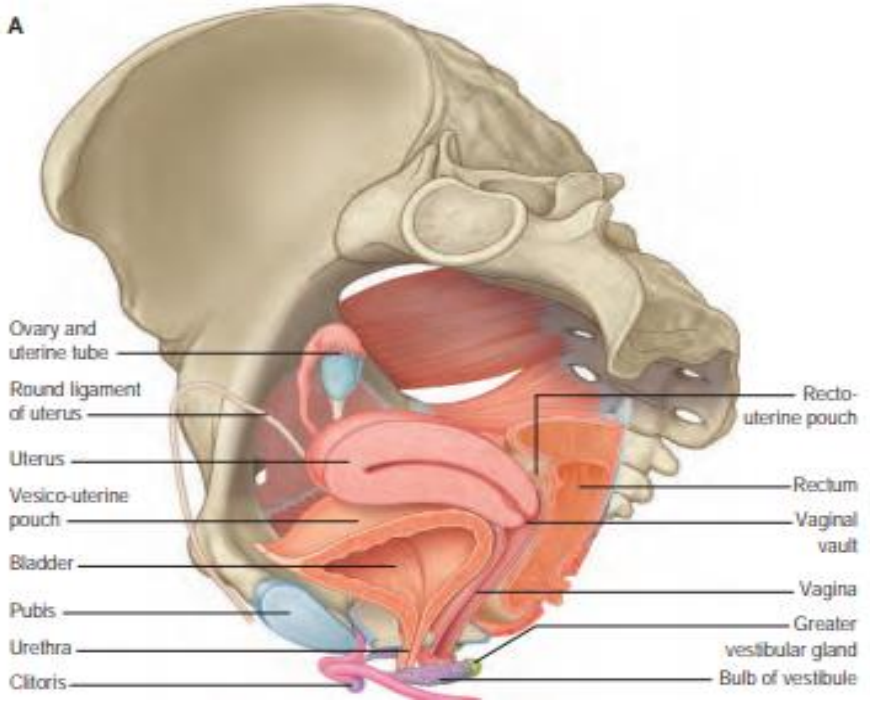

Figure (4): Anatomical relations of the uterus ***(Standring, 2016).***

D. Axes

In the adult nulliparous state, the cervix usually tilts forwards relative to the axis of the vagina (anteversion), and the body of the uterus tilts forwards relative to the cervix (anteflexion). In 10–15% of women, the whole uterus leans backwards at an angle to the vagina and is said to be retroverted. A uterus that angles backwards on the cervix is described as retroflexed **(Figure 5)** ***(Standring, 2016).***

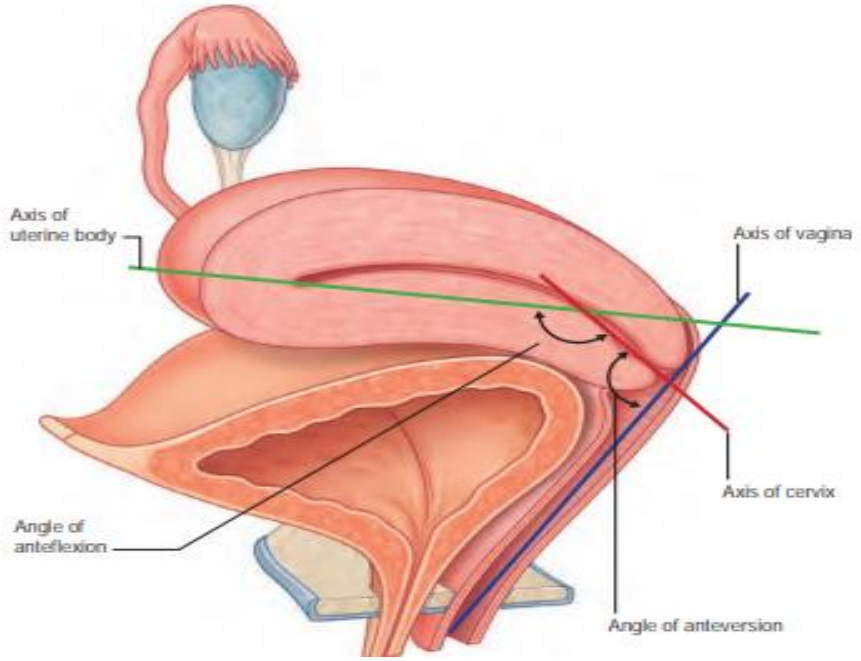

Figure (5): Angles of the uterus ***(Standring, 2016).***

E. Blood supply

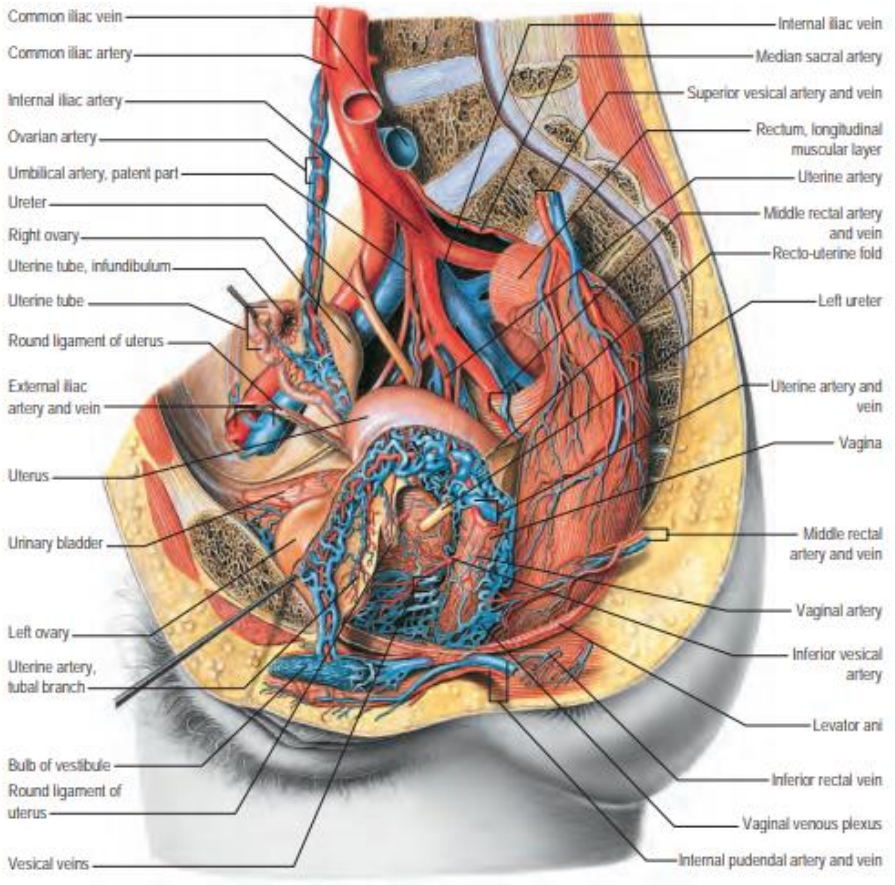

Figure (6): Blood supply to the uterus ***(Standring, 2016).***

The uterine artery, a main branch of the internal iliac artery enters the base of the broad ligament and makes its way medially to the side of the uterus. Once the uterine artery has reached the supravaginal portion of the cervix, it divides. The smaller cervicovaginal artery supplies blood to the lower cervix and upper vagina ***(Cunningham et al., 2014).***

The main branch turns abruptly upward and extends as a highly convoluted vessel that traverses along the lateral margin of the uterus. A branch of considerable size extends into the upper portion of the cervix, whereas numerous other branches penetrate the body of the uterus to form the arcuate arteries ***(Cunningham et al., 2014).***

Each uterine artery gives off numerous branches. These enter the uterine wall, divide and run circumferentially as groups of anterior and posterior arcuate arteries. They ramify and narrow as they approach the anterior and posterior midline so that no large vessels are present in these regions. Terminal branches in the uterine muscle are tortuous and are called helicine arterioles. They provide a series of dense capillary plexuses in the myometrium and endometrium. From the arcuate arteries, many helical arteriolar rami pass into the endometrium **(Figure 6)** ***(Standring, 2016).***

In addition to the uterine artery, the uterus receives blood supply from the ovarian artery. This artery is a direct branch of the aorta and enters the broad ligament through the infundibulopelvic ligament ***(Cunningham et al., 2014).***

Uterine veins accompany their respective arteries. As such, the arcuate veins unite to form the uterine vein, which empties into the internal iliac vein and then the common iliac vein. Some of the blood from the upper uterus, the ovary, and

the upper part of the broad ligament is collected by several veins ***(Cunningham et al., 2014).***

Within the broad ligament, these veins form the large pampiniform plexus that terminates in the ovarian vein. From here, the right ovarian vein empties into the vena cava, whereas the left ovarian vein empties into the left renal vein ***(Cunningham et al., 2014).***

F. Lymphatic drainage

The uterine fundus, together with the uterine tubes and ovaries, drains along the ovarian vessels to the para-aortic lymph nodes. In addition, some lymphatic channels to the inguinal lymph nodes. The body drains to nodes that lie alongside the external iliac vessels **(Figure 7)** ***(Berek , 2012).***

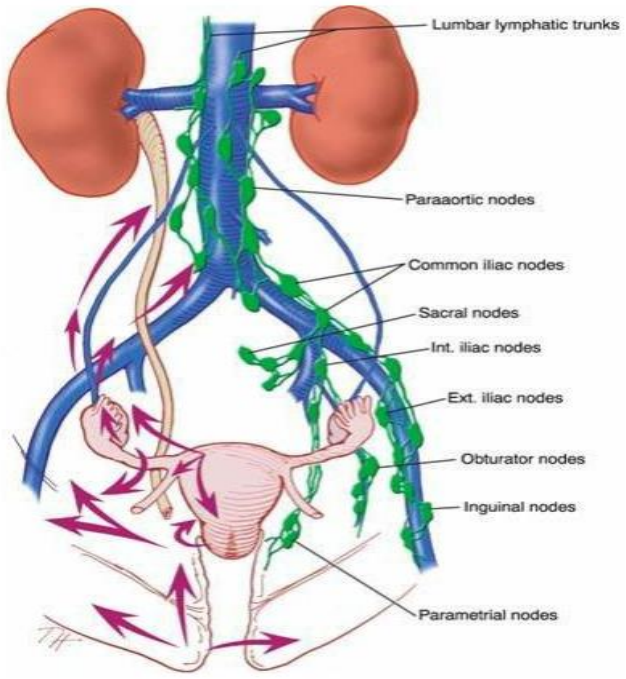

Figure (7): Lymphatic drainage ***(Berek , 2012).***

G. Nerve supply

Afferent nerves supplying uterus are T11 and T12. Sympathetic supply is from hypogastric plexus and ovarian plexus. Parasympathetic supply is from second, third and fourth sacral nerves. Some branches ascend with, or near, the uterine arteries in the broad ligament. They supply the uterine body and tubes, and connect with tubal nerves from the inferior hypogastric plexus and with the ovarian plexus. The uterine nerves terminate in the myometrium and endometrium, and usually accompany the vessels ***(Standring, 2016).***

H. Histology

The endometrium consists of a single layer of columnar epithelium resting on the stroma, a layer of connective tissue that varies in thickness according to hormonal influences. Simple tubular uterine glands reach from the endometrial surface through to the base of the stroma, which also carries a rich blood supply of spiral arteries ***(Scanlon et al., 2018).***

In a woman of reproductive age, two layers of endometrium can be distinguished. These two layers occur only in endometrium lining the cavity of the uterus, not in the lining of the uterine (Fallopian) tubes ***(Scanlon et al., 2018).***

The functional layer is adjacent to the uterine cavity. This layer is built up after the end of menstruation during the first part of the previous menstrual cycle.

Proliferation is induced by estrogen (follicular phase of menstrual cycle), and later changes in this layer are engendered by progesterone from the corpus luteum (luteal phase), It is adapted to provide an optimum environment for the implantation and growth of the embryo. This layer is completely shed during menstruation ***(Scanlon et al., 2018).***

In the absence of progesterone, the arteries supplying blood to the functional layer constrict, so that cells in that layer become ischaemic and die, leading to menstruation ***(Scanlon et al., 2018).***

Shedding of the functional endometrial lining is responsible for menstrual bleeding, with a cycle of approximately 28 days, +/-7 days of flow and +/-21 days of progression) throughout the fertile years of a female and for some time beyond ***(Cunningham et al., 2014).***

It is possible to identify the phase of the menstrual cycle by observing histological differences at each phase **(Table 1)**:

Phase	Days	Thickness	Epithelium
Menstrual phase	1–4	Thin	Absent
Proliferative phase	4–14	Intermediate	Columnar
Secretory phase	15–28	Thick	Columnar. Also visible are helicine branches of uterine artery

Table (1): Histological description of endometrium in phases of menstrual cycle ***(Scanlon et al., 2018)***

The basal layer is adjacent to the myometrium and below the functional layer, is not shed at any time during the menstrual cycle, and from it the functional layer develops ***(Scanlon et al., 2018).***

Cervix

The cervical portion of the uterus is fusiform and open at each end by small apertures the internal and external cervical os. Proximally, the upper boundary of the cervix is the internal os. It is covered by peritoneum on its posterior surface, the cardinal ligaments attach laterally, and it is separated from the