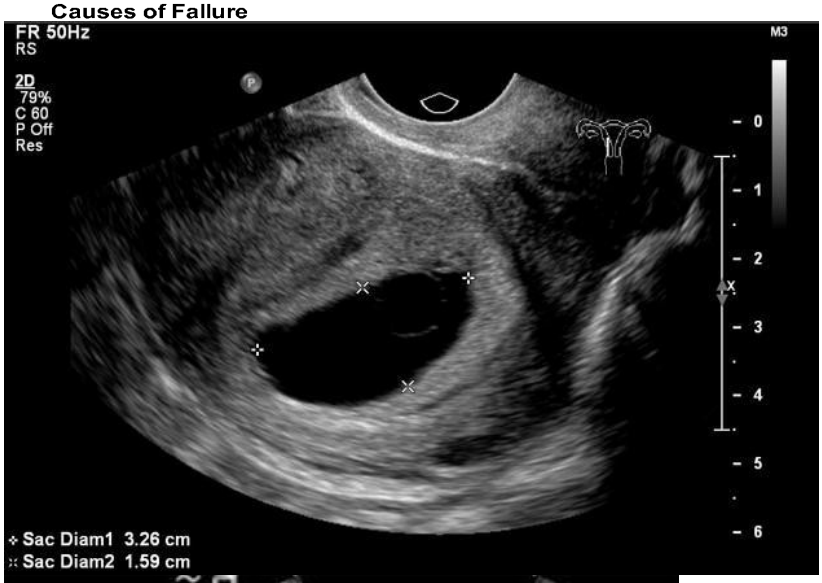
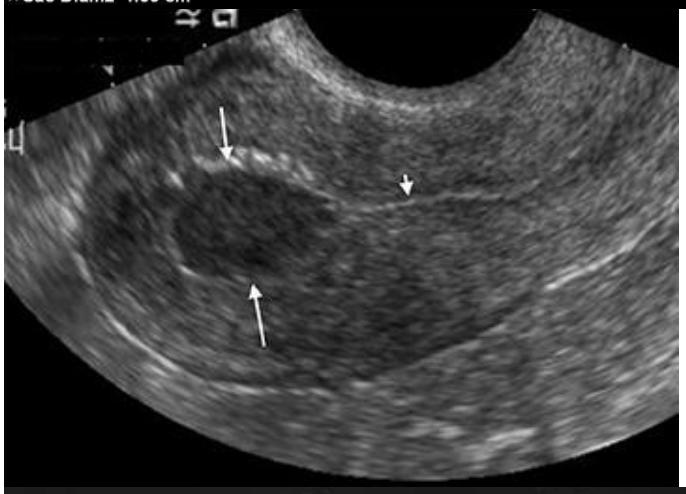
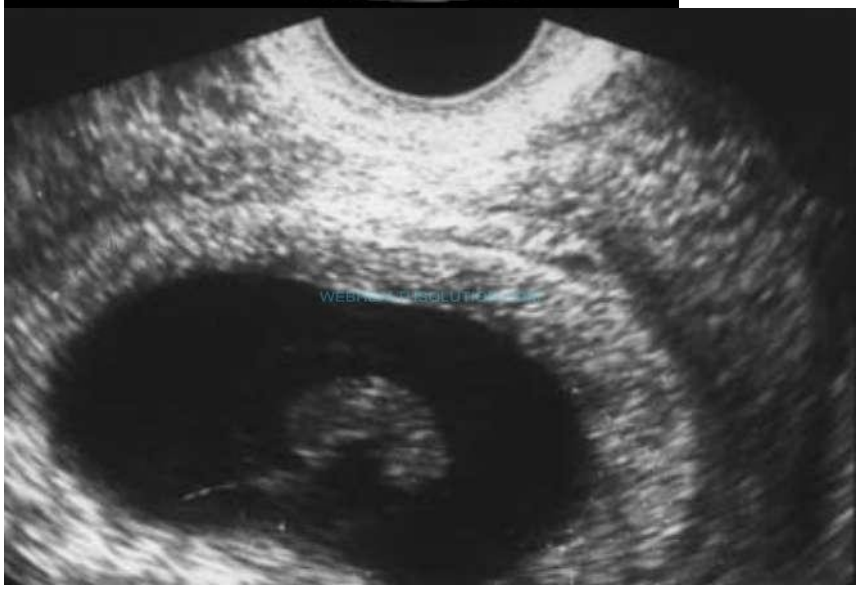
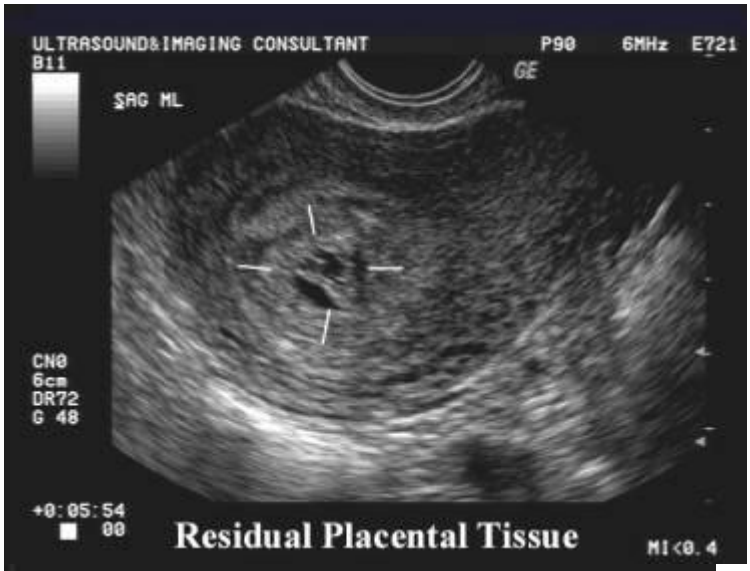
Causes of Fallure








ULTRASOUND&IMAGING CONSULTANT
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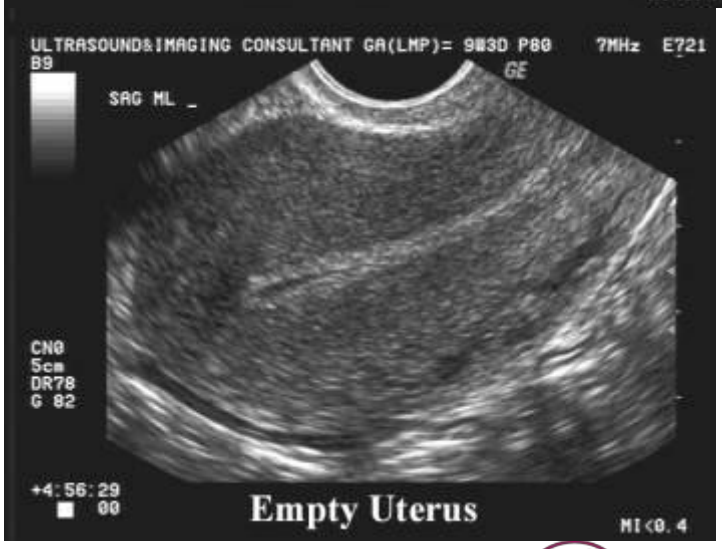
DR72
G 48
+0:05:54
00
Residual Placental Tissue
MI<0.4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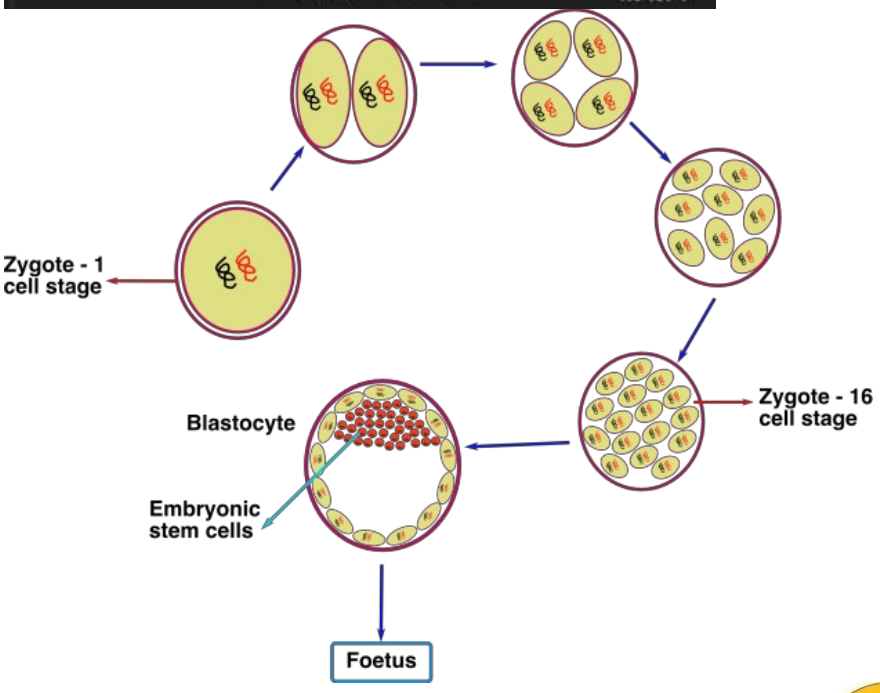
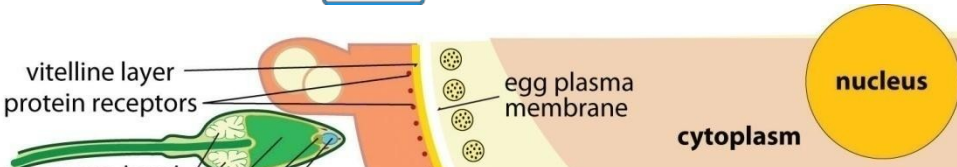

Zygote - 1 cell stage
Zygote - 16 cell stage
Blastocyte
Embryonic stem cells
Foetus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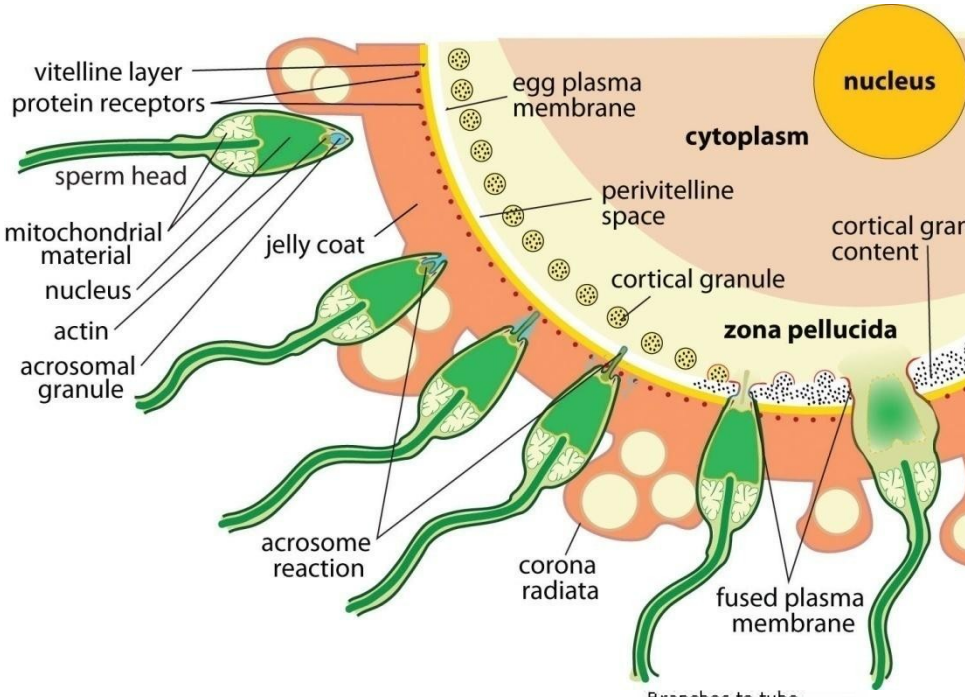
protein receptors
egg plasma membrane
nucleus
cytoplasm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mitochondrial material
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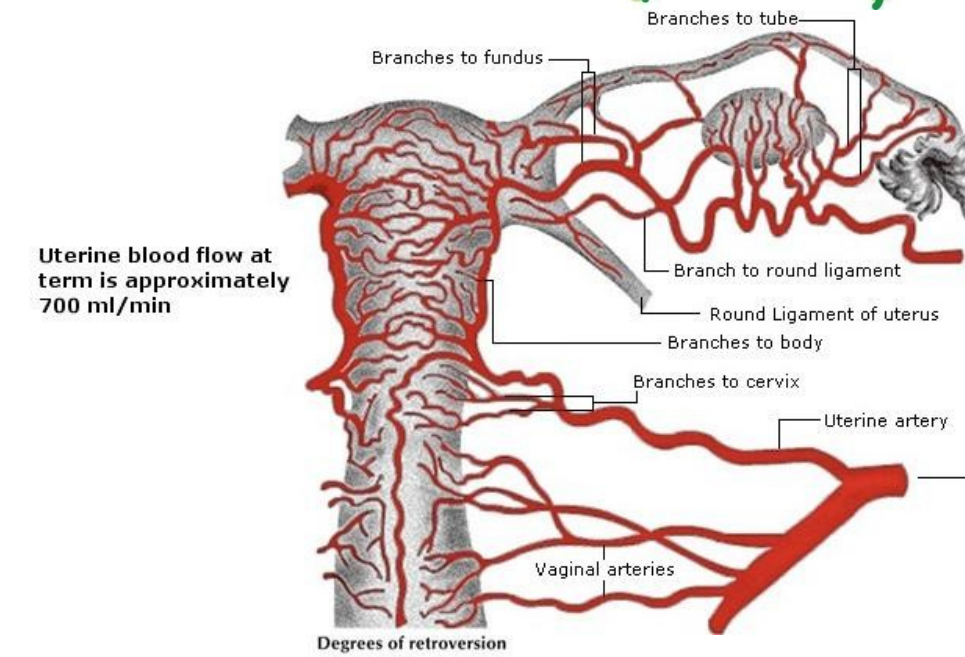
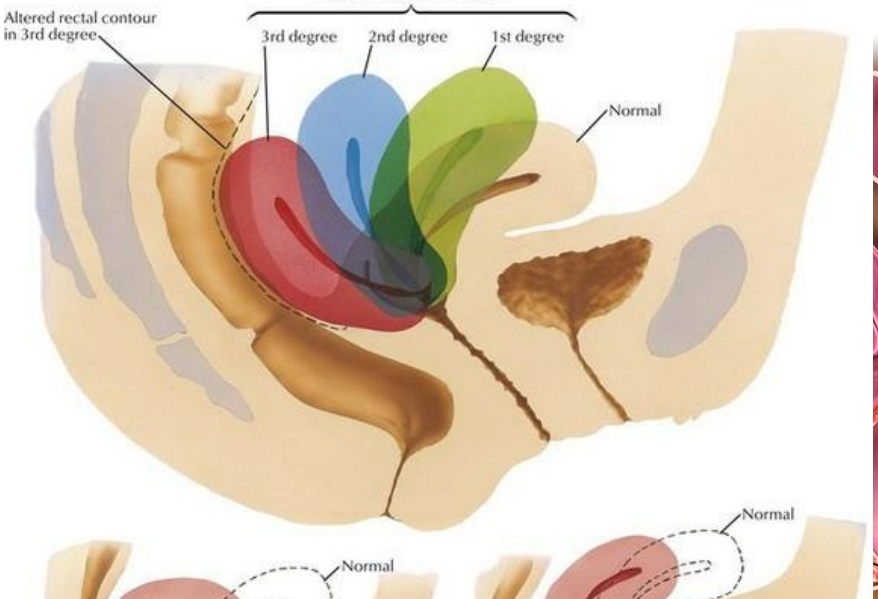
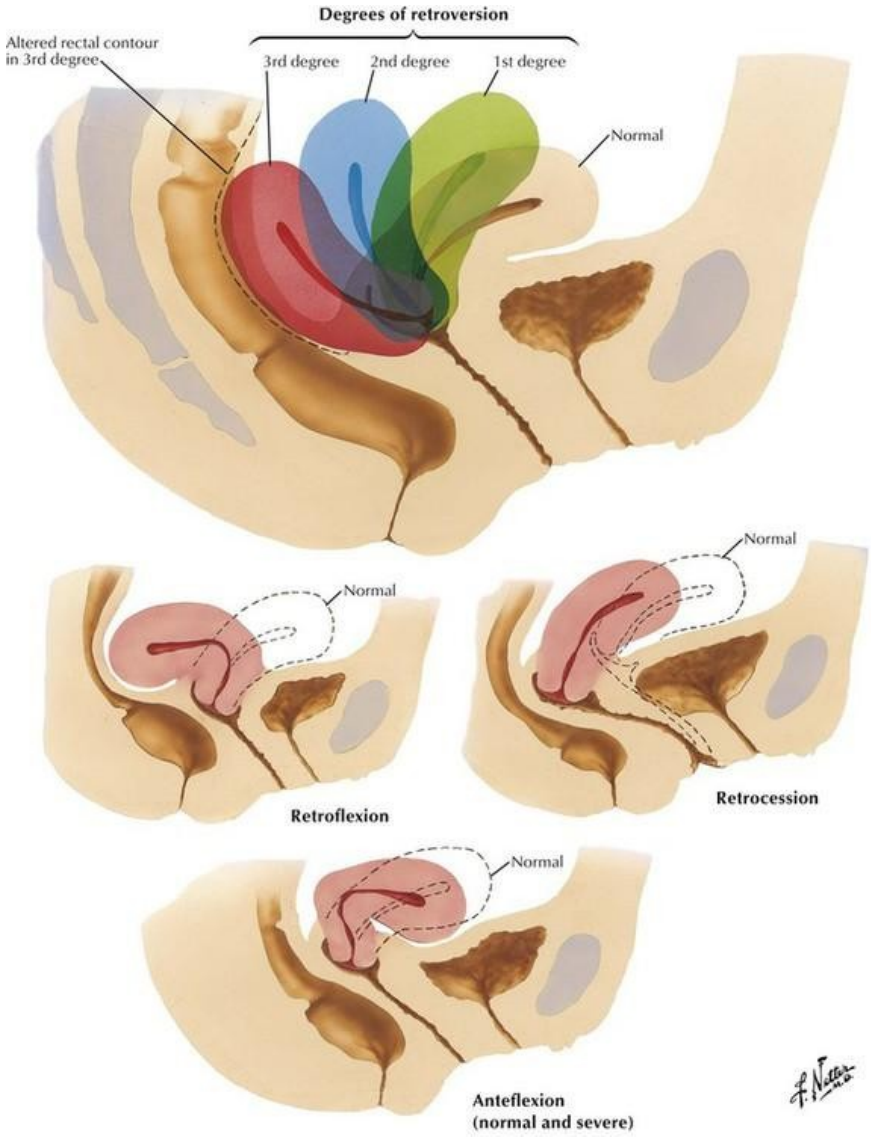
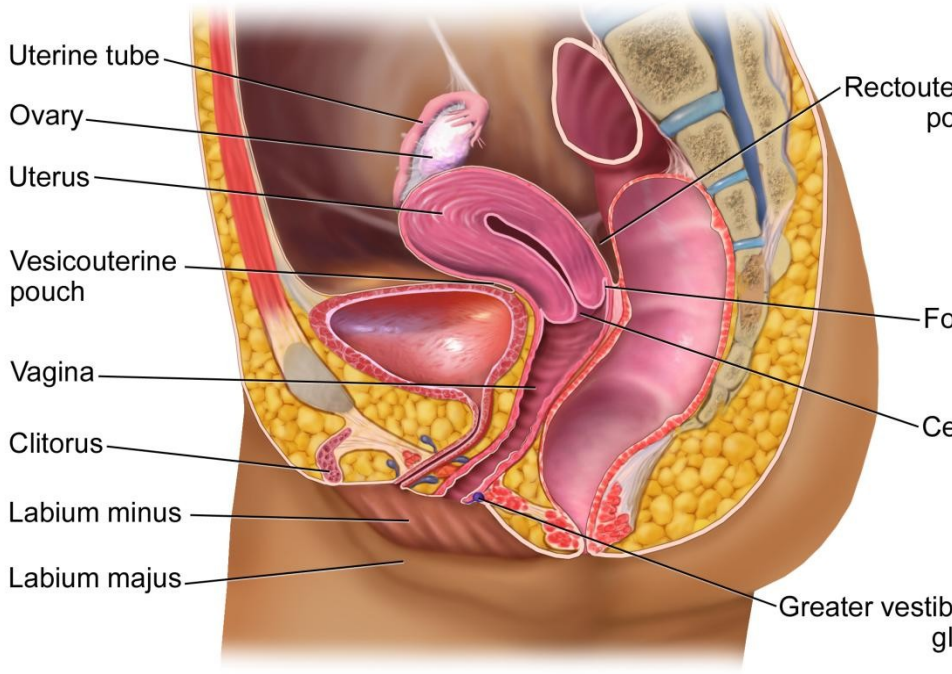
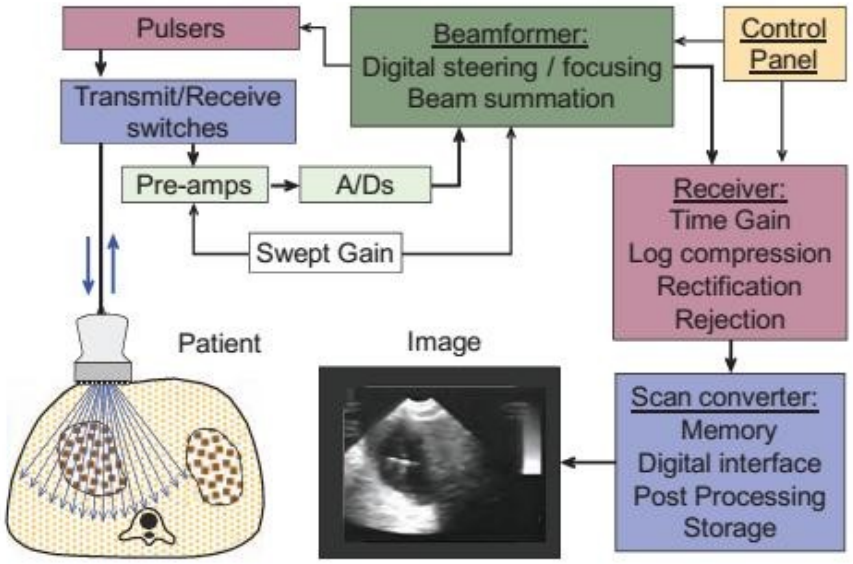
perivitelline space
cortical granule
zona pellucida
acrosome reaction
corona radiata
fused plasma membrane


Uterine blood flow at term is approximately 700 ml/min
Branches to tube
Branches to fundus
Branch to round ligament
Round Ligament of uterus
Branches to body
Branches to cervix
Uterine artery
Vaginal arteries


Degrees of retroversion
Altered rectal contour in 3rd degree
3rd degree
2nd degree
1st degree
Normal
Normal
Normal


Degrees of retroversion
Altered rectal contour in 3rd degree
3rd degree
2nd degree
1st degree
Normal
Normal
Retroflexion
Normal
Retrocession
Normal
Anteflexion
(normal and severe)





DEDICATION

I dedicate my researcfi work to my (itt(e fami(y. A specia(fee(ing of gratitude to my (oving parents, for tfieir words of encouragement. 9y cfii(dren

fiave never (eft my side and
are very specia(.

I a(so dedicate tfiis researcfi to my
fius6and wfio fias

Supported me tfirougfiout tfie process. I wi((
a(ways appreciate a((

tfiey
fiave

done, fie(ping me to master
tfie (eader dots.

I dedicate tfiis work and give specia(tfianks to

my 6est friend Amani for fie(pingme.

Acknowledgment

I would like to thank God for enabling me to complete this thesis. I wish to thank specially my husband who encouraged me throughout this study. I sincerely thank Dr. Ahmed Mostafa Abukonna the supervisor of my thesis for his continues help, supervision and guidance.

I greatly thank all those who supported and helped me to complete this thesis.

I am very grateful to all teachers in all educational levels, especial thanks to Dr. Mohammed M. Omer and Dr. Elsafi Ahmed.

Thanks also extended to the staff of Mohammed Ali Fadul Hospital especially Sonologist Jadi Osman for their help and support.

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Abstract

Early pregnancy failure is a general term that indicates failure of a clinically recognized pregnancy to progress to fetal viability. The aim of this study was to evaluate early pregnancy failure. Fifty patients with different types of pregnancy failure were examined. Trans- abdominal ultrasound scanning technique was performed with patient laying in supine position, most of the patients were scanned with full bladder for good viewing of the entire uterus and adnexa.

The result of the study revealed that the age of both parents has a significant role as the risk of an adverse pregnancy outcome is increased if the parents are 35 years old or older, and it is 50% higher if the mother is 42 years of age. The study showed that 19 patients with severe vaginal bleeding, 16 patients with moderate and the remaining were mild vaginal bleeding. The heavy bleeding in the first trimester, particularly when accompanied by pain, is associated with higher risk of miscarriage. Furthermore, sever vaginal bleeding was associated with complete abortion. Regarding the causes of miscarriage, the study showed that the most common causes of miscarriage in study sample was pelvic inflammatory disease.

An investigation of maternal clinical history revealed that history of pregnancy failure was associated with recurrent miscarriage. Therefore assessment of causes of miscarriage and management can reduce number of occurrence of miscarriage again.

الخلاصة

الأجهاض هو الفقدان الفجائي للحمل أثناء الاربع و عشرون الاسبوع الأولى من الحمل و يعرف ايضا بفقدان الحمل في فترة الحمل الأولى (اقل من 12 إسبوع) و يحدث في ما يصل الى واحد في خمسة حالات حمل .

كان هدف من هذه الدراسة التعرف على أسباب الإجهاض و كذلك مقارنة نتائج الموجات فوق الصوتية مع الأسباب الرئيسية و السريرية للأجهاض .

أجريت الدراسة بمستشفى محمد على فضل ؛ تم تسجيل 50 مريض في الدراسة . شملت كل المرضى الذين تم مسحهم بالموجات فوق الصوتية فوق جدار البطن . تم جمع البيانات السريرية و كذلك نتائج الموجات فوق الصوتية و تحليلها .

و كشف نتائج الدراسة أن عمر كلا الوالدين بمثل دورا كما يزيد خطر حدوث اجهاض الحمل إذا كان الوالدان 35 سنة أو اكثر ؛ و يكون أعلى بنسبة 50% إذا كان عمر الأم 42 سنة . و أظهرت الدراسة أن 19 مريضا يعانون من نزيف مهبلي شديد ؛ 16 مريضا نزيف متوسط و المتبقي كان المهبلي الخفيف .

النزيف الحاد في الأشهر الثلاثة الأولى ؛ لا سيما عندما يكون مصحوب بألم ؛ يرتبط بخطر الأجهاض . و علاوة على ذلك ؛ قطع النزيف المهبلي كان مرتبطا مع الأجهاض الكامل . و فيما يتعلق أسباب الإجهاض ؛ و أظهرت لبدراسة أن اكثر الأسباب شيوعا للأجهاض في عينة الدراسة كانت مرض التهاب الحوض.

ان التحقق في تاريخ الأم الطبي كشف أن اجهاض الحمل كان مرتبطا بالأجهاض المتكرر . و بالتالي تقييم أسباب الأجهاض و ادارته يمكن أن تقلل من حدوث الأجهاض مرة اخرى .

Chapter One

Introduction

1.1 Introduction

Early pregnancy refers to different duration of pregnancy depending on the purpose of an author's discussion. In most cases, early pregnancy from an ultrasound perspective indicates the first trimester of pregnancy. Some authors may refer to the first trimester as l2weeks or l4 weeks (Ticconi et al., 2016).

Early pregnancy failure is a general term that indicates failure of a clinically recognized pregnancy to progress to fetal viability. Fetal viability refers to the capability of a fetus to survive outside the uterus at birth (Ticconi et al., 2016)

Miscarriage is the loss of fetus before the 20th week of pregnancy. The medical term for a miscarriage is spontaneous abortion, but the condition is not an abortion in the common definition of that term (Vale-Fernandes et al., 2015).

Miscarriage is one of the most common yet under-studied adverse pregnancy outcomes. In the majority of cases the effects of a miscarriage on women's health are not serious and may be unreported. However in the most serious cases symptoms can include pain, bleeding and a risk of hemorrhage. Feelings of loss and grief are also common and the psychology and mental health of those affected can suffer.

Recurrent miscarriage is generally defined as spontaneous abortions repeated consecutively over three or more times. At present, there exist a small number of accepted aetiologies for RPL these includeparental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic

abnormalities, and antiphospholipid antibody syndrome. Other probable or possible aetiologies include additional endocrine disorders, heritable and/or acquired thrombophilias, immunologic abnormalities, infections, and environmental factors (Vale-Fernandes et al., 2015).

The most common causes of early pregnancy failure include chromosome aberrations, uterine abnormalities, and an exposure to teratogens, hormonal dysfunction and pregnancy with an IUCD. The most common uterine abnormalities associated with early pregnancy failure include mullerian anomalies, myomatous disease of the uterus and incompetence of cervix (Stamatopoulos et al.,
2015).

Ultrasound evaluation of an early pregnancy failure include detection of the pregnancy location; intrauterine or extrauterine, the type of pregnancy; one- fetus pregnancy, multiple pregnancy, molar pregnancy, the viability of the pregnancy and establishment of the gestational age. Ultrasonographer also recognizes the complications that occur in first trimester (Field and Murphy, 2015).

1.2 Problem of the study:

Late diagnosis of early pregnancy failure is a big problem, it may expose the pregnant lady to the risk of infection; i.e. incomplete abortion of the products of conception in the uterus are good media for bacteria, and continuous of vaginal bleeding associated with spontaneous abortion lead to anemia. Therefore, early diagnosis of the patients by ultrasound aided in management &preventing this entire problem.

1.3 Objectives of the study:

1.3.1 General objective:

The objective of this study was to evaluate early pregnancy failure.

1.3.2 Specific objective

This study intended to:

1. Visualize and localize of the gestational sac.
2. Evaluate the early embryonic demise.
3. Detect and differentiate all types of abortions.

1.4 Thesis outline:

This thesis was aimed to evaluate the causes of early pregnancy failure using trans- abdominal Ultrasound. Accordingly, it was divided into the following chapters

Chapter 1 includes Introduction, Chapter 2: provides background information on previous study, normal anatomy of the female pelvic, pathology, role of ultrasound in first trimester and normal &abnormal ultrasound appearance of early pregnancy failure.

Chapter 3 provides an outline of equipment and methods used in this thesis. While the results were presented in chapter 4, Chapter 5, discusses the results, concludes the thesis and recommends for further studies.

Chapter Two

Theoretical Background and literature review

2.1 Basic principles of Ultrasonography

Sound is a physical phenomenon that transfers ener from one point to another. One of the most significant characteristics of sound is its frequency, which is the rate at which the sound source and the material vibrate. The basic unit for specifying frequency is the hertz, which is one vibration, or cycle, per second. Pitch is a term commonly used as a synonym for frequency of sound (Shriki, 2014).

The human ear cannot hear or respond to all sound frequencies. The range of frequencies that can be heard by a normal young adult is from approximately 20 Hz to 20 kHz. Ultrasound has a frequency above this range. Frequencies in the range of 2 IVI Hz (million cycles per second) to 20 MHz are used in diagnostic ultrasound (Shriki, 2014).

Figure 2-1 Components of the ultrasound imager

2.1.1 Ultrasound Machine

The transducer is the component of the ultrasound imaging equipment that is placed in direct contact with the patient's body. It performs several functions as will be described in detail later. Its first function is to produce the ultrasound pulses when electrical pulses are applied to it. A short time later, when echo pulses return to the body surface they are picked up by the transducer and converted back into electrical pulses that are then processed by the system and formed into an image.

When a beam of ultrasound pulses is passed into a body, several things happen. Most of the ultrasound energy is absorbed and the beam is attenuated. This is undesirable and does not contribute to the formation of an image like in x-ray imaging. Some of the pulses will be reflected by internal body structures and send echoes back to the surface where they are collected by the transducer and used to form the image (Bandyk, 2013).

2.1.1.1 The Basic Ultrasound Imaging Process:

Echoes, which show up as bright or white spots in the image is produced by surfaces or boundaries between two different types of tissues. Most anatomical areas are composed of a "mixture" of different tissue types and many surfaces that produce the general gray and white background that we see in the image. Since there are no reflecting surfaces within a fluid, such as a cyst, it is dark in the image. Therefore, the general ultrasound image, sometimes called a "B mode image, is a display of echo producing sites within the anatomical area (Shriki, 2014).

The ultrasound image is a display showing the location of reflecting structures or echo sites within the body. The location of a reflecting structure (interface) in the horizontal direction is determined by the position of the beam. In the depth

direction, it is determined by the time required for the pulse to travel to the reflecting site and for the echo pulse to return.

Another physical characteristic that can be imaged with ultrasound is motion, specifically the motion of flowing blood. This uses the Doppler principle and the images are usually displayed with different colors representing the different flow velocities and directions (Shriki, 2014).

2.1.2. Transducer

The transducer is the component of the ultrasound system that is placed in direct contact with the patient's body. It alternates between two major functions: (1) producing ultrasound pulses and (2) receiving or detecting the returning echoes.

2.1.2.2 Pulse generators:

The pulse generator produces the electrical pulses that are applied to the transducer.

2.1.2.3 Amplification:

Amplification is used to increase the size of the electrical pulses coming from the transducer after an echo is received.

2.1.2.4 Scan Generator

The scan generator controls the scanning of the ultrasound beam ove r the body section being imaged. This is usually done by controlling the sequence in which the electrical pulses are applied to the piezoelectric elements within the transducer (Bandyk, 2013).

2.1.2.5 Scan converter

Scan conversion is the function that converts from the format of the scanning ultrasound beam into a digital image matrix format for processing and display.

2.1.2.6 Image processor

The digital image is processed to produce the desired characteristics for display. This includes giving it specific contrast characteristics and reformatting the image if necessary.

2.1.2.7 Display:

The digital ultrasound images are viewed on the equipment display (monitor).

2.2 Previous Studies

A similar study was done by Mohamed Ahmed Adlan. A total of 194 patients were referred for ultrasound examination with the history of vaginal bleeding. 84 patients were diagnosed sonographically as threatened abortion making this diagnosis is very reassuring to the patients of the84 patients 76 (90%) progressed normally in pregnancy while 8 patients (95%) had spontaneous abortion.

A total of 42 patients were referred with the clinical diagnosis of incomplete abortion. 38 were diagnosed as incomplete abortion other 5 patients as complete abortion. The cases of complete abortion were examined bimanually and the cervix was found to be closed and the bleeding stopped.

The cases of incomplete abortion were evacuated surgically and the fmdings confirmed the diagnosis. In this study 4 cases were referred with the clinical diagnosis of hydatidiform mole,2 of these cases were diagnosed as complete and partial mole respectively, in the third case no defmite diagnosis could be made ,but

the ultrasonic examination was highly suggestive of a molar pregnancy, and with missed abortion put in the differential diagnosis.

In the 4 case molar pregnancy was excluded by finding that it was twin pregnancy.

Surgical management findings and histology confirmed that diagnosis in the 3 cases. The patient diagnosed as twin pregnancy was reassured and discharged.

Other studies done by Goldstein DP, Ber Kowitz& et al concluded in

(1920). 1979&1987, Ultrasound was found to provide a reliable method of demonstrating hydatidiform mole. In another study done by Donald, et al (21). urge that repeated examinations to be performed, the results of this study also reaffirms Jouppila S,et al (23) concluded that in the absence of the an embryo, serial examination are required to confirm abnormal growth and development.

Ultrasound is an accurate method for evaluating threatened abortion, because it can readialy demonstrate the presence or absence of embryonic cardiac motion.

In these studies the common and difficult problem arises when the gestation sac lacks an embryo, this was solved by measuring the mean sac diameter and by repeated scans and early pregnancy could be differentiated from an embryonic pregnancy.

Jauniaux F et al assessed the role of ultrasound imaging in diagnosing and investigating early pregnancy failure. The advent of high-resolution transvaginal ultrasound (TVS) has revolutionized our understanding of the pathophysiology and the management of early pregnancy failure. Knowledge of the ultrasound appearances of normal early pregnancy development and a good understanding of

its pitfalls are essential for the diagnosis and management of early pregnancy failure. Ultrasound imaging has rapidly replaced all other techniques used to study

normal human development in the first trimester, and ultrasound features of the early gestational sac have corroborated anatomical studies showing that the first structures to appear are the celomic cavity and the secondary yolk sac. No single ultrasound measurement of the different anatomical features in the first trimester has been shown to have a high predictive value for determining early pregnancy outcome. Similarly, Doppler studies have failed to demonstrate abnormal blood flow indices in the first-trimester uteroplacental circulation of pregnancies that subsequently end in miscarriage. Ultrasound parameters combined with maternal serum hormone levels, maternal age, smoking habits, obstetric history and the occurrence of vaginal bleeding have all been combined in multivariate analyses, with mixed results. Combined ultrasound and in-vitro experiments have demonstrated that the maternal circulation inside the placenta starts at the periphery at around 9 weeks of gestation and that this is associated with a physiological oxidative stress which could be the trigger for the formation of the placental membranes. Abnormal development of these membranes can result in subchorionic hemorrhage and threatened miscarriage with subsequent long-term consequences such as preterm rupture of the membranes and preterm labor, irrespective of the finding of a hematoma on ultrasound. In both euploid and aneuploid missed miscarriages there is clear ultrasound evidence for excessive entry of maternal blood at a very early stage inside the developing placenta resulting in oxidative stress and subsequent degeneration of villous tissue. The fmding of blood flow in the intervillous space in cases of first-trimester miscarriage using color Doppler also appears to be useful in the prediction of success of expectant management. Miscarriages with blood flow within the intervillous space are up to four times more likely to complete with expectant management. TVS is considered the gold standard in the diagnosis and

management of incomplete miscarriage. Expectant management of miscarriage,

using ultrasound parameters to determine eligibility, could significantly reduce the number of unnecessary evacuations of the retained products of conception, depending on the criteria used.

Perriera and Reeves (32). evaluated the early pregnancy failure and ectopic pregnancy. Pregnancy failure is a common clinical diagnoses for which ultrasound can provide useful information. They reviewed the use of ultrasound to diagnose early pregnancy failure and ectopic pregnancy. By documenting the developmental milestones of early normal pregnancy using ultrasound, clinicians can distinguish nonnal from abnormal intrauterine pregnancies. An early pregnancy failure can be diagnosed by the absence of a visible yolk sac with a mean sac diameter of 13 mm; the absence of a visible embryo with a mean sac diameter of 20 mm; the absence of cardiac motion with an embryo measuring 5 mm or more in maximal length; or the presence of an empty amnion. In most settings, documentation of a normal intrauterine pregnancy effectively eliminates the possibility of ectopic pregnancy. The presence of an adnexal mass in the absence of an intrauterine gestational sac may indicate an ectopic pregnancy.

2.3 The female pelvic organs

The female external genital organs include; The vulva includes the mons pubis, the labia majora ,the labia minora, the clitoris and the greater vestibular glands.

2.3.1 Labia majora

The labia majora are prominent folds of the skin extending from the mons pubis to unite posteriorly in the midline. They contain fat, and hair covers their outer surfaces.

2.3.2 Labia minora

The labia minora are two smaller folds of skin which are devoid of hair, that lie between the labia majora. Their posterior ends are united to form a sharp fold. (The fourchette), interiorly, they spilt to enclose the clitoris, thus forming an anterior prepuce and posterior frenulum (Herschorn, 2004).

2.3.3 Vestibule of the vagina:

The Vestibule of the vagina is the space between the labia minora. The vestibule has the clitoris at its apex and the openings of the urethra, the vagina and the ducts of the greater vestibular glands in its floor (Herschorn, 2004).

2.3.4 Clitoris:

The clitoris in females corresponds to the penis in males. The gland of the clitoris is partly hidden by the prepuce, and the root of the clitoris is comprised of three masses of erectile tissue; bulb of the vestibule, and the right and the left crura of the clitoris.

2.35Greater vestibular glands

Greater vestibular glands are a pair of mucus secreting glands that lie under cover of the posterior parts of the bulb of the vestibule and the labia majora. The duct of each gland opens into the groove between the hymen and the posterior part of the labium minus.

2.3.6 Ovary;

2.3.6.1 Location and description

Each ovary is oval shaped, measured 4*2cm, and is attached to the back of broad ligament by the mesovarium. The part of broad ligament extending between the

attachment of the mesovarium and the lateral wall of the pelvis is suspensory ligament of the ovary, the round ligament of the ovary, which represents the remains of the upper part of the gubernaculurns, connect the lateral margin of the uterus to the ovary. The ovary usually lies against the lateral wall of the pelvis in a depression called the ovarian fossa, bounded by the external iliac vessels above and internal iliac vessels behind. the position of the ovary is ,however, extremely variable, and it is often found hanging down in the pouch of Douglas (Mayor et al.,
2011).

During pregnancy the enlarged uterus pulls the ovary up into the abdominal cavity after childbirth, when the broad ligament is lax, the ovary takes up a variable position in the pelvis. The ovaries are surrounded by a thin fibrous capsule, the tunica albuginea. Before puberty the ovary is smooth, but after puberty the ovary becomes progressively scarred as successive corpora lutea degenerate. After menopause the ovary becomes shrunken and surface is pitted with scars (Mayor et al., 2011).

2.3.6.2Function:

The ovaries are the organs responsible for the production of the female germ cells, the ova, and the female sex hormones, estrogen and progesterone, in the sexually mature female.

2.3.6.3 Blood supply:

The ovarian artery arises from the abdominal aorta at the level of the first lumber vertebra. The ovarian vein drains into the inferior vena cava on the right side and into the left renal vein on the left side.

2.3.6.4 Lymph drainage;

The iyrnph vessels of the ovary follow the ovarian artery and drain into the Para - aortic nod s at the level of the first lumbar vertebra.

2.3.6.5 Nerve supply;

The nerve supply of the ovary is derived from the aortic plexus and accompanies the ovarian artery.

2.3.7 Uterine tube:

2.3.7.1 Location and description;

The two uterine tubes are each about 10cm long and lie in the upper border of the broad ligament. Each connects the peritoneal cavity in the region of the ovary with the cavity of the uterus. The uterine tube is divided into four parts; The infundibulum;is the funnel-shaped lateral end that projects beyond the broad ligament and overlies the ovary, the free edge of the funnel has several fmgerlike processes ,known as fimbriae, which are draped over the ovary. The ampulla is the widest part of the tube. The isthmus is the narrowest part of the tube and lies just lateral to the uterus. The intramural part is the segment that pierces the uterine wall (Mayor et al., 2011).

2.3.7.2 Function;

The uterine tube receives the ovum from the ovary and provides a site where fertilization of the ovum can take place (usually in the ampulla).it provides nourishment for the fertilized ovum and transports it to the cavity of the uterus. The tube serves as a conduit along which the spermatozoa travel to reach the ovum (Mayor et al., 2011).

2.3.7.3 Blood supply;

The uterine artery originates from the internal iliac artery and ovarian artery from the abdominal aorta. The veins correspond to the arteries.

2.3.7.4 Lymph drainage;

The lymph vessels follow the corresponding arteries and drain into the internal iliac and Para-aortic nodes.

2.3.7.5 Nerve supply;

Sympathetic and Para sympathetic nerves originate from the inferior hypo gastric plexuses.

Figure 2-2 the female reproductive system

2.2.8.1 Location and description:

The uterus is hallow, pear-shaped organ with thick muscular walls. In the young nulliparous adult it measures' 8cm long, 5cm wide, and 2.5 cm thick. It is divided into the fundus, body, and cervix. The fundus is the part of uterus that lies above the entrance of the uterine tubes. The body is the part of the uterus that lies below the entrance of uterine tubes. It narrows below, where it becomes continuous with the cervix. The cervix pierces the anterior wall of the vagina and is divided into the supra-vaginal and vaginal part of the cervix. The cavity of the uterine body is triangular in coronal section .but it is merely a cleft in the sagittal plane. The cavity of the cervix, the cervical canal, communicates with the cavity of the body through the internal os and with the vagina through the external Os (Mayor et al., 2011).

2.3.8.2 Relations Anterior

The body of the uterus is related anteriorly to the uterovesical pouch and the superior surface of the bladder. The supravaginal cervix is related to the superior surface of the bladder .the vaginal cervix is related to the anterior fornix of the vagina. Posteriorly

The body of the uterus is related posteriorly to the recto uterine pouch with coils of ileum or sigmoid colon within it. Laterally: the body of the uterus is related laterally to the broad ligament and the uterine artery and vein. The supravaginal cervix is related to the ureter as it passes forward to enter the bladder. The vaginal cervix is related to the lateral fornix of the vagina. The uterine tubes enter the superolateral angles of the uterus, and the round ligaments of the ovary and of the uterus are attached to the uterine wall just below this level (Mayor et al., 2011).

2.3.8.3 Function

The uterus serves as a site for the reception, retention, and nutrition of the fertilized ovum.

2.3.8.4 Position of the uterus

Figure 2-3 various position of the uterus

In most women, the long axis of the uterus is bent forward on the long axis of the vagina; this position is referred to as ante version of the uterus. Furthermore, the long axis of the body of the uterus is bent forward at the level of the internal os with the long axis of the cervix; this position is termed anteflection of the uterus. Thus in the erect position, with the bladder empty, the uterus lies in an almost horizontal plane.

In some women, the fundus and body of the uterus are bent backward on the vagina so that they lie in the pouch of Douglas. In this situation the uterus is said to be *retroverted*. if the body of the uterus is, in addition ,bent backward on the cervix, it is said to be retro flexed (Herschorn, 2004).

2.3.8.5 Structure of the uterus

The uterus is covered with peritoneum except anteriorly, below the level of the internal os, where the peritoneum passes forward onto the bladder. Laterally, there is also a space between the attachments of the layers of the broad ligament. The muscular wall or myometrium ,is thick and made up of smooth muscle supported by connective tissue.

The mucous membrane lining the body of the uterus is known as the endometrium.it is continuous above with muocus membrane lining the uterine tube and below with the muocus membrane lining the cervix. The endometriurn is applied directly to the muscle, there being no sub mucosa from puberty to menopause, and the endometrium undergoes extensive change during the menstrual cycle in response to the ovarian hormones. The supra vaginal part of the cervix is surrounded by visceral pelvic fascia, which in this region is often referred to as the parametriu. It is in this fascia that the uterine artery crosses the ureter on each side of the cervix (Herschorn, 2004).

2.3.8.6 Blood supply

The arterial supply to the uterus is mainly from the uterine artery; a branch of the internal iliac artery .it reaches the uterus by running medially in the base of the broad ligament .it crosses above the ureter at right angle and reaches the cervix at the level of the internal os. the artery then ascends along the lateral margin of the uterus, within the broad ligament and ends by anastomosing with the ovarian artery, which also assists in supplying the uterus. The uterine artery gives off a small descending branch that supplies the cervix and the vagina.

Figure 2-4: blood supply of the uterus (25)

2.3.8.7 Lymph drainage

The lymph vessels from the fundus of the uterus accompany the ovarian artery and drain into the Para-aortic nodes at the level of the first lumbar vertebra. The vessels from the body and cervix drain into the internal and external iliac lymph nodes. A

few lymph vessels follow the round ligament of the uterus through the inguinal canal and drain into the superficial inguinal lymph nodes.

2.3.8.8 Nerve supply

Sympathetic and parasympathetic nerves from branches of the inferior hypo gastric plexuses.

2.3.8.9 Support of the uterus

The uterus is held in apposition of ante flexion and antevertion by its weight, by the round ligament, which hold the fundus forwards, and by the uterosacral ligaments, which keep the supra vaginal cervix far back in the pelvis. The broad ligament and their cellular tissues also have a steadying effect on the uterus. The round and broad ligament do not however, have any significant action in preventing descent of the uterus. This function is performed almost entirely by the transverse cervical ligaments and their posterior extensions the uterosacral ligament. These ligaments also contribute to support the vaginal vault, which is also important in preventing uterine prolapsed (Herschorn, 2004).

2.3.8.10 Uterus in child

The fundus and body of the uterus remain small until puberty, when they enlarge greatly in response to the estrogens secreted by the ovaries.

2.3.8.11 Uterus after menopause

After menopause, the uterus atrophies and becomes smaller and less vascular, these changes occur because the ovaries no longer produce estrogens and progesterone.

2.3.8.12 Uterus in pregnancy

During pregnancy, the uterus becomes greatly enlarged as a result of the increasing production of estrogens and progesterone, first by the corpus luteum of the ovary and later by the placenta.

At first it remains as pelvic organ, but by the third month the fundus rises out of the pelvis. And by the ninth month it has reached the xiphoid process. the increased in size is largely a result of hypertrophy of the smooth muscle fibers of the myometrium, although some hyperplasia takes place.

2.3.9 Vagina

2.3.9.1 Location and description

The vagina is a muscular tube that extends upward and backward from the vulva to the uterus. It measures about 8cm long and has anterior and posterior walls, which are normally in apposition. At its upper end the anterior wall is pierced by the cervix, which projects downward and backward into the vagina. The area of the vaginal lumen, which surrounds the cervix, Is divided into four regions, or fornices: anterior, posterior, right lateral, and left lateral. The vaginal orifice in a virgin possesses a thin mucosal fold called the hymen that is perforated at its center. After childbirth the hymen usually consists only of tags.

2.3.9.2 Relations

Anteriorly; the vagina is closely related to the bladder above and urethra below.

Posteriorly; the upper third of the vagina is related to the recto uterine pouch and its middle third to the ampulla of the rectum.

The lower third is related to the perineal body ,which separates it from the anal canal.

Laterally; in its upper part, the vagina is related to the ureter; its middle part is related to the anterior fibers of the levator an., as they run backward to reach the perineal body and hook around the anorectal junction. In its lower part, the vagina is related to the urogenital diaphragm and the bulb of the vestibule.

2.3.9.3 Function;

The vagina not only is the female genital canal but also serves as the excretory duct for the menstrual flow and forms part of the birth canal.

2.3.9.4 Blood supply;

Vaginal artery, a branch of the internal iliac artery, and the vaginal branch of the uterine artery.

2.3.9.5 Lymph drainage;

The lymph vessels from the upper third of the vagina drain to the external and internal iliac nodes, from the middle third to the internal iliac nodes, and from the lower third to the superficial inguinal nodes.

2.3.9.6 Nerve supply;

The nerve supply to the vagina is from the inferior hypogastric plexuses.

2.3.9.7Support of the vagina;

The upper part of the vagina is supported by the levator ani muscles and the transverse cervical, pubocervical, and sacrocervical ligaments. The middle part of

the vagina is supported by the urogenital diaphragm. The lower part of the vagina, especially the posterior wall, is supported by the perineal body.

2.4. Early development:

The development of anew individual begins by the union of two cells; one from the male called the sperm and other from female called the ovum

Figure 2-5 Fertilization process

The union between the sperm and the ovum is called fertilization, it takes place in the lateral third of the fallopian the (ampulla),and results in a fertilized ovum called zygote. Once the ov14m is fertilized, it starts its cleavage division, it first division into 2,then 4,then 6 etc. Each cell resulting from the cleavage division is called ablastomere when the zygote reaches the 12-16 cell stage it is called amorula.

Figure 2-6 Zygote division

While the morula continues to divide, fluid from the uterine cavity passes into the intercellular spaces between its cells; these spaces then join each other, finally forming a single large cavity called the blastocele, and the zygote is now called the blastocyst. The cells of the outer cell mass form the wall of the blastocyst and are now called the trophoblast, while the cells of the inner cell mass stick together become located at one side (pole) of the blastocys and are now called the embryoblasj

The blastocyst reaches the cavity of the uterus about the 5th days and becomes attached to the endometrium at about days, this attachment called implantation. Normally implantation takes place in the endometrium of the posterior wall of the fundus of the uterus. Implantation begins about the 6th or 7 days and is complete about 11th days after fertilization.

2.4.1 Second week of pregnancy:

The blastocyst completes its implantation in the endometrium. The cells of the trophoblast differentiate into two layer; an outer syncytiotrophoblast and an inner cytotrophoblast. The cell of the inner cell mass become organized to form a plate called the embryonic disc. The embryonic disc is formed of two germ layers only the ectoderm and the endoderm. They are formed also two cavity in second week:

Amniotic cavity; is a space formed between the ectodermal and the trophoblast and primary yolk sac; a space formed between the endoderm and trophoblast.

2.4.2 Third week of pregnancy:

The bilaminar embryonic disc is transformed into a trilaminer disc duo to the formation of the mesodermal germ layer. The notochord which is a supporting element for the embryonic disc develops in this week. Three types of chorionic villi (primary, secondary and tertiary) are formed and cover the whole surface of the blastocyst.

2.4.3 Fourth to eighth week of pregnancy;

During this period of development the fallowing change occur:

I. The shape of the embryo changes greatly externally; by the end of the eight week all the main external features of the body can be seen. Each of the three germ layers, ectoderm, mesoderm and endoderm differentiates to produce a number of tissues and organs. Internally by the end of the eighth week all the main systems of the body are laid down.

The external appearance of the embryo during the second month includes: the limbs, face, ears, nose, eyes are formed, the two otic placodes, and the optic vesicles.

2.4.4 Third to tenth month:

Main features during the third month; the face becomes more human looking than before is use:

The eyes which were looking laterally become placed on the ventral aspect of the face. The ears come to lie at the sides of the head. The external genitalia become developed to the extent that the sex of the fetus can be known at this stage. The limbs are better developed. Growth as a whole during the fetal period. The body, as a whole grows very rapidly; the head grows at as a slower rate than the growth of the rest of the body (Ticconi et al., 2016).

2.5 Pathology

2.5.1 Introduction

For both the physician and the patient, early pregnancy loss is a frustrating and heart-wrenching experience. Early pregnancy loss is unfortunately the most common complication of human gestation, occurring in at least 75% of all women trying to conceive. Most of these losses are unrecognized and occur before or with the next expected menses. Of those that are or with a fetal weight of <500 g. Most investigators recognized, 15- 20% are spontaneous abortions (SABs) or ectopic pregnancies diagnosed after the pregnancy is clinically recognized. Approximately

5% of couples trying to conceive have 2 consecutive miscarriages, and approximately 1% of couples have 3 or more consecutive losses (Ticconi et al., 2016).

Early pregnancy loss is defined as the termination of pregnancy before 20 weeks' gestation agree that both ectopic and molar pregnancies should not be included in the definition.

2.5.2 Incidence;-

The incidence of spontaneous miscarriage is 10-15%, whereas the rate of recurrent miscarriage is 3-5% Most studies demonstrate a spontaneous miscarriage rate of 10-15%. However, the true rate of early pregnancy loss is close to 50% because of the high number of chemical pregnancies that are not recognized in the 2-4 weeks after conception. Most of these pregnancy failures are due to gamete failure (e.g., sperm or oocyte dysfimction). In a classic study by Wilcox et al in 1988, 221 women were followed up during 707 total menstrual cycles. A total of 198 pregnancies were achieved. Of these, 43 (22%) were lost before the onset of menses, and another 20 (10%) were clinically recognized losses.

The likelihood for an SAB increases with each successive abortion. Data from various studies indicate that, after 1 SAB, the baseline risk of a couple having another SAB is approximately 15%. However, if 2 SABs occur, the subsequent risk increases to approximately 30%. The rate is higher for women who have not had at least 1 live born infant. Several groups have estimated that the risk of pregnancy loss after 3 successive abortions is 30-45%. Therefore, controversy exists regarding how many pregnancy losses should occur before a diagnostic evaluation is considered. One could argue that the diagnostic evaluation should be performed after 2 losses rather than 3 because diagnostic yields after 2 versus 3 miscarriages are identical (Van den Bosch et al., 2015).

2.5.3 ETIOLOGY

The etiology of early pregnancy loss is varied and often controversial. More than 1 etiologic factor is often present. The most common causes of recurrent miscarriages are as follow Genetic,(Mendelian disorders, Genetic translocations, Muitifactorial disorders, Chromosomal inversions& Sex-chromosome aneuploidies).

Autoimmune causes ,(lmmunologic causes, Alloinmmne causes); Anatomic causes, Uterine mullerian anomaly(Uterine septum (the anomaly most common associated with pregnancy loss) ,Hemiuterus (unicomuate uterus) ,Bicornuate uterus, Diethylstilbestrol-linked condition ,Acquired defects (e.g, asherman syndrome) ,Incompetent cervix, Leiomyomas &Uterine polyps. Infectious causes, Environmental causes (Smoking ,Excessive alcohol consumption.)

Endocrine factors, (Diabetes mellitus, Antithyroid antibodies, Lutealphase deficiency).

Hernatological disorders The gestational age at the time of the SAB can provide clues about the cause. For instance, nearly 70% of SABs in the first 12 weeks are due to chromosomal anomalies. However, losses due to antiphospholipid syndrome (APS) and cervical incompetence tend to occur after the first trimester (Van den Bosch et al., 2015).

2.5.4 Genetic causes:

Most spontaneous miscarriages are caused by an abnormal (aneuploid) karyotype of the embryo. At least 50% of all first-trimester SABs are cytogenetically abnormal. (Note that this figure does not include abnormalities caused by single genetic disorders, such as Mendelian disorders or mutations at several loci).

The highest rate of cytogenetically abnormal concepti occurs earliest in gestation, with rates declining after the embryonic period (>30 mm crown-rump length). The rate of normal (euploid) and abnormal (aneuploid) abortuses increases with maternal age. Recurrent miscarnage may result from 2 chromosomal abnormalities: (1) a structural abnormality derived from 1 parent or (2) the recurrence of a numerical abnormality, which is usually not inherited (Joiner and Newcomer, 2013).

2.5.5 Aneuploidy:

Cytogenetically abnormal embryos are usually aneuploid because of sporadic events, such as meiotic non disjunction, or polyploid from fertilization abnormalities. One half the cytogenetically abnormal abortuses in the first trimester involve autosornal trisomy. Triploidy is found in 16% of abortions, with fertilization of a normal haploid ovum by 2 sperm (dispermy) as the primary pathogenic mechanism. Trisomies may arise de novo because of meiotic non disjunction during gametogenesis in parents with a normal karyotype. For most trisomies, maternal rneiosis I errors have been implicated. Abnormal meiotic segregation results in either complete tnsomies or monosornies.

Trisomy 16, which accounts for 30% of all trisomies, is the most common. Viable trisomies have been observed for chromosomes, and approximately one third of fetuses with Down syndrome (trisomy 21) fetuses survive to term. All chromosome trisomies except for trisomy 1 are reported in abortuses. Of interest, trisomy 1 is reported in embryos obtained with in vitro fertilization (IVF). This finding logically suggests that trisomy 1 is most likely lethal at the preimplantation stage. Autosomal monosornies are rarely, if ever, observed. In contrast, monosoniy X (Turner syndrome) is frequently observed, and it is the most common

chromosornal abnormality observed in SABs. Turner syndrome accounts for 20 -

25% of cytogenetically abnormal abortuses.

Other abnormalities include those related to abnormal fertilization (eg, tetraploidy, Iriploidy). These abnormalities are not compatible with life. Tetraploidy occurs in approximately 8% of chromosomally abnormal abortions, resulting from failure of an early cleavage division in an otherwise normal diploid zygote (Joiner and Newcomer, 2013).

2.5.6 Parental chromosomal abnormalities:

Structural rearrangements occur in approximately 3% of cytogenetically abnormal ab ortuses. Structural chromo sornal abnormalities are thought to be most commonly inherited from the mother. Of note, structural chromosomal problems found in men often to lead to low sperm concentrations, male infertility, and, therefore, a reduced likelihood of pregnancy and miscarriage. The exception to this situation is the couple undergoing assisted reproductive technologies in which selected sperm can be injected into oocytes to force fertilization by using potentially genetically abnormal sperm Among structural rearrangements, translocations (most commonly reciprocal and Robertsonian) can be balanced or unbalanced. The incidence of translocations increases with the number of abortions. Slightly more than one half of unbalanced rearrangements result from abnormal segregation of Robertsonian translocations. Approximately one half of all unbalanced translocations arise de novo during gametogenesis. In reciproca l translocations, children created from these gametes have normal and carrier karyotypes. Adjacent segregation results in unbalanced distribution of the

chromosomes involved in the translocation, leading to partial trisomy for 1 chromosome and partial monosomy for the other chromosome. The severity of the

phenotype depends on the chromosomes involved and on the positions of their breakpoints. The risk is increased if the female partner carries the translocation.

Other structural rearrangements, such as inversions or ring chromosomes, are relatively rare. These chromosomal abnormalities can be associated with congenital malformations and mental retardation, as well as SAB (Joiner and Newcomer, 2013).

2.5.7 Genetic abnormalities

Certain genetic mutations thought to be involved with implantation may predispose a patient to infertility or even miscarriage. An example of a single gene disorder associated with recurrent pregnancy loss is myotonic dystrophy, an autosomal dominant neuromuscular disorder with high penetrance. The cause of the abortion is unknown, but it may be related to abnormal gene interactions combined with disordered uterine function.

Other presumed autosomal dominant disorders include lethal skeletal dysplasias (eg, thanatophoric dysplasia and type II osteogenesis imperfecta). Maternal disease associated with increased fetal wastage includes connective tissue disorders, such as Marfan syndrome, Ehiers-Danlos syndrome, homocystinuria, and pseudoxanthoma elasticum. Hematologic abnormalities associated with recurrent pregnancy loss include dysfibrinogenernia, factor XIII deficiency, congenital hypofibrinogenemia and afibrinogenemia, and sickle cell anemia.

Women with sickle cell anemia are at increased risk for fetal loss, possibly because of placental-bed micro infarcts.

2.5.8 Immunologic Causes

2.5.8.1 Autoimmune abnormalities

Associations and predictive factors

Recurrent pregnancy loss is associated with autoimmune diseases. In specific terms, systemic lupus erythematosus (SLE) has been implicated in increasing the rate of miscarriage and pregnancy loss, as associated with antiphospholipid antibodies (APLAs) since 1954. APS is an autoimmune disorder in which patients have elevated levels of APLAs and recurrent pregnancy loss, fetal death, and/or thrombosis.

Compared with the general population, the median rate of spontaneous miscarriage among patients with SLE is 10%. However, the 8% median rate of late pregnancy loss (ie, loss in the second and third trimesters) is considerably higher than that observed in the healthy general population. In 75% of patients with SLE, excess pregnancy loss seems to be isolated to fetal death in the second and third trimesters. Most, if not all, fetal deaths in these women are associated with the presence of APLAs three other factors that are predictive are disease before conception, an onset of SLE during pregnancy, and underlying renal disease.

At least 3 APLA findings are well known to have important clinical relevance: lupus anticoagulant (LAC), anticardiolipin antibodies (aCLs), and a biologically false-positive serologic test result for syphilis. APS, also known as LAC syndrome and Hugh syndrome, is diagnosed when both obstetric and medical findings are clinically present and when specific levels of APLAs are present. Other obstetric and medical conditions associated with APLAs are listed below.

Obstetric conditions associated with APLAs:

1. Preeclampsia
2. Growth restriction
3. Abnormal fetal heart rate tracings
4. Preterm deliveries
5. Pregnancy wastage

Medical conditions associated wit/i APLAs

1. Arterial and venous thrombosis
2. Autoimmune thrombocytopenia
3. Autoinirnune hemolytic anemia
4. Livedo reticularis
5. Chorea
6. Pulmonary hypertension
7. Chronic leg ulcers

2.5.9 Anatomic Causes:

Anatomic uterine defects are known to cause obstetric complications, including recurrent pregnancy loss, preterm labor and delivery, and malpresentation. Therefore, a uterine malformation should be considered in any woman with recurrent pregnancy loss. However, not all women with abnormal uteri have obstetric complications. Impaired vascularization and fetal growth restriction due to uterine distortion are 2 commonly discussed reasons for pregnancy loss.

The incidence of uterine anomalies is estimated to be 1 per 200-600 women, depending on the method used for diagnosis. When manual exploration is

preformed at the time of delivery, uterine anomalies are found in approximately

3% of women. Howerer, in women with a history of pregnancy loss, uterine abnormalities are present in approximately 27%.

2.5.10 Infectious Causes:

The theory that microbial infections can cause miscarriage has been presented in the literature since as early as 1917, when DeForest et al observed recurrent abortions in humans exposed to farm animals with brucellosis. Although infection has been reported as a cause of pregnancy loss, few studies have been conducted, and results are inconsistent.

Numerous organisms have been indicated in sporadic causes of miscarriage, but common microbial causes have not been confirmed. In fact, infection is viewed as a rare cause of recurrent miscarriage.

Any patient undergoing an infertility workup should be treated for any recognized vaginitis or cervicitis. In addition, chronic genital infection may be the most obvious initial manifestation of a general health problem. Chronic vulvovaginitis is associated with diabetes, other endocrinopathies, and, possibly, lupus erythernatosus. In addition, gonorrhea and chlarnydia should be eliminated before the infertility workup (eg, hysterosalpingograms) to avoid spreading the infection to the upper genital tract (Joiner and Newcomer, 2013).

A recent review failed to show suffieient evidence for the notion that any type of infection can be identified as a causal factor for recurrent miscarriage. Most patients with a history of recurrent miscarriage do not benefit from an extensive infection workup. Exposure to a microbe that can establish chronic infection that can spread to the placenta in a patient who is inimunocomprornised is probably the most obvious risk situation in recurrent abortions.

Specific pathogens include Neisseria gonorrhoeae, which is associated with premature rupture of membranes and chorioamnionitis, and C trachornatis. Previous chiamydial infection is not associated with fetal loss in women with recurrent abortion. However, neonatal conjunctivitis and pneumonia are known sequelae.

Women who are in high-risk groups are the only patients who should be screened. Serologic studies have suggested an association between C trachomatis and recurrent abortion, and routine C trachoinatis screening has been recommended for all patients undergoing an infertility workup. However, microbiologic testing for endocervical chiamydial infection during pregnancy has failed to confirm the association with recurrent abortion (Soslow, 2016).

In 1992, Witkin and Ledger reviewed the relationship between high-titer TgG antibodies to C trachoinatis and recurrent SAB. They found that high- titer IgG antibodies to C trachomatis were associated with recurrent SABs. They proposed the mechanism to be reactivation of a latent chiamydial infection, endometrial damage from past chiarnydial infection, or an immune response to an epitope shared by a chiamydial and a fetal antigen.

Bacterial vaginosis is associated with pretenn labor, intrauterine growth retardation, chorioamnionitis, and late miscarriage. However, no studies have been conducted to investigate its role in women with recurrent miscarriages. Most women are screened at their first prenatal visit and more frequently than this if they have a history of late miscarriages or preterm delivery.

Regarding genital mycoplasma M horninis and Ureapiasma species are isolated from the vagina in as many as 70% of pregnant women. Although these organisms are most frequently found in women with recurrent miscarriages, their elimination

has not improved subsequent pregnancy outcome. Therefore, screening for Mycopiasma and Ureaplasma species is not recommended for the typical patient with a history of recurrent miscarriage.

L monocytogenes typically produces asymptomatic colonization of the maternal lower genital tract, though symptomatic maternal listeriosis characterized by bacteremia and influenza-like symptoms may occur.

Symptomatic listerial infection is typically described as a complication of the third trimester, resulting from ingestion of unpasteurized milk or cheese.

Asymptornatic genital Listeria colonization may result in high perinatal mortality and morbidity rates if the organism is spread to the fetus during labor and delivery. However, no evidence suggests that Listeria organisms play a role in patients with a history of recurrent pregnancy loss. Screening for Listeria during pregnancy or in routine cases of recurrent miscarriage is not recommended.

T pailiduin is known to cause stillbirth and abortion in the second trimester. The timing of death is probably associated with the maturation of the fetal immune system at the 20th week of gestation. However, syphilis is unlikely to substantially contribute to the general problem of recurrent miscamage (Soslow, 2016).

Lyme disease (which is due to Borrelia burgdorferi) can result in stillbirth and fetal infection. Perform serologic testing if the patient relates a history suggestive of Lyme disease. However, Lyrne disease is unlikely to substantially contribute to the general problem of recurrent abortion.

CMV is associated with random miscarriage but not recurrent miscarriage. In a large study, Stagno et al (1982) observed 3712 pregnant patients and documented

21 cases of primary maternal CMV infection during pregnancy. Only 11 of the 21 showed neonatal infection, and SABs did not occur in this group.

Primary HSV infection has been associated with SAB, and chronic HSV infection is a possible cause of recurrent abortion (especially in a patient who is immunocompromised). The risk rate for in utero HSV transmission from chronic maternal disease is low (approximately 0-3% of pregnancies). Therefore, the incidence of recurrent abortion secondary to chronic HSV infection is extremely low in the general population and does not warrant routine screening in patients with recurrent pregnancy loss.

Malaria due to P falciparuin during pregnancy is associated with SAB, stillbirth, low birth weight, and prematurity. Screening is only important in those women who live where the disease is endemic or in symptomatic patients who have traveled to endemic countries.

Primary toxoplasmosis can lead to miscarriage and stillbirth. However, if the infection develops during the first trimester, the risk is less than 5%. In addition, repeated infections in subsequent pregnancies are unlikely, unless chronic infection develops in patients who are immunocompromised. Studies have failed to show an increase in miscarriage rates for asymptornatic patients with HIV infection.

2.5.11 Environmental, Endocrine, and Hematologic Causes

2.5.11.1 Environmental causes

Environmental causes of human malformation account for approximately 10% of malformations, and fewer than 1% of all human malformations are related to exposures to prescription drugs, chemicals, or radiation. Isotretinoin (Accutane), a retirioic acid used to treat severe acne, is associated with SAB.

Recognizing these preventable exposures is important. For example, the relationship between exposure to trace concentrations of waste anesthetic gases in the operating room and the possible development of adverse health effects has been a concern for many years. However, the studies that showed an increased incidence of miscarriage and congenital anomalies had many flaws.

Maternal exposure to tobacco and its effect on reproductive outcomes has been the subject of many studies. Cigarette smoke contains hundreds of toxic compounds. Nicotine is thought to have vasoactive actions and is thought to reduce placental and fetal circulation. Carbon monoxide depletes both fetal and maternal oxygen supplies, and lead is a known neurotoxin.

Maternal smoking appears to only slightly increase the risk of SABs. Maternal exposures to excess alcohol and coffee consumption were reported to be associated with an increased risk for SAB.

2.5.11.2 Endocrine causes:

Ovulation, implantation, and the early stages of pregnancy depend on an integral maternal endocrine regulatory system. Most attention was historically directed at maternal systemic endocrine disorders, luteal-phase abnonnalities, and hormonal events that follow conception, particularly progesterone levels in early pregnancy.

2.5.11.3 *Diabetes mellitus:*

Women with diabetes mellitus who have good metabolic control are no more likely to miscarry than women without diabetes. However, women with diabetes with high glycosylated Aic levels in the first trimester are at a significantly increased risk of both miscarriage and fetal malformation. Women with insulin-dependent diabetes with inadequate glucose control have a rate of SAB 2-3 times higher than that of the general population of women. Screening for occult diabetes in asymptomatic women is not necessary unless a random glucose value is elevated. For a patient with an unexplained loss in the second trimester or with clinical signs of diabetes mellitus, investigation is needed.

No direct evidence suggests that thyroid disease is associated with recurrent miscarriages. However, the presence of antithyroid antibodies (to thyroid antigens thyroglobulin and thyroid peroxidase) may represent a generalized autoimmune abnormality rather than a specific thyroid dysflmction. Screening for thyroid disease is not useful unless the patient is symptomatic.

Low progesterone levels:

Progesterone is the principal factor responsible for the conversion of a proliferative to a secretory endometrium, rendering the endometrium receptive for embryo implantation. In 1929, Allen and Corner published their classic results on physiologic properties of the corpus luteum. Since then, low progesterone levels have been assumed to be associated with miscarriage.

Luteal support remains critical until approximately the seventh week of gestation, at which time the placental trophoblast has acquired enough steroidogenic ability to support the pregnancy. In patients in whom the corpus luteum is removed

before the seventh week, miscarriage results. If progesterone is given to these patients, the

pregnancy is salvaged. Recent developments with RU486 (an antiprogestin) have shown that this can effectively terminate a pregnancy up to 56 days from the last menstrual period.

Luteal-phase defects:

In 1943, Jones first discussed the concept of insufficient luteal progesterone resulting in either infertility or early pregnancy loss. This disorder was characterized by inadequate endometrial maturation resulting from a qualitative or quantitative disorder in corpus luteal function, which has been reported in 23-60% of women with recurrent miscarriage.

However, no reliable method is available to diagnose this disorder, and controversy exists because of the inconsistencies in the methods of diagnosis.

Methods used to diagnose luteal-phase defects (LPDs) include records of basal body temperature records, evaluation of progesterone concentrations, and histologic dating of endometrial biopsy specimens.

The criterion standard has been endometrial biopsy performed in the luteal phase. This criterion uses the development of stromal and glandular cells to determine how many days after ovulation the patient was at the time of the biopsy. A delay of more than 2 days in maturation compared with when the patient exactly is on the basis of her surge in luteinizing hormone (LH) defined as LPD. However, substantial interobservational and intraobservational discrepancies occurs when the standard histologic criterion is applied.

Most studies use the patients subsequent menses as a reference point, with the assumption that the patient has a normal 28-day cycle. This defmition accounts for many of the discrepancies in the literature. As a consequence, as many as 31% of

normally fertile women have an LPD according to the results from serial endometrial biopsy procedures.

In 1 of the few prospective studies in which women with 3 or more consecutive miscarriages were examined, LPD was believed to be the cause in 17%. The pathologist accurately dated the biopsy samples using LH assays to pinpoint the time of ovulation. In this study, luteal-phase serum progesterone levels were normal in the women with LPD. Luteal-phase deficiency is most likely the result of an abnormal response of the endornetrium to progesterone rather than a subnormal production of progesterone by the corpus luteum. This is evident because as many as 50% of women with histologically defined LPD have normal serum progesterone levels (Almeida et al., 2016).

In treating LPD, realizing that post implantation failure or that an early nonviable pregnancy is associated with low serum progesterone levels is important. Only 1 randomized trial has shown that treatment with progesterone supplementation has a beneficial effect on pregnancy outcomes. Most studies have had opposite results, failing to show that any type of support (eg, progesterone, human chorionic gonadotropin) has beneficial results. Therefore, the physician must be selective in deciding who should be screened for LPD. One approach is to screen patients with either a history of recurrent miscarriages or recurrent failures with infertility therapy. In addition, the best accuracy is achieved if the same pathologist reviews the histologic findings and if the day of ovulation is based on LH levels rather than subsequent menses. The dose of progesterone should be adequate to stimulate luteinization of the endometrium with the fewest adverse effects.

2.5.11.3 Hematologic defects

Many recurrent miscarriages are characterized by defective placentation and microthrombi in the placental vasculature. In addition, certain inherited disorders that predispose women to venous and/or arterial thrombus formation are associated with thrombophilic causes for pregnancy loss. Various components of the coagulation and fibrinolytic pathways are important in embryonic implantation, trophoblast invasion, and placentation. Because the association between APLA and recurrent miscarriage is now firmly established, interest has been garnered in the possible role of other hemostatic defects in pregnancy loss. Pregnancy is a hypercoagulable state because of an increase in the levels of procoagulant factors, a decrease in the levels of naturally occurring anticoagulants, and a decrease in fibrinolysis.

Levels of factors VII, VIII, X, and fibrinogen increase during a normal pregnancy, as early as 12 weekst gestation. This increase in factors is not balanced by an increase in anticoagulants (ie, antithrombin III, proteins C and S). In fact, protein S levels decrease by 40-50%. Antithrornbin III and protein C levels remain constant. Fibrinolytic activity is also altered, with levels of plasminogen activator inhibitor-i (PAT-i) and plasminogen activator inhibitor-2 (PAI-2) progressively increasing during pregnancy. PAT-i is produced by endothelial cells and inhibits release of plasminogen activator. PAI-2 is produced by the trophoblast and helps regulate placental growth. Platelet activation increases and contributes to the prothrornbic state of pregnancy, as reflected by an increase in platelet production of thromboxane and decreased platelet sensitivity to the antiaggregation effects of prostacyclin. The hemostatic changes in pregnancy favor coagulation.

Urokinase plasminogen (uPA) activator is active around the time of implantation. It triggers the localized production of plasmin, which catalyzes the destruction of the extra-cellular matrix, facilitating implantation. uPA is also found in the maternal venous sinuses and, therefore, plays a role in maintaining the patency of these channels. uPA receptors are also expressed on first-trimester human trophoblast cells, primarily those that are not actively invasive, which serves to facilitate generation of plasmin at the interface of these cells with maternal plasma, limiting deposition of fibrin in the intervillous spaces (Stamatopoulos et al., 2015).

2.5.11.4 Activated protein C resistance:

Resistance to the anticoagulant effects of activated protein C (APC) is inherited as an autosomal dominant trait and is the most important cause of thrombosis and familial thrombophilia. In more than 90% of patients, it is due to a single-point mutation (glutamine for arginine) at nucleotide position 1691 in the gene for factor V. This mutated gene is known as factor V Leiden. APC cleaves and inactivates coagulation factors Va and VIIIa in the presence of cofactor protein S. The mutated factor V is resistant to inactivation by APC, resulting in increased thrombin production and a hypercoagulable state. Its prevalence rate is 3-5%. In those with a previous venous thrombosis, the prevalence rate is as high as 40%.

In 1995, Rai and colleagues evaluated 120 women with a history of recurrent miscarriages. None of the women had a history of thrombosis, LAC, or aCL. The prevalence of APC resistance was higher in women who had a second-trimester miscarriage than in those with a first-trimester loss (20% vs. 5.7%).

In normal pregnancies, APC resistance naturally decreases. However, women with APC resistance before pregnancy tend to have an even further decrease in resistance. The best way to detect APC resistance is both coagulation-based assay

and DNA testing to detect the actual mutation. They complement each other because one is a genetic test and one is a functional test (Almeida et al., 2016).

2.6 Pathophysiology; (14)

Pathologically, SAB begins with hemorrhage into the decidual basalis. Inflammation and necrosis occurs around the region of implantation w ith subsequent detachment of the conceptus. Uterine contraction and expulsion of intrauterine contents occur through a dilated cervix.

Missed abortion occurs when some of the products of conception remain and there may be organization of the blood clot surrounding the conceptus.

2.6.1 Spontaneous abortion

Types of spontaneous abortion include;

2.6.1 .lcomplete abortion

refers to complete passage of conception

2.6.2 Sonographic Finding:

-

I. Empty uterus with clean endometrial stripe.

11. Moderate to bright endometrial echoes.

III.Presence of trophoblastic Doppler waveforms surrounding the endometrium normally persist for 3days post SAB.

Figure 2-8: complete abortion

2.6.1.2 Incomplete abortion:

Refers to retention of products of conception, typically residual trophoblastic tissue.

Clinical signs:

I. Slow fall of HCG levels.

II. Moderate cramping.

III. Persistent, heavy bleeding.

Senographic Finding:

I. presence of complex collection of echoes within endometrium duo to air bubbles or retained bony fragments.

II. persistence of trophoblastic waveforms near the endornetrial cavity after 5 days post abortion.

Figure 2-9 incomplete abortion

2.6.1 .3 Missed abortion:

The Presence of an embryo within the uterus without evidence of cardiac activity may be retained for months following the embryonic demise.

A calcified fetus associated with a missed abortion is known as a

lithopedion. Occurs more commonly is the second trimester (Jolic and Gilja,

1997). ***Sonograpizic Finding:***

I. presence of gestational sac with or without fetal

component. II. absence of fetal cardiac activity or limb

motion.

III. acoustic shadowing arising from the endornetrium indicating the presence of air bubbles or calcified fetal parts.

IV. fetal size less than expected for dates.

V. uterus smaller than expected for dates.

Figure 2-10 missed abortion

2.6.1.4 Threatened abortion:

A condition in which the future of the pregnancy may be in jeopardy but the pregnancy continues.

Clinical signs:

I. closed cervix.

II. Slight bleeding or cramping.

Sonographic Finding:

In the most groups of patients presenting with threatened abortion who subsequently abort, the embryo is usually already dead at the time of ultrasound evaluation (Jolic and Gilja, 1997).

Figure 2.11 Threatened abortion

2.6. 1.5 Inevitable a abortion:

SAB is imminent when are of two or more of the following

clinical signs are noted;

I. moderate affacernent of the cervix.

II. cervical dilatation >3 cm.

III. rupture of membranes.

IV. bleeding for more than 7days.

V. persistent cramprng.

Sonographic Finding:

I. gestational sac identified in the cervix or lower uterine

segment. II. cervical dilatation.

III. sonolucent crescent surrounding the gestational sac.

2.6.1.6 An embryonic pregnancy ;-

The presence of a gestational sac in the uterus in which an embryo has failed to develop or died at a stage too early to be visualized. Also known as blighted ovum.

Sonographic findingt -

I. no identifiable embryo in a gestational sac of 25mm or larger. II. absence of double sac sign.

Figure 2-12 An embryonic pregnancy

2.6.1.7 Habitual abortion:

Is three consecutive spontaneous a bortions.The most common cause

of habitual abortion in second trimester is an incompetence of the cervicx (2).

2.6.1. Prior to Sonographic Detection of the Gestational Sac:

There are no reliable ultrasound findings to confirm the presence of an IUP prior to detection of a gestational sac. The decidua may appear relatively thick and uterine

vessels may be more prominent however these changes are too subtle to be reliable.

Endovaginal colour Doppler prominent radial - spiral artery associated with the implantation site referred to as the (EVSCD) may provide the first sonographic clue of the presence of an early IUP by showing increased uterine flow signals, especially a "sentinel artery". The increased uterine vascularity observed with EVSCD during early pregnancy has been referred to as the "warm uterus sign" (Jolic and Gilja, 1997).

Chapter Three

Materials and Method

3.1 Materials:

3.1.1 Machine used

The study conducted at Mohammed Ali Fadul Hospital using GE ultrasound machine with nice probes ranges from 3.5 to 7.5 Hz

3.1.2 Subjects:

Fifty patients with different types of pregnancy failure were examined

3.2 Meth

od:

observers then all sheets were analyzed using SPSS software.

3.2.1 Data collection

A data collection sheet has been designed to meet the purpose of the study, it has been filled by three mentioned

3.2.2 Technique used:

In pelvic ultrasound the uterus should be scanned clearly to check intra uterine gestational sac, Care should be taken to confirm the fetal heart beat.

Most pelvic ultrasounds are performed using both the transabdominal and transvaginal approaches; Transabdominal ultrasound involves scanning through your lower abdomen. Transabdominal ultrasound usually provides an overview of the pelvis

rather than detailed images. The transabdominal assessment is particularly helpful for the examination of large pelvic masses extending into the abdomen, which are not always well viewed with transvaginal ultrasound.

A small amount of ultrasound gel is put on the skin of the lower abdomen, with the ultrasound probe then scanning through this gel. The gel helps improve contact between the probe and your skin.

Chapter 4

Result

Table 4 -1 Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
age	50	17	45	29.20	6.827
Valid	50				

Table 4 – 2 Type of Vaginal Bleeding

				Valid Percent	Cumulative Percent
Valid	Mild	16	32.0	32.0	32.0
	Moderate	15	30.0	30.0	62.0
	Severe	19	38.0	38.0	100.0
	Total	50	100.0	100.0	

Figure 4-1 type of vaginal bleeding

Table 4 – 3 severity of pain

				Valid Percent	Cumulative Percent
Valid	NO	9	18.0	18.0	18.0
	Mild	19	38.0	38.0	56.0
	Severe	22	44.0	44.0	100.0
	Total	50	100.0	100.0	

Figure 4 -2 pain categories distribution

Table 4 – 4 Clinical History

	Frequency	Percent	Valid Percent	Cumulative Percent
Hypertension	13	26.0	26.0	26.0
Diabetes	9	18.0	18.0	44.0
Allergy	2	4.0	4.0	48.0
Cesarean Section	4	8.0	8.0	56.0
Previous Failure	22	44.0	44.0	100.0
Total	50	100.0	100.0	

Figure 4 – 3 Clinical History

Table 4 -5 Causes of Failure

			Valid Percent	Cumulative Percent
Myoma	20	40.0	40.0	40.0
IUCD	3	6.0	6.0	46.0
PID	22	44.0	44.0	90.0
Trauma	5	10.0	10.0	100.0
Total	50	100.0	100.0	

Figure 4 - 4 Causes of Failure

Table 4-6 Types of Miscarriage

				Valid Percent	Cumulative Percent
Valid	Complete	18	36.0	36.0	36.0
	Incomplete	14	28.0	28.0	64.0
	Missed	14	28.0	28.0	92.0
	Threaten	4	8.0	8.0	100.0
	Total	50	100.0	100.0	

Figure 4 - 5 Types of Miscarriage

Table 4 – 7 Type of Vaginal Bleeding * Types of Miscarrage Crosstabulation

		Types of Miscarrage				
		Complete	Incomplete	Missed	Threaten	
Type of Vaginal Bleeding	Mild	0	1	11	4	16
	Moderate	1	11	3	0	15
	Severe	17	2	0	0	19
Total		18	14	14	4	50

Table 4 – 8 Causes of Failure * Types of Miscarrage Crosstabulation

		Types of Miscarrage				
		Complete	Incomplete	Missed	Threaten	
Causes of Failure	Myoma	8	8	4	0	20
	IUCD	0	0	3	0	3
	PID	7	5	7	3	22
	Trauma	3	1	0	1	5
Total		18	14	14	4	50

Chapter 5

Discussion, conclusion and recommendations

5.l Discussion:

Spontaneous pregnancy loss can be physically and emotionally taxing for couples, especially when faced with recurrent loss that's one of the reasons this research has been carried out to spot more light on this universal challenge. Fifty pregnant women of different ages were enrolled in this study.

The age distribution showed that the majority of age was 30 years old and more, which put the maternal at risk factor of miscarriage as suggested by previous studies. The age of both parents has a significant role as the risk of an adverse pregnancy outcome is increased if the parents are 35 years old or older, and it is 50% higher if the mother is 42 years of age (Moonachie et al., 2007).

Concerning vaginal bleeding type, the study showed that 19 patients with severe one, 16 patients with moderate and the remaining were mild vaginal bleeding. This result consistent with the previous studies which stated that heavy bleeding in the first trimester, particularly when accompanied by pain, is associated with higher risk of miscarriage (Hassan et.al, 2009). Furthermore, sever vaginal bleeding was associated with complete abortion.

Regarding the causes of miscarriage, the study showed that the most common causes of miscarriage in study sample was pelvic inflammatory disease (44%), this result also confirmed with previous studies which stated that the the contribution of infection is much greater (McClure et.al, 2009). Furthermore in a recent study,78% of 101 tissue samples from miscarriage were infected with bacteria, whereas all the control samples from medically induced abortions were uninfected (Alanson et al.,

2010). It is well established that pregnancy is a balance between tolerance and rejection, as the maternal immune system is re-programmed to tolerate the allergenic (paternal) fetal antigens (Thellin and Heinen, 2003). An active infection could destabilize this balance resulting in rejection, especially if it leads to a serious illness of the mother.

An investigation of maternal clinical history revealed that history of pregnancy failure was associated with recurrent miscarriage. Therefore assessment of causes of miscarriage and management can reduce number of occurrence of miscarriage again.

5.2
Conclusion

The most common type of early pregnancy failure is an incomplete abortion and the least common types is molar pregnancy. The study showed that ultrasound is an easy and accurate in diagnosis of early pregnancy failure. The incidence of early pregnancy failure higher in house wife than employee. The passive smoking is highest predisposing factor caused early pregnancy failure. The hypertension is most disease associated with early pregnancy failure. Vaginal bleeding is most symptom presenting early pregnancy failure.

5.3
Recommendations

Ultrasound has important role in fetal screening in first trimester of pregnancy had estimate pregnancy in case of vaginal bleeding or any of pregnancy complication.

Every pregnant lady should examined by ultrasound in order to reduce the risk of bleeding and infections. Therefore, all clinics should be equipped with ultrasound machine with competent staff over all the regions of Sudan for emergency cases. Furthermore, Ultrasound is cheap, quick, safe methods of diagnosis of most of pregnancy complication.

More advance ultrasound machine should be used to obtain accurate results.

Due to high incidence of abortion in first trimester pregnancy found which needs further investigations and studies.

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