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Case Study

To Goulash or Not to Goulash: A Case Report on Blighted Ovum

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Introduction

What is a Blighted Ovum?

A blighted ovum is a fertilized egg that implants but does not develop. In a blighted ovum, a gestational (embryo) sac forms and grows, but the embryo does not develop. A blighted Ovum is also known as anembryonic pregnancy. A blighted ovum is the leading cause (50%) of miscarriage.

In the first trimester, the terms early pregnancy loss, miscarriage, or spontaneous abortion is used as there is no consensus in the literature (ACOG, 2015).

Early Pregnancy Loss is defined as spontaneous loss of pregnancy before 13wks of gestation (AAFP, 2011).

What is a Miscarriage?

In the UK, miscarriage is defined as loss of intrauterine pregnancy before 24 complete weeks of gestation. The WHO and CDC defines miscarriage as the loss of pregnancy before 20wks of gestation or the expulsion or extraction of an embryo or fetus weighing 500 g or less. This definition is generally used in the USA, however it might vary as per the State laws. The State of Utah defines some miscarriages "as criminal homicide". There are currently 38 states that have fetal homicide laws and 23 states which have fetal homicide laws that apply to the earliest stages of pregnancy (2015).

Biochemical Miscarriage (a loss that occurs after positive Urine pregnancy test (hCG) or a raised serum β-hCG before Ultrasound or histological verification).

The term *Clinical Miscarriage* is used when ultrasound examination or histologic evidence has confirmed the existence of an intrauterine pregnancy [1] In general, clinical miscarriage is classified as *early* (before 12wks of pregnancy) and *late* (12wks to 20wks). In Europe late loss is defined as that which occurs between 12 and 22 weeks. Miscarriages are also classified as *sporadic* and *recurrent*.

Sporadic miscarriage is the more common than recurrent. Sporadic miscarriage is when two or three consecutive pregnancy losses occur. According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines, *recurrent miscarriage* (RM) is defined as three or more consecutive pregnancy losses before 22 weeks of gestation. RM is also known as recurrent pregnancy loss (RPL). According to Judy Siegel-Itzkovich of the Jerusalem Post [2], there is a gynecologist- Dr. Bashri in Israel who runs a clinic devoted to only RPL at Soroka for more than 15 years and promoting awareness on this issue. RPL in Israel is also defined as three or more consecutive pregnancy losses whereas in the U.S it is two or more. RPL is also classified as Primary and Secondary. Primary is two or three consecutive miscarriages whereas secondary is at least having one child after two losses.

Etiology

The most common cause of blighted ovum is genetic. This is often due to chromosomes defects which maybe from a poor-quality sperm or egg (too many or too few chromosomes in them). However, in India in addition to genetic cause, it includes infections (TB) and structural defects of the uterus.

Genetics:

According to Buckett, WM and Regan [3] (Sporadic and Recurrent Miscarriage, Clinical Gate), L trisomies are the major fetal chromosomal abnormality in sporadic cases of miscarriage (30% of all miscarriages) and 60% of chromosomally abnormal miscarriages (recurrent miscarriage). **Trisomies with Monosomy X (15-25%) and triploidy (12-20%) account for over 90% of all chromosomal abnormalities found in sporadic cases of miscarriage.**

Trisomies of all chromsomes have been found except for Chromosome 1 and Y. However, the frequency of these trisomies varies (Chromosome 16 and to a lesser extent 2, 13, 15, 18, 21, 22 account for the majority of trisomic abnormalities). According to the study by Edmonds, 1992, trisomy 16 has been found to give rise to the most rudimentary embryonic growth with an empty sac. While other trisomies often result in early embryonic demise.

As per the study by Alberman conducted in 1992, trisomies and monsomies have been implicated for miscarriage at modal peak of 9 weeks whereas triploidy pregnancy losses spanning at 5-16 weeks of gestation.

Recurrent Miscarriage due to Blighted Ovum.

Recurrent miscarriage due to Blighted ovum was significantly higher (68.5% vs 31.5%) in consanguineous marriages according to the study (*Chromosomal Study of Couples with the History of Recurrent Spontaneous Abortions with Diagnosed Blighted Ovum*) by Shekoohi et al. [4] done in Iran.

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Sperm DNA Fragmentation.

There is a link between DNA damage in sperm and miscarriage. According to the research article by Larsen et al. [1]," a meta-analysis of 16 studies found a highly significant increase in miscarriage rate in couples where the male partner had elevated levels of sperm DNA damage compared to those where the male partner had low levels of sperm DNA damage (risk ratio = 2.16 (1.54, 3.03, P <0.00001)".

Nutrition/BMI Status

According to the study done by Popovic et al. [5] in Serbia, published in the European Review for Medical and Pharmacological Sciences low levels of Copper (Cu), Prostaglandin E2, and anti-oxidative enzymes (except for Superoxide Dismutase) and significant high levels of lipid peroxidation products in the plasma have been attributed to the etiology of blighted ovum/miscarriages.

According to Larsen et al. [1], there are many pregnancy-related complications associated with obesity, including miscarriage. "A meta-analysis from 2008 including primarily studies on infertile populations showed significantly increased miscarriage rates in women with a body mass index (BMI) ≥25 kg/m2 were compared to women with a BMI <25 kg/m2".

"This tendency has also been demonstrated in women with recurrent marriage although it must be emphasized that a significantly increased risk of another miscarriage was demonstrated only in obese women; that is, BMI ≥30 kg/m2"

Infections

According to the WHO [6] 1 in 5 women who have an unsafe abortion, suffer from reproductive tract infections (RTI's) and as a result lead to infertility. According to the study done by Maharana [7], the occurrence of Spontaneous abortion (defined as pregnancy loss without the application of any deliberate method to terminate it during early weeks of pregnancy) is 10% and induced abortion (often done using several dangerous procedures and under substandard clinical and sanitary conditions) is 3%.

In India, which includes 11 major states, the occurrence of induced abortion among women with RTI's is two times higher than those not affected by RTI's [7]. (*Maharana, 2011, International Institute for Population Sciences, Mumbai, India*).

According to Patki & Chauhan [8]*, the most common cause of blighted ovum/miscarriage in addition to genetics is infections (TB) and structural defects of the Uterus.*

Anomalies of the Uterus

According to the study (New Insights into mechanisms behind miscarriage) by Larsen et al. [1], uterine malformations which can be congenital or acquired are cause of recurrent miscarriage. Congenital includes arcuate, didelphic, bicornuate and septate uteri.

Drugs/Vaccines

According to the SAGE Working Group On Dengue Vaccines and WHO Secretariat [6], an additional SAE (serious adverse event) found by the investigator in the 28 days to 6 months post CYD (dengue) injection was blighted ovum.

Other Causes

•*Immunologic*

Immunologic disorders in the mother (such as NK Cell Dysfunction, autoantibodies, Hereditary and Acquired Thrombophilia etc.) can lead to the maternal immunological rejection of the implanting embryo in the uterus resulting in miscarriage.

•*Hormonal*

Low levels of progesterone can lead to miscarriage.

•*Endocrine Disorders*

Thyroid disorders (thyroid autoimmunity & thyroid dysfunction) and Ovarian Disorders (e.g. Polycystic Ovarian Syndrome- PCOS) are associated with infertility and pregnancy loss. According to Larsen et al. [1], "the prevalence of PCOS among women with Recurrent Miscarriage is estimated to be 8.3% to 10%".

•*Alcohol Consumption*

Alcohol Consumption: Even small amounts of alcohol increased the risk of a miscarriage significantly and further, the results suggested that the risk increased in a dose related manner.

Epidemiology

A blighted ovum causes 1 out of 2 miscarriages in the first trimester of pregnancy. The incidence of early pregnancy loss (before 12 weeks) is estimated to be about 15% of conceptions with significant variations according to age. The incidence ranges from 10% in women 20-24 years of age to 51% in women 40-44 years of age. Late Loss (*between 12 and 22 weeks) occurs less and is about 4% of pregnancies.*

The prevalence of Recurrent Miscarriage is lower (ranges from 0.8%-3%) compared to Sporadic Miscarriage [1].

Clinical Miscarriages only, prevalence is only 0.8% to 1.4% and if biochemical losses are included, then it is slightly higher and to be about 2% to 3%.

The recent study done by Patki & Chauhan [8] indicates that miscarriage without medical termination of pregnancy is about 10% globally. However, Indian women are more prone to miscarriages at 32% in comparison to the world.

History and Physical

A **21**-year-old female is accompanied by her husband with **main C/o** of spotting (couple of blood drops seen in the urine), no pain when passing urine, no emesis gravidarum (*vomited only once on September 26, 2016 which could be due to urinary infection*). **LMP: September 19, 2016** with missed periods, Urine Pregnancy test done on Oct 31, 2016 -weakly positive

Past Medical History

•$\mathbf{H_x}$ of urinary infection treated a month ago, culture revealed E-Coli, sensitivity done.

•No history of TB, Dengue or Chikungunya before or during pregnancy

Drug History- Treated for Urinary infection with Chloromycetin for a week (completed dose) based on urine culture and sensitivity results. Stopped taking antibiotic after pregnancy test was weakly positive. Not on any other drugs.

Social History

•Not in Consanguineous marriage

•Did not undergo genetic testing or counseling

On Physical Exam- breast tenderness bilaterally, retracted nipples.

Height: 4" 9'; Weight: 46.9 Kg – Oct 31, 2016, Nov 12, 2016-47.6 Kg. Therefore, her BMI is :22.5 (Normal)

Initial Ultrasound report indicates 4 weeks pregnant (presence of sac).

Preliminary diagnosis: Normal (1st) Pregnancy, R/O Missed

Abortion?

Management/Treatment

1) Repeated Pregnancy Test:

Placed 2 drops of Urine on Pregnancy Test Kit indicator. Waited to see the dark red line appear on Control side first and then wait 5 minutes for test side line to appear. The test side was darker than earlier pregnancy test done, however not as dark (red) as the Control side.

2) *Repeated Routine Urine examination,* which revealed no RBC, 4-6 pus cells (*18-20 pus cells were found when she was having urinary infection*) which is normal, couple of epithelial cells, and 1 calcium oxalate crystal.

Urine Report

Volume-10ml

Ph- Acidic

Albumin- Nil

Sugar- Nil

Color- Pale Yellow

Appearance- Clear

Epithelial Cells- ++

Pus Cells- 4-6

RBC-Nil

Crystals- 1 Calcium Oxalate (in the shape of a star)

3) Advised the woman/couple for repeat Ultrasound on Nov 14, 2016 to confirm (8 weeks) heartbeat of fetus.

4) Advised and showed the woman on massaging breasts so that the nipples are not retracted and to take complete bed rest.

5) Also to consult with an Ob & Gyn -Dr. Saroj Menon on Nov 15, 2016. If U/S on Nov 14, 2016 confirms fetus than will conduct other tests (HIV, HsAg etc.). If not advise her for D/C.

6) And continue taking Folic Acid (Fovit) 5 mg 1 Tab OD.

7) Wait 1-3 regular menstrual cycles before attempting to conceive.

Follow Up

A D & C was performed after 2 days by her Ob & Gyn, when the repeat Ultrasound showed the Blighted Ovum at 8 weeks (November 14, 2016). Please see Figure 1.

On May 31, 2017 a follow up was done on the patient. The patient conceived again and is 3 months pregnant, weight- 50 kg. She is taking Folic Acid like the first pregnancy.

Case Summary

In Summary, the final diagnosis for this case was Blighted Ovum based on her clinical symptoms, medical history of Urinary Tract Infections and Ultrasound confirmation of empty gestational sac with no embryo.

The blighted ovum case report discussed here has infectious etiology of Urinary Tract Infections which is similar with the Indian study findings of infections, though they attributed it to TB. In the case study, the patient had a normal Basal Metabolic Index of 22.5, so Goulash is not needed. However, having a protein, Iron and trace elements rich diet such as Goulash could enhance the immune system to fight or prevent infections (Urinary tract infections) which the patient had.

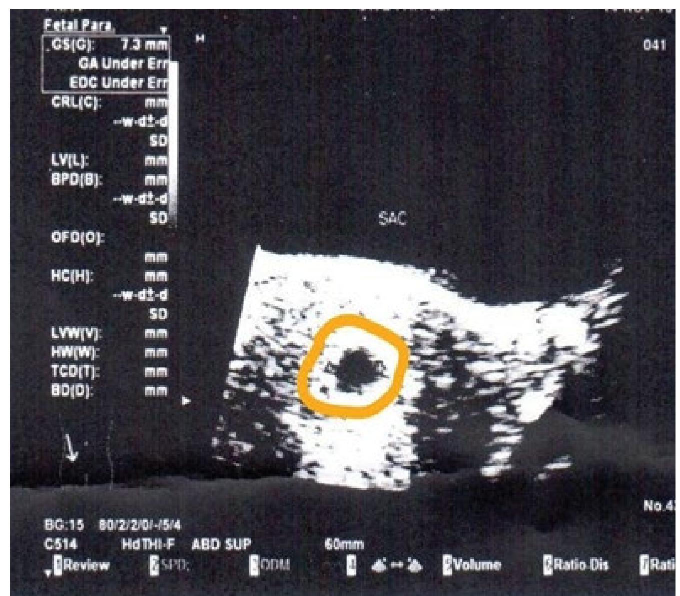

Figure 1: Final Transabdominal Ultrasound at 8 weeks (Nov 14, 2016) shows gestational sac 7.3 mm with no fetus.

Evaluation

Diagnosis is made by clinical signs & symptoms, pregnancy test and confirmed by ultrasound exam.

1) The *Clinical Signs and Symptoms* are: Abdominal cramps, vaginal spotting or bleeding and a period that is heavier than usual.

2) *Pregnancy test* can be done using Urine or Serum. There is an increase in serum and Urine hCG. And the indicator of the pregnancy test kit shows a weak positive (usually a pink color instead of red).

3) An *Ultrasound exam* transabdominal or transvaginal showing an empty sac with no embryo confirms the diagnosis of Blighted Ovum. The criteria of the Ultrasound for diagnosis is as follows: According to Campion et al. [9], "A pregnancy is anembryonic if a transvaginal ultrasound reveals a sac with a mean gestational sac diameter (MGD) greater than 25 mm and no yolk sac, or an MGD >25 mm with no embryo. Transabdominal imaging without transvaginal scanning may be sufficient for diagnosing early pregnancy failure when an embryo whose crown–rump length is 15 mm or more has no visible cardiac activity". [5]

There are other diagnostic criteria for confirming with an Ultrasound. "According to the Encyclopedia of Medical Imaging, the criteria for a diagnosis of blighted ovum are:

1) Failure to identify an embryo in a gestational sac measuring at least 20 mm via transabdominal ultrasound.

2) Failure to identify an embryo in a gestational sac measuring approximately 18mm or more via transvaginal ultrasound.

3) Failure to identify a yolk sac in a gestational sac measuring 13mm or more".

In the UK, the Royal College of Obstetricians and Gynecologists recommends doctors to use the new guidelines to diagnose a blighted ovum, which is to monitor a growing gestational sac until it reaches at least 25mm.

4) Genetic Testing/Histopathology (Karyotyping of the conceptus) will show trisomies, monosomy or triploidies as discussed earlier in the etiology section.

The diagnosis codes of Blighted Ovum are shown below:

Blighted Ovum Diagnosis Code

ICD-10 O0.20

ICD-9-CM 631

Prevention

Although there is no prevention for blighted ovum cases (most often it is a onetime occurrence), steps can be taken to increase the chance of successful pregnancy based on its multifactorial etiology.

a) Fertility Diets

Since Blighted Ovum has multifactorial etiology, the overall health, and wellbeing of the patient should be considered. To conceive one of the things emphasized by an Obstetrics and Gynecologist is having a well-balanced diet (consume food for both mother and baby) with all the necessary and recommended daily intake of nutrients and maintaining a healthy weight, is necessary. The diet must be rich in all recommended elements (example Copper, Folic Acid, Iron etc.) required for the development of the fetus. In countries like India, where Hindus eat usually vegetarian diet lacks sufficient iron. This is found in meats, eggs, etc.

The Serbian/Hungarian Goulash is a meat and vegetable soup or stew. The meat is usually ram, goat, stallion or beef's reproductive organs (testis). Goulash (pronounced as Guyash and written as Gulyas) is a national dish of Hungary since Medieval Times. There is World Testicle Cooking Championship held in Serbia annually. The championship is always held on the first weekend after August 28th and lasts for three days. Goulash festivals in Serbia/Hungary where cooks make some of the finest Goulash and serve them to judges and attendees of the festivals. The tastiest Goulash is awarded a prize. Goulash is considered an aphrodisiac and a dish that might enhance fertility. In a woman with a low BMI, such diets rich in Iron and other elements might increase the chance of conception.

b) Medicines

There are herbal medicines (alternatives to Viagra and Cialis) used by different cultures for conceiving, enhancing fertility. In India, some Ayurvedic medicines include Speman for men, Evecare and Shatavari for women manufactured by Himalaya drug company. Speman enhances sperm motility and increases the chance of conception in women.

Then there is Mandrakes mentioned in the Bible, ("In the days of wheat harvest Reuben went and found **mandrakes** in the field and brought them to his mother Leah. Then **Rachel** said to Leah, "Please give me some of your son's **mandrakes**." **Genesis 30:14**) which Rachel asked from Leah her sister.

Rachel consumed the Mandrakes, however after several years of prayer to God she conceived and had Joseph. Jesus was a descendant of Joseph. Some people (Jews and others) wear the Red string Kabbalah Bracelet and recite Rachel's Prayer, "Ana Bekoach" in Hebrew for protection from God against evil, others to find their soul mates (it is believed that when God shows the person wearing this red string bracelet their would be soul mate/spouse, it breaks) and other women for fertility purpose. The lead author (who is of Ashkenazi Jewish Ancestry maternal grandmother's family) also wears it and recites the prayers for God's Protection against Evil. There is all kind of folklore about Mandrakes out there. It is not easy to pluck the roots of a Mandrake. If one does try to pluck the roots of the mandrake, there is an ear-piercing scream from the plant and whoever tries to pluck it, dies. So, some people use a hungry dog and tie its leash on the roots of the plant and show the dog food. Then make it run and this way the plant is uprooted, in the process dog dies and the owner gets the plant in its entirety. The Mandrake roots resemble a human being, both males and females have been found and some people consider them as hanged men and women (people who committed suicide).

It is interesting to note here the recycling of souls or rebirth of a soul from a plant- Mandrake (which were before men and women who were hung or hung themselves). This is another topic/concept/theory- Gene recycling, Hindu's reincarnation, Catholic's purification of souls in Purgatory as described in Pistis Sophia, and their rebirth. (Life is Sacred even if it is an embryo and the Prolife Movement ideology against abortion) etc. These topics are not in the capacity of this lecture/presentation.

According to some Jewish scholars [10] *(TorahTots.com), if a woman who does not have a child swallows the powder of a ruby, she will bear children. Ruby is the gemstone of the Reuben tribe (one of the twelve tribes of Israel) and is one of the gemstones on the breast plate of the High Priests.*

At present there is a pharmaceutical company located in Hawaii (Hawaii Pharma.com), USA that manufactures products from the Mandrake roots. It is exported from Morocco and marketed as tinctures which they are selling for general well-being and for different ailments including male fertility problems. However, there are no mandrake products for female infertility problems under women's health, only other plants as an aphrodisiac.

c) Genetic Testing & Counseling. Genetic testing (Karyotype) and counseling is recommended if recurrent miscarriage is there in the couple's history. As mentioned earlier in the etiology section, recurrent miscarriage due to Blighted ovum was significantly higher (68.5% vs 31.5%) in consanguineous marriages according to the study (*Chromosomal Study of Couples with the History of Recurrent Spontaneous Abortions with Diagnosed Blighted Ovum*) by Shekoohi et al. [4] done in Iran. Therefore, couples need to be aware of this at the time of marriage and send to a genetic counselor when planning to start a family.

d) Religious Belief. Some couples are hesitant to do a D & C as per the Ob & Gyn/Doctors recommendation. There are several cases when the couple is told that they are going to miscarry, however they wait it out through prayer and meditation and when an ultrasound is done again after some time, they find the embryo in the sac. Some cases have been reported from the UK at misdiagnosedmiscarriage.com as error in diagnosis. Another case was shown on an Indian Religious Channel- Surya TV.

e) Guidelines: As per the Royal College of Obstetrics and Gynecologist new guidelines, monitor until gestation sac is at least 25 mm on Ultrasound (i.e. Wait 1 week more if no complications or symptoms of miscarriage) so that viable pregnancies are not misdiagnosed as miscarriages.

f) Recommendation: Doctors most often recommend couples to wait 1-3 regular menstrual cycles before trying to conceive again after any type of miscarriage (americanpregnancy.org).

Treatment/Management

Treatment/Management of Blighted Ovum consists of the following ways:

a) Expectant Management. Wait to have the tissues pass away on its own if there is spotting or wait another week (9 weeks) to see if there is any sign of the fetus in the gestational sac

b) Medical Treatment consisting of Misoprostol on an outpatient basis is another option. However, it may take several days for the body to expel all tissue, may have more bleeding and side effects. The recommended dose of Misoprostol is per the International Federation of Gynecology and Obstetrics (FIGO), 2017 guidelines as published in

the article by Morris et al. [11].

c) Surgical Treatment is Dilation and Curettage (D & C) as per the national or international guidelines. This procedure involves dilating the cervix and removal of the contents of the uterus [12-15]. The pathologist can examine the tissues to confirm the reason for the miscarriage. Since the procedure immediately removes the tissue, it brings mental & physical closure soon.

Health Policy Implications

According to Chauhan et al (2010), recommendations of the common obstetric guidelines by ACOG and RCOG on different topics were not comparable, majority of the time. In the UK, the Royal College of Obstetricians and Gynecologists (RCOG) as per the new guidelines, recommends that Physicians monitor a growing gestational sac until it reaches at least 25mm (this would be about 9 weeks into pregnancy) before diagnosing a blighted ovum (*an empty gestational sac with no fetal pole or yolk sac*). Therefore, one can be misdiagnosed with having a Blighted Ovum if diagnosed at eight weeks or sooner [16-20].

Many women who have a tilted uterus look one to two weeks behind and can be misdiagnosed as having a blighted ovum, so wait until at least 9 weeks (if no complications) when most women see the baby.

The expertise of different Ultrasound technicians (positioning of the woman especially with a tilted uterus) in the same day can affect the ultrasound measurements. These measurements can be off 4 mm or 5 mm which can result in misdiagnosis.

Hence, the different definitions of miscarriages, diagnosis of blighted ovum have psychological, societal and legal implications.

With regards to ethnic practices, is Ruby gemstone powder, mandrakes and other fertility enhancing herbal medications, diets or products used by women who do not have children to conceive today? Are traditional medical practices (Ayurveda, etc.) and religious ethnic practices by women/a couple better than current day In-Vitro Fertilization (IVF) which has ethical, biological and societal issues? If so, such ethnic medical practices need to be discussed by the patient with their primary care provider and providers in turn ask their patients on such practices during history taking.

Therefore, health policies/laws on definitions of miscarriages, diagnosis of blighted ovum, termination of pregnancy and promotion of awareness on blighted ovum/recurrent pregnancy loss need to be developed carefully, taking these recommendations and international/ethnic practices into consideration.

Disclosures

I have no financial relationships to disclose. This project was self-funded by the lead presenter with no travel grants or scholarships.

The views expressed in this article are solely that of the author (s), please consult your healthcare provider/Doctor/Ob & Gyn before trying any new diet or taking any medicines.

The Blighted Ovum Case Report discussed here is with permission from the patient (written/signed informed consent form).

This paper/abstract, "To Goulash or Not to Goulash? A Case Study on Blighted Ovum" was presented online at the 6th International Conference of Clinical and Medical Case Reports, October 16-18, 2017, San Francisco, CA as an e-Poster.

Questions/Quiz

1) What is the most common cause of Blighted Ovum?

a) Genetics – Trisomy 16

b) Infections

c) Consanguineous marriage

d) Anomalies of the Uterus

2) A Blighted Ovum causes

a) 70% of miscarriages in the first trimester of pregnancy

b) 40% of miscarriages in the second trimester of pregnancy

c) 50% of miscarriages in the first trimester of pregnancy

d) 60% of miscarriages in the second trimester of pregnancy

3) What does this Ultrasound show?

a) Hydatidiform Mole

b) Blighted Ovum

c) Tumor in the Uterus

d) Endometriosis

4) Which of these statements are correct?

The criteria for Ultrasound diagnosis of Blighted Ovum is as follows:

a) According to Campion et al [9], "A pregnancy is anembryonic if a transvaginal ultrasound reveals a sac with a mean gestational sac diameter (MGD) greater than 25 mm and no yolk sac, or an MGD >25 mm with no embryo.

b) Transabdominal imaging without transvaginal scanning may be sufficient for diagnosing early pregnancy failure when an embryo whose crown–rump length is 15 mm or more has no visible cardiac activity".

c) There are other diagnostic criteria for confirming with an Ultrasound. "According to the Encyclopedia of Medical Imaging, the criteria for a diagnosis of blighted ovum are:

1) Failure to identify an embryo in a gestational sac measuring at least 20 mm via transabdominal ultrasound.

2) Failure to identify an embryo in a gestational sac measuring approximately 18mm or more via transvaginal ultrasound.

3) Failure to identify a yolk sac in a gestational sac measuring 13mm or more.

d) In the UK, the Royal College of Obstetricians and Gynecologists recommends doctors to use the new guidelines to diagnose a blighted ovum, which is to monitor a growing gestational sac until it reaches at least 25mm.

e) All of the Above

Answers 1 a) 2 c) 3) b) 4) e

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