Introduction

Threatened spontaneous abortion is the diagnosis of a live fetus of less than 20 weeks' gestation in the presence of a history of vaginal bleeding and a closed cervix; it is the most common complication of ongoing early prgnancy, with an incidence of 14–20% ***(Hasan, 2009)***. After 6weeks of gestation, threatened spontaneous abortion is associated with around a 10% risk of subsequent complete spontaneous abortion. Threatened spontaneous abortion has also been associated with long-term adverse pregnancy outcomes, such as preterm delivery, placental abruption, intrauterine growth restriction and low birth weight ***(Johns and Jauniaux, 2006)***.

Intrauterine bleeding with or without the formation of a sub chorionic hematoma in threatened spontaneous abortion may disrupt placentation and can lead to a chronic inflammatory reaction and oxidative stress damage within the decidua, the fetal membranes, or both**.** It has been suggested that this may alter the biological function of the villous trophoblast, and therefore the placental synthesis of proteins, but also the levels of circulating inflammatory molecules

such as cytokine ***(Calleja-Agius et al., 2011; Hannan et al., 2014)***.

C-reactive protein (CRP) is the most prominent serum marker of the "acute phase response"; the formation of various plasma proteins by the liver in response to an inflammatory stimulus in humans. The role of CRP in the inflammatory process, although not well defined, may involve modulation through binding to inflammatory mediators such as platelet activating factor or complement inhibitory factor H **(*Kumru et al., 2006).***

Although CRP concentrations may increase many folds in the acute phase response, with de novo hepatic synthesis starting very rapidly, serum concentrations beginning to rise by about 6 hours, and peaking around 48 hours after a single stimulus ***(A. J. Szalai 2011)***.

There is considerable evidence that CRP is present at low concentrations in asymptomatic individuals and may reflect baseline activity of circulating cytokines .The determination of CRP concentrations in healthy individuals by high sensitivity assay (HS-CRP) has only recently become available HSCRP is a protein measured by either antibodies that are labeled with an enzyme (ELISA) or a fluorescence

compound or polystyrene beads coated antibodies or by latex agglutination slide test. It has been reported that in atherosclerotic cases increased levels of plasma (CRP) are associated with obesity ***(Yan Bao et al., 2015)***.

High-sensitivity c-reactive protein (HSCRP) is now routinely used in cardiovascular disease risk stratification and management. Recent studies have also reported a possible role for HSCRP in the first-trimester screening of pre-eclampsia in predicting long-term cardiovascular risks in women who have hypertensive disorders late in pregnancy ***(Hermes et al., 2013)***.

Other studies revealed that elevated CRP concentrations in early pregnancy are associated with an increased risk of preterm delivery, particularly nearly 3-fold increased risk of medically indicated preterm delivery ***(Jauniaux E, Gulbis B et al., 2015)***.

Aim of the Work

This study aims to assess the accuracy of serum High-sensitivity C – reactive protein (HSCRP) in predicting pregnancy outcome in women presenting with threatened abortion in first trimester.

Research Question:

In women with threatened abortion does serum HSCRP level predict occurrence of miscarriage accurately?

Research hypothesis:

In pregnant women with threatened abortion in the first trimester HSCRP serum level may predict occurrence of miscarriage.

Chapter (1)
Miscarriage

A miscarriage is a pregnancy loss that occurs before 20 weeks, well before the fetus is able to survive outside the uterus. About 10 to 15 percent of recognized pregnancies end this way ***(Hassan et Al., 2009)***. As many as 40 percent of all pregnancies may end in miscarriage, because many losses occur before a woman realizes she is pregnant ***(American College of Obstetricians and Gynecologists (ACOG), 2008).***

Defining pregnancy as beginning at time of implantation, pregnancy wastage can take place at any time after implantation of the blastocyst. **First**, fetal loss may occur after the time of expected viability for reasons of preterm labor, fetal anomalies, and intrauterine or neonatal death. **Second,** spontaneous abortion may occur usually within the first trimester. **Third**, pregnancy loss may occur before or at about the time of the next anticipated menstruation, in such cases the pregnancy is not clinically recognized ***(Cunningham et al., 2010).***

First-trimester bleeding is one of the most common obstetric complications, occurring in 25% of all pregnancies .In about 50% of these patients a non–viable pregnancy is immediately diagnosed with sonography. In the remaining cases, cardiac activity in the conceptus is demonstrated. Although this finding is apparently reassuring, a considerable proportion of these pregnancies will eventually result in miscarriage (about 15%). Ultrasound evaluation of these pregnancies is the mainstay of the examination. ***(Milli et al., 2008)***

Physiological and embryological background

Maternal physiology and embryo development:

During the follicular phase of the cycle. Initially, under the influence of FSH and basal LH, mature ovarian follicle develops. Estrogen elaborated by the follicle causes the functional layer of endometrium to proliferate and become thicker as the spiral arteries elongate and the uterine glands increase in number and length ***(Halvorson, 2012)***.

Ovulation occurs as a result of an abrupt surge in LH, and an oocyte is extruded, typically on day 14 of the cycle. After ovulation, the follicle collapses and transforms into the glandular corpus luteum, which produces progesterone and a

small amount of estrogen. This hormonal activity is responsible for additional histologic changes of the endometrium as it enters the secretory phase. ***(Moore et al., 2007)***

Fertilization most often occurs within 1 day of ovulation (day 15 of the 28 day cycle), typically in the ampulla, the longest and widest portion of the fallopian tube, with subsequent development of the morula, blastocyst, and bilaminar and ultimately trilaminar, or flat, embryo. Over the next 2 days, the cell mass transgresses the tube while dividing repeatedly to form a solid ball of 12 or more cells, the morula. ***(Callen, 2008)***

As the morula enters the uterine cavity on day 18 or 19 of the cycle, endometrial fluid collect in between the cell mass to create a central cavity. When this occurs, the morula is transformed into a blastocyst and its tissue is divided into two important layers. The outer cell layer, or trophoblast, will ultimately create the chorionic membranes and the fetal contribution to the placenta. **The inner cell layer** will develop into the embryo, amnion, umbilical cord, and the primary and secondary yolk sacs. By the end of the 3rd week, the blastocyst begins to implant into the decidualized endometrium, a term

applied to the functional layer of the thickened and edomatous gravid endometrium. ***(Moore et al., 2007)***

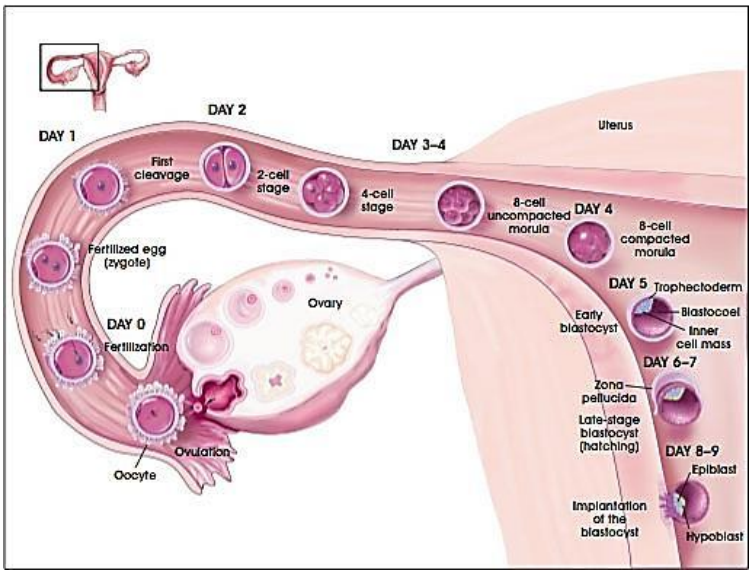

Figure (1): Diagram demonstrating the sequence of ovulation, fertilization, and early development of the embryo ***(www.activisionlife. com)*** 18-4-2010

During the 4th week, the blastocyst, measuring only 1 mm in diameter, it is a time of rapid cell proliferation and differentiation, affecting multiple primordial structures. The primary yolk sac shrinks and disappears gradually while the secondary yolk sac forms. The latter structure plays a critical role by providing nutrients for the embryo. ***(Moore et al., 2007)***

A tiny bilaminar embryo also forms between the secondary yolk sac and developing amnion, and a primitive

uteroplacental circulation is established. By the end of the 4th week the gestational sac has attained a diameter of 2 to 3 mm and is at the threshold of detection by the transvaginal ultrasound transducers. In addition, the pregnancy test becomes positive because a measurable quantity of human chorionic gonadotropin (hCG) is produced by trophoblastic tissue. ***(Moore et al., 2007)***

Weeks 6 through 10 constitute the embryonic stage, during which time all major internal and external structures begin to form. Although most organ function remains minimal, the cardiovascular system develops rapidly, and the primordial heart starts to beat at the beginning of the 6th week. During embryogenesis, crown rump length (CRL) grows rapidly, measuring 30 mm by the end of the 10th week**.** ***(Moore, 2007)***

The final 2 weeks of the first trimester (11th and 12th weeks GA) are known as the fetal period, during which there is continued rapid growth and ongoing organ development. During the initial phase of fetal development, the head is disproportionately large and constitutes one half of the CRL and the body growth subsequently accelerates. ***(Moore, 2007)***

Pathophysiology of miscarriage:

The pathophysiology is unclear. Vaginal bleeding originates from the decidual implantation site or from the placenta. The onset of bleeding may follow or precede fetal demise. Immunogenic, hypoxic, and vascular causes lead to a final common pathway of severe villous or placental dysfunction resulting in embryonic or fetal demise. A possible hypothesis is that local bleeding of variable severity accompanies all miscarriages but its persistence is revealed, concealed, or followed by fetal demise. This hypothesis is consistent with findings of abnormal vascular development at the maternal-embryonic interface. ***(Callens et al., 2008)***

Local dysfunction of implantation-modulating factors as well as systemic abnormalities has also been demonstrated**.** The 2 major directions of current research appear to be the assessment of natural killer cell activity and impaired decidualization. ***(Carrington et al., 2005)***

Etiological factors of miscarriage:

More than 80 percent of abortions occur in the first 12 weeks of pregnancy and at least half result from chromosomal anomalies. After the first trimester, both the abortion rate and the incidence of chromosomal anomalies decrease. ***(Cunningham et al., 2010)***

Embryonic factors:

The majority of first-trimester miscarriages (6 to 12 weeks) are attributable to primary embryonic disease, disorder, or damage ***(Silver, 2011)***. Up to 80% of early pregnancy tissue from first-trimester; miscarriages is chromosomally abnormal **.**A study found that miscarriage appeared to be twice as likely in couples who had a first-degree female relative that had experienced spontaneous miscarriage compared with couples who had a third-degree female relative that had experienced spontaneous miscarriage. Therefore, positive family history for spontaneous miscarriage may be a causal factor for recurrent spontaneous miscarriage; however, further studies are required. ***(Moore et al., 2007)***

A. Abnormal Zygotic Development

Early: spontaneous abortions commonly display a developmental abnormality of the zygote, embryo, early fetus, or at times the placenta. Of 1,000 spontaneous abortions analyzed by ***Hertig and -Sheldon (2000)***. In 50 to 60 % spontaneously aborted embryos and early fetuses, abnormalities in chromosomal numbers account for most wastage ***(Cunningham et al., 2010).***

B. Aneuploid Abortion

Over 90% of chromosomal abnormalities observed among abortions are numerical (aneuploidy, polyploidy) abnormalities as a result of errors occurring during gametogenesis, during fertilization or during the first division of the fertilized ovum, the reminder are split between structural abnormalities (translocation, inversion) & mosaicism. ***(Merel et al., 2012)***

1. Autosomal trisomy

It is the most frequently identified chromosomal anomaly with first-trimester miscarriages although most trisomies result from isolated nondisjunction, balanced structural chromosomal rearrangements are present in one

partner in 2 to 4 percent of couples with recurrent miscarriage ***(American College of Obstetricians and Gynecologistsl, 2008).***

2. MonosomyX (45, X)

It is the single most common specific chromosomal abnormality, this cause Turner syndrome, which usually results in abortion and much less frequently in live-born females. Conversely, autosomal monosomy is rare and incompatible with life, and considered to be responsible for preclinical abortions ***(Cunningham et al., 2010).***

3. Triploidy

Is often associated with hydropic placental degeneration, Incomplete hydatidiform moles may be triploid or trisomic for only chromosome 16 ***(Cunningham et al., 2010).***

4. Tetraploidy

Abortuses are rarely live born and are most often aborted early in gestation ***(Cunningham et al., 2010).***

5. Chromosomal structural abnormalities

Identified only since the development of banding techniques, infrequently cause abortion. ***(Cunningham et al., 2010)***

C. Euploid Abortion

Chromosomally normal fetuses tend to abort later in gestation than in those with aneuploidy. For example, although 75 percent of aneuploid abortions occurred before 8 weeks, euploid abortions peaked at about 13 weeks. ***(Kajii, 2011)***

Maternal factors:

Many second-trimester miscarriages (13 to 22 weeks) are due to maternal genital tract dysfunction or systemic illness. It has been suggested that the overwhelming majority of cases are associated with ascending infection from the lower genital tract. ***(Hawkins, 2015)***

Maternal exposure to high doses of toxic agents, irradiation or chemotherapy, major endocrinopathies, immunological diseases, and transplacental infections have all been implicated. Asymptomatic bacterial vaginosis may have an important role in second-trimester miscarriage**.** Large submucous fibroids compromise early embryonic angiogenesis

and microhemodynamics. The anti-phospholipid antibody syndrome may underlie both first- and second-trimester recurrent miscarriage. The-Antiphospholipid Syndrome, Cervical incompetence, insufficiency, or weakness account for most recurrent second-trimester miscarriages. Previous consecutive pregnancies might have been delivered prematurely ***(American Collegeof Obstetricians and Gynecologists, 2008).***

Using a predictive model incorporating nuchal trans-luscencies, pregnancy-associated plasma protein A, and maternal characteristics in singleton pregnancies between 11 and 14 weeks (comparing 2396 women who had chorionic villus sampling to 33,856 who did not, at the same gestational age), the risk of miscarriage was increased in pregnancies resulting from ovulation induction, fetuses with high nuchal translucency, and in women with pre-existing diabetes mellitus ***(Centers for Disease Control and Prevention, 2013)***.

Clinical classification of spontaneous abortion:

1- Threatened miscarriage:

Threatened miscarriage is a diagnosis that is made during the first 20 weeks of pregnancy. While some women