INTRODUCTION

Recurrent spontaneous abortion (RSA) is defined as women with a history of three or more consecutive abortion up to twenty two gestational weeks ***(Zaki and Goda, 2007).***

Parvovirus B19 is a single stranded DNA – virus that was discovered in the mid – 1970 by Yvonne Crossart, medical virologist, screening blood donors for hepatitis ***(Young et al., 2004).***

During electrophoresis, an abnormal band was noted in sample number 19, panel B. Therefore, the virus was named" B19", and subsequently identified as a parvovirus. Parvoviruses are the smallest DNA – containing viruses that infect mammalian cells. Parvovirus B19 infection, an acute self-limiting disease also known as the fifth disease or erythema infectiosum, commonly occurs in primary school-aged children. The typical rash ('slappedcheek' appearance) is immune mediated, since it coincides with the appearance of IgM and IgG specific antibodies. The IgM antibody response peaks 28 days after exposure to parvovirus B19. This is followed by a rapid decline of specific IgM over 2 – 3 months to non – detectable levels. Antiparvovirus B19 IgG usually persists for life ***(Young et al., 2004).***

The clinical presentation of parvovirus B19 infection in seronegative adults is usually silent or mild with variable

non – specific symptoms. Gratacos et al. reported symptoms of low – grade fever, non – specific rash or arthralgias in only 30% of women who seroconverted during pregnancy ***(Gratacos et al., 1995).***

The virus is particularly threatening to the fetus since it has a unique affinity for the a cellular receptor (p – antigen) in fetal erythroid precursor cells in fetal liver ***(O'Malley et al., 2003)***.

Infection of erythroid lineage cells by parvovirus B19 is characterized by a gradual cytotoxic effect, which leads to cell death (apoptosis). The p – antigen is present not only on erythroid lineage cells, but also on megakaryocytes, endothelial cells, synovium, cardiac myocytes and villous trophoblast cells ***(Yaegashi et al., 2000).***

Parvovirus B19 infection in the fetus results in anemia due to hemolysis and transient aplastic crisis. Fetal anemia is primarily responsible for the development of heart faiure, skin edema and effusions ***(Chisaka et al., 2003).***

Sonographic features of fetal parvovirus B19 infection during the second trimester of pregnancy include increased skin edema, increased cardiac biventricular diameter, pericardial and pleural effusions, ascites, bilateral hydroceles and amniotic fluid volume disorders ***(Von Kaisenberg et al., 2001).***

Measurement of peak flow velocity in the middle cerebral artery is a potentially useful diagnostic tool for the detection of fetal anemia ***(Delle Chiaie et al., 2001).***

Reversed flow in the ductus venosus is a sonographic marker of fetal heart failure ***(Mari et al., 2000)***.

Parvovirus B19 is linked to both late abortion and stillbirth ***(Lazzarotto et al., 2000).***

Parvovirus B19 infections are associated with different clinical manifestaions that vary from asymptomatic to severe symptoms. The main clinical manifestations are erythema infectiosum, transient aplastic crisis in individuals with hemo-globinopathies, chronic anemia in the immuno-compromised patients, spontaneous abortion and stillbirth ***(Corcoran et al., 2004).***

Post-exposure prophylaxis with immunoglobulins in pregnancy is presently not recommended; however, pre-exposure prophylaxis has been proven to beneficial in patients with chronic Parvovirus infection and in nosocomial outbreaks in hospitals. Antiviral drugs are not available for treatment and a parvovirus B19 vaccine is presently not licensed for use ***(Ballou et al., 2003)***.

It is now evident from all the available information that approximately 94% of parvovirus B19–affected pregnancies have a normal outcome, that the risk of fetal

damage is low and no malformations were observed, and that in case of moderate to severe fetal anemia intrauterine transfusion (s) reduse the risk of fetal death. Therefore a pregnancy dose not need to be terminated when B19 infection occurs ***(Ballou et al., 2003).***

Parvovirus B19 viremia was positive in 48% RSA, herpes simplex virus 2 was positive in 32% RSA ***(Arch et al., 2007).***

Another virus that could be implicated in recurrent abortion is herpes simplex. There are two closely related viral types, Herpes simplex type 1 (HSV–1) and Herpes simplex type 2 (HSV–2), which are genetically different. Genital herpes is result of infection by HSV–2 and to a lesser extent HSV-1 .The number of women who acquire HSV 1 or HSV2 infection during pregnancy has been calculated about 0,5 -2% ***(Brown et al., 2003).***

Recently there has been a rise in the prevalence of genital HSV infections in both industrialized and developing countries. The main factors attributed to the spread of HSV include asymptomatic virus shedding and underrecogniton and underdiagnosis of the disease. At the level of individual patient, genital herpes is associated with significant psychological morbidity and complications such as neonatal herpes, that result from transmission of HSV from mother to baby ***(Cusini et al., 2001).***

The incidence of asymptomatic cervical HSV2 infections was considerably higher in patients with a history of spontaneous abortion with a possible etiologic connection between HSV and spontaneous abortion ***(Bujko et al., 1998)***.

Primary HSV infections in pregnant women can result in more severe diseases than in non - pregnant ones. In particular, gingivostomatitis and vulvovaginitis herpetica tend towards dissemination. As a result, women can develop disseminated skin lesions associated with visceral involvement such as hepatitis, encephalitis, thrombocytopenia, leucopenia and coagulopathy ***(Young et al., 1996).***

Although disseminated HSV infection is uncommon in pregnancy, the mortality is about 50%. In particular, pregnant women with primary mucous membrane infection during the third trimester have an increased risk for dissemination ***(Peacock et al., 1983)***.

The most important HSV infection during pregnancy is the primary genital HSV infection, since it can cause the most severe neonatal diseases. However, a first manifestation of genital herpes during pregnancy is in most cases not a primary infection ***(Hensleigh et al., 1997).***

Intrauterine HSV is a rare disorder and accounts for 5% of HSV infections in neonates. The highest risk of

intrauterine infection with about 50% has been observed in pregnant women who develop disseminated HSV infections. Among HSV infections acquired in utero, 90% of those with an identified type are due to HSV – 2 ***(Overall et al., 1994).***

Both primary and recurrent maternal infection can result in congenital disease, even so the risk after recurrent infection must be regarded as smaller. The danger to intrauterine viral transmission is highest during the first 20 weeks of gestation leading to abortion, stillbirth and congenital anomalies. Prenatal diagnosis is not recommended because the fetus is rarely transplacentally infected until mid-gestation. Termination of pregnancy in women with disseminated disease is not an option ***(Hutto et al., 1987).***

Acyclovir or its derivatives are the mainstay of anti-viral therapy for both topical and systemic application. Although this drug is not licensed for use in pregnancy, no association has so far been identified between its use in pregnancy and adverse effects in mother or child ***(Kroon and Whitley, 1995).***

In maternal primary disseminated infection, early intravenous treatment with acyclovir (iv 10 mg /kg every 8 h for 10-14 days) at any stage of pregnancy is recommended. Oral treatment with acyclovir (400 mg three times daily for 14 days) is considered beneficial for women

with recognized primary or non-primary first- episode genital infection in the later stages of pregnancy. This is also the case in maternal primary oral infection (e.g. gingivostomatitis) shortly before term or at delivery ***(Haddad et al., 1993)***.

Demographic, medical and clinical data were collected in each case based on personal interviews and medical records.

AIM OF THE WORK

The aim of this work is the assessment of the prevalenace of ParvovirusB19 and herpes Simplex virus 2 in patients with history of second trimesteric recurrent abortion

HABITUAL ABORTION

Definition:

Recurrent miscarriage or habitual abortion (also called recurrent abortion, recurrent spontaneous abortion) is usually defined as three or more losses in a row ***(Zaki and Goda, 2007).***

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Incidence:

About 15% of couples lose one recognized pregnancy, and 2% lose two. The theoretical risk of three or more losses is only 0.5 %. The risk of fetal loss increases steeply after the age of 35 years, rising from 9% at 20–24 years to 75% at 45 years and older ***(Nybo Andersen et al., 2000)***. The chance of a successful pregnancy in women aged 40 years or more is poor, with risks of miscarriage, ectopic pregnancy, or stillbirth becoming much higher than in women in their 30s ***(Nybo Andersen et al., 2000).***

Classification:

Losses are classified as:

1- Pre-embryonic<5 weeks

2- Embryonic 5-10 weeks

3- Fetal >10 weeks

(Porter and Scott, 2005)

Causes:

Chromosomal Abnormalities

Chromosomal abnormalities account for more than half of recurrent pregnancy losses. Most of the losses are in the first trimester; about 2% to 5% of all fertilized ova contain chromosomal abnormalities at conception, but this number falls to fewer than 1% in fetuses at term ***(Alberman, 1988; Carr, 1972)***.

Aneuploidy

Aneuploidy means having a different number of chromosomes than the 46 found in the normal (euploid) cell.

Trisomy (having one additional whole or partial chromosome) accounts for 52% of all pregnancy losses due to chromosomal abnormalities. About 16% of losses due to chromosomal abnormalities are due to trisomy 16; trisomy 13, 18, and 21 account for 9% and are found in 0.1% of live births, with trisomy 21 being the most common ***(Simpson, 1986)*.**

Monosomy (having only one chromosome of a normally diploid pair) accounts for 18% of pregnancy losses due to chromosomal abnormalities; 98% of these losses are in the first trimester. The 45,X genetic pattern is the most common genetic cause of recurrent pregnancy

loss; nevertheless, this pattern is present in up to 7 of 10,000 live births.

Triploidy (having three complete haploid sets of chromosomes instead of two, for a total of 69 chromosomes) accounts for 17% of pregnancy losses due to chromosomal abnormalities.

Mosaicism is more than one chromosomal pattern in a single person. The most common mosaic abnormality is 45,X/46,XX.

Translocation

In 6% to 7% of cases of recurrent pregnancy loss, one or both parents carry a chromosomal translocation. Of these, 35% are robertsonian translocations (the fusing of the two long arms of paired chromosomes into a single chromosome, usually followed by the loss of the short arms), and 65% are reciprocal translocations (reciprocal exchange of segments between nonhomologous chromosomes with no gain or loss of genetic material) ***(Campana et al., 1986)*.**

Many translocations involve chromosomes 13, 14, 15, 21, and 22 ***(Alberman, 1988; Carr, 1972).***

More women than men carry translocations, because many affected men are sterile ***(Chandley et al., 1972).*** If a man carries a translocation, the chance of passing it on to

an offspring is 2% to 5%; a woman has a 10% to 20% chance of passing on a translocation she carries ***(Campana et al., 1986; Tharapel et al., 1985).***

If a parent has a balanced translocation, the risk of an unbalanced translocation occurring in the fetus is about 4%.

Evidence is mixed as to whether chromosomal abnormalities tend to recur in subsequent pregnancies. Hassold studied 40 couples and found a 70% recurrence risk with a prior aneuploid pregnancy vs 20% with a prior euploid pregnancy ***(Hassold, 1980). Warburton et al.*** found no increased risk of chromosomal abnormalities in subsequent pregnancies after spontaneous abortions if the fetus carried an aneuploidy that is always lethal in utero or if the parents had normal chromosomes ***(Warburton et al., 1987).***

Carriers of a translocation in chromosome 22 almost always miscarry; a woman with a translocation involving breaks in chromosome 13 or 14 has a 25% risk of spontaneous abortion.

Parity and older maternal age. Rates of pregnancy loss are higher in women who have had more children, possibly because these women tend to be older: the risk rises with maternal age, whether or not the fetus is normal. In older women, oocytes tend to have more chromosomal abnormalities and the endometrium is less receptive.

Treatment of genetic problems

Selected couples who have lost pregnancies because of aneuploidy can undergo in vitro fertilization. The blastocysts are examined, and they are implanted only if they are chromosomally normal ***(Pellicer et al., 1999).***

Uterine abnormalities

From 10% to 15% of women who have lost multiple pregnancies have uterine anomalies such as a partial or complete septum ***(Hill, 1999; Rock and Murphy, 1986).***

These anomalies can cause fetal loss in all trimesters ***(Hammond, 1980)*** via poor implantation because of abnormal vascularization of the septum ***(Homer Li and Cooke, 2000)***, uterine distention (possibly resulting in cervical incompetence), abnormal placentation, an abnormal lower uterine segment and cervix, or an increase in uterine contractility resulting in preterm birth or pregnancy loss.

Congenital müllerian abnormalities

The paired müllerian ducts develop into the fallopian tubes, uterus, cervix, and the upper two thirds of the vagina. The prevalence of congenital müllerian anomalies used to be estimated as 2% of women, but now that magnetic resonance imaging, ultrasonography, and laparoscopy are being performed more often, it is estimated to be as high as

6%. Septate uterus, resulting from failure of resorption of the septum between the two uterine horns, is associated with the greatest number of pregnancy losses, particularly if a complete septum remains ***(Homer et al., 2000; Proctor and Haney, 2003).***

Other anomalies include uterus didelphys (a double uterus, resulting from complete nonfusion of the müllerian ducts) and bicornuate uterus (from partial nonfusion of the müllerian ducts), but they are less likely to cause recurrent pregnancy loss ***(Proctor and Haney, 2003).***

Whereas an arcuate uterus is the most commonly identified Müllerian anomaly, its association with adverse reproductive outcome, including RPL, is uncertain. One study found an arcuate uterus in 15% of women with RPL compared to only 3% of women in the general population ***(Jurkovic et al., 1995)*** arcuate uterus have a greater proportion of second trimester loss and preterm delivery ***(Woelfer et al., 2001).***

Reproductive outcome in women with congenital uterine anomalies detected by of three-dimension ultrasound screening. Other investigator s have reported no association between arcuate uterus and RPL ***(Lin, 2004)***.

Women who have an untreated uterine septum have a fetal survival rate of only 6% to 28%, and more than 60% have recurrent pregnancy loss ***(Harger et al., 1983)***.

Treatment with transcervical uteroplasty results in a high pregnancy success rate ***(March and Israel, 1981).***

Diethylstilbestrol exposure Diethylstilbestrol (DES) was used in the United States until 1971, and women exposed to DES in utero have high rates of recurrent pregnancy loss ***(Kaufman et al., 1980).***

For many, the cause is an abnormal lower uterine segment and cervix, resulting in cervical incompetence and preterm labor and birth. This problem should become rare as women of the generation exposed to DES reach the end of their childbearing years.

Asherman syndrome (intrauterine synechiae)

The prevalence of intrauterine synechiae (adhesions) is difficult to determine. In a series of 200 patients with adhesions, 43% were sterile and 14% had recurrent pregnancy loss ***(Pabuccu et al., 1997).***

Uterine leiomyomata

Uterine fibroids are present in up to 30% of women, but their effect on reproductive outcome is controversial ***(Hart et al., 2001).***

Most studies report that implantation failure after in-vitro fertilisation is linked to either intramural or