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Exploration of Infectious causes of Miscarriage In Taif City, Saudi Arabia

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Although the etiological factors of pregnancy loss have been recognized, there have been many other factors suggested to be the possible risk factors. The aim of this study is to investigate current evidence regarding high-risk pathogens that could possibly be related to pregnancy loss. One hundred female patients with abortion were enrolled in this study and subjected to history taking, histopathological section of the placenta and blood samples obtained for complete blood count and serological detection of different infectious diseases determining antibodies by using a commercially available enzyme-linked immuno sorbent assay (ELISA). Infection was detected in only 10%, (N =10) of the cases. *Toxoplasma gondii* was detected in five cases (5%) while *Herpes simplex* in only one case (1 %). *Rubella* and *Cytomegalovirus* co-infection was detected in two cases (2%). Meanwhile *Rubella* infection and *Hepatitis B* infection were detected in 1%, each. Of the total 10 cases from 100 abortion cases included in the study had documented infection exhibited significantly associated abnormal findings in the product of conception ($p < 0.001$).

Keywords: Miscarriage, POC ,TORCH, ELISA.

INTRODUCTION

Miscarriage – the fetal loss from uterus– is the most common adverse pregnancy outcomes. In most cases the effects of a miscarriage on women health are not serious and may be unreported. However, pain and bleeding are considered the most serious associated symptoms. Feelings of loss and grief are the commonest psychological effects of miscarriage (Adams & Mac Adams,2013).

Early miscarriage is the pregnancy loss during the first trimester of pregnancy (less than 12 weeks of gestation) that occurs in up to one in five pregnancies. While late miscarriage occurs during the second trimester of pregnancy (between 12 and 24 weeks of gestation) and occurs in 1–2% of pregnancies (Al Khalili et al. 2020). A three or more successive miscarriages is known as recurrent miscarriage (Al-Ansary et al. 1995).

According to WHO, there is a yearly 40 – 60 million abortions worldwide. About 8 – 20% of women who knew they were pregnant have early abortion before 20 weeks of gestation. Studies show that 80% of abortions are early miscarriage/abortion where chromosomal abnormalities account for 50% them. Exposure to radiation is another cause of early abortion. Diseases can also lead to abortion such as uncontrolled diabetes mellitus, thyroid diseases, and some immune associated diseases (Al-Hakami et al.2020). Several etiological factors have been recognized in early pregnancy loss including uterine malformations and chromosomal aberrations such as parental balanced chromosomal rearrangements that lead to significant proportion of recurrent pregnancy losses (Al-Meshari et al. 1989).

Parents' age (35 years old or more) is one of the risk factors associated with early miscarriages due to higher

incidence of genetic and chromosomal abnormalities (Almogren, 2011).

Infections are also risk factors for miscarriages either systemic infections with malaria, *Brucella*, *Cytomegalovirus* (CMV), Human Immunodeficiency Virus (HIV), dengue fever and *Influenza* virus or local infections as bacterial vaginosis. However, some infections do not seem to adversely affect pregnancy like Q-fever, *Adenovirus*, *Bocavirus*, *Hepatitis C* virus and *Mycoplasma genitalium* infection. While, the effects of *Chlamydia trachomatis*, *Toxoplasma gondii*, *Human Papillomavirus*, *Herpes simplex* virus, *Parvovirus B19*, *Hepatitis B* virus and *Polyomavirus* (BKV) infections on pregnancy outcomes remain controversial. The global antenatal screening programs for rubella and syphilis lead to significant decrease in the frequency of their reported associations with pregnancy losses (Al-Meshari et al. 1989). although several pathogens have been associated with pregnancy loss, their exact mechanisms to induced miscarriage are still unclear. In Saudi Arabia, a study conducted in King Khalid University Hospital reported the risk factors for spontaneous pregnancy loss including older age of menarche, husband's age more than 50 years, blood-related parents, family history and previous pregnancy loss, increased consumption of daily caffeine, abdominal trauma, and fever during pregnancy (Al-Mohammad et al. 2010).

Nevertheless, to the best of our knowledge no previous study was carried out to explore potential infectious factors that could possibly be related to pregnancy loss in Taif City - Saudi Arabia. Thus, our aim was to investigate high-risk pathogens associated with pregnancy loss among females in Taif city.

MATERIALS AND METHODS

A cross-sectional descriptive study was conducted in King Faisal Medical Complex – Taif – KSA included one hundred female patients admitted in maternity hospital complaining of abortion between December 2022 and May 2023 who were eligible to be included in this study. Each patient gave a detailed clinical history including age, age of husband, parity, contact with pet animals, previous congenital malformation and pregnancy loss.

Laboratory investigations

Five millilitres of venous blood were withdrawn under sterile conditions from each participant. EDTA-whole blood was used for complete blood count (CBC) and serum was separated and stored at -20°C for subsequent serological testing of TORCH infections on Abbott Alinity® (Abbott Laboratories, USA) using *Toxoplasma gondii* IgM, IgG antibodies, Rubella IgM, IgG antibodies, CMV IgM, IgG antibodies, Herpes Simplex (HSV) I IgM, IgG antibodies and HSV-II IgM, IgG antibodies according to manufacturer's protocol.

Histopathological examination

Product of conception (POC) tissue biopsies were sent to histopathology laboratory in 10% buffered formaldehyde to be examined grossly and microscopically. Samples were routinely processed in an automatic tissue processor and embedded in paraffin wax. Three to five serial sections of four-micron thickness were cut on rotatory microtome and stained with haematoxylin and eosin (H&E). Sections were examined microscopically by qualified pathologist to detect any pathological changes and to reach the histopathological diagnosis.

Statistical analysis:

The study data were analysed with IBM SPSS Statistics version 22.0 software. Studied subjects were grouped into two groups (abortion with or without infection). Data normality was tested by Shapiro-Wilk test. The patients' data were reported as number and percentage for categorical variables or median and interquartile range (IQR) for continuous variables. The relationships between studied groups were tested by Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. All statistical tests were two-tailed. P-value < 0.05 is considered significant.

Ethical considerations

The study protocol was approved by Research Committee of King Faisal Medical Complex (H-02-T-123). Informed written consent was obtained from each patient. All the collected data are kept confidential and will not be disclosed except for the study purpose.

RESULTS

During the study period between December 2022 and May 2023, 100 female patients with median age of 32 years had a confirmed abortion. An outline of the socio-demographic, clinical, and laboratory characteristics of the studied patients is shown in Table 1. The study population was divided into two groups; patients who had abortion with documented infection and those who did not. Infection was detected in only 10 cases (10 %) (N =10). Of them, *Toxoplasma* was detected in five cases (50%) IgM one case and IgG four cases, while herpes simplex -I IgG was detected in only one case (10%). Rubella IgG and cytomegalovirus IgG co-infection was detected in two cases (20%). Rubella infection IgM and hepatitis B IgG infection was detected in 1% each. Abortion with infection was substantially more common in younger females ($p=0.008$).

All abortion cases with infection exhibited abnormal histopathological findings in the product of conception. Eighty percent of them had evidence of nonspecific chronic endometritis in their product of conception. Nonspecific chronic endometritis was characterized by the presence of chronic inflammatory cells, including lymphocytes and plasma cells, infiltrating the endometrial tissue. (Table 2). The presence of infection appeared to

be significantly associated with these aberrant histopathological findings ($p < 0.001$).

Among the 90 abortion cases included in the study without documented infection, histopathological analysis revealed that 53 cases (59%) presented with normal products of conception. However, in the remaining 37

cases (41%), various abnormal findings were observed during examination. (Table 2)

Table 1: Characteristics of studied cases

Variables		Studied Patients (N=100)	Abortion with infection (N= 10)	Abortion without infection (N= 90)	P
Sociodemographic characteristics					
Age (yrs)		32 (11)	26.5 (11)	32.5 (10)	0.008
Age of father (yrs)		40 (9)	36.5 (11.5)	40 (9)	0.084
Residence	Urban area	79 (79)	8 (80)	71 (78.9)	0.649
	Rural area	21 (21)	2 (20)	19 (21.1)	
Work status	Yes	16 (16)	0 (0)	16 (17.8)	0.160
	No	84 (84)	10 (100)	74 (82.2)	
Clinical characteristics					
Time of abortion	Early (<12 weeks)	44 (48.9)	4 (40)	48 (48)	0.562
	Late (>12 weeks)	46 (51.1)	6 (60)	52 (52)	
Congenital anomalies	Yes	10 (10)	0 (0)	10 (11.1)	0.330
	No	90 (90)	0 (0)	80 (89.9)	
Pet animals	Present	6 (6)	1 (10)	5 (5.5)	0.420
	Absent	94 (94)	9 (90)	85 (94.5)	
Gravity		4 (2)	3 (2)	4 (2)	0.084
Parity		2 (2)	1.5 (1.25)	2 (1)	0.065
Number of abortions		1 (0)	1 (0.25)	1 (0)	0.865
Laboratory characteristics					
WBC ($\times 10^3/\mu\text{l}$)		9.10 (3.81)	8.47 (3.08)	9.18 (3.93)	0.539

Data presented as median (IQR) or number (%). Mann-Whitney U-test or Fischer exact test were used respectively. P-value <0.05 is significant. WBC: white blood cell count.

Table 2: Histopathological findings in studied cases.

Histopathological findings	Studied Patients (N= 100)	Abortion with infection (N= 10)	Abortion without infection (N= 90)	Chi-Square	P-value
Normal POC (chorionic villi and decidua)	53 (53)	0 (0)	53 (59)	60.49	0.001
POC (decidua only)	9 (9)	0 (0)	9 (10)		
Septic abortion	3 (3)	1 (10)	2 (2.2)		
POC with nonspecific chronic endometritis	10 (10)	8 (80)	2 (2.2)		
Degenerated POC	19 (19)	1 (10)	18 (20)		
POC with Arias Stella reaction	6 (6)	0 (0)	6 (6.6)		

Data presented as number (%). POC: product of conception.

DISCUSSION

The most frequent adverse pregnancy outcome that still understudied is miscarriage. Worldwide, almost 15% of all clinically confirmed pregnancies end with spontaneous pregnancy loss (Al-Mulhim& Al-Qurashi, 2001).Unexpected pregnancy loss -especially if occurs frequently- has physical and emotional impact on couples. A habitual or recurrent pregnancy loss is defined as three consecutive miscarriages occur before 20 weeks of gestation (Al-Nakib et al. 1983).

A number of risk factors for spontaneous pregnancy

loss were reported in Taif population (Al-Mohammad et al. 2010) but infectious disease-related factors are understudied. Thus, we investigated the potential infectious causes of miscarriage in a group of patients admitted at King Faisal Medical Complex – Taif – KSA.

Sometimes, infections may severely harm the embryo and fetus or even lead to miscarriage (AlShamlan et al. 2021; Alshora& Mohammad, 2018). TORCH infections (Toxoplasmosis, Rubella, CMV, and HSV) during pregnancy are the most common causes of congenital disorders (Bearak et al, 2020). TORCH infections can cause wide range of clinical manifestations depending on

the stage of pregnancy. If infection occurs in the first trimester, it can cause congenital malformations, intrauterine growth restriction (IUGR), or even fetal death (Borna et al. 2013).

The current study included 100 pregnant ladies admitted in maternity hospital at KFMC – Taif for abortion. Ninety per cent of miscarriages were not associated with TORCH infection while 10% were tested positive for TORCH infection. Of them, 5% were seropositive for *Toxoplasma*, 2% were seropositive for Rubella and CMV co-infections, 1% was seropositive for each rubella and hepatitis B, and 1% was seropositive for HSV-1.

We found a significant association between younger maternal age and miscarriage ($P= 0.008$). A study conducted in Baljurashi Hospital in southern Saudi Arabia reported miscarriages in the first trimester in 10% of studied females who were older than 25 years, mostly housewives from moderate to good socioeconomic backgrounds (Bullelli et al. 1996).

Among the 100 participants only six confirmed to have pet animals, one of them had an infection-related miscarriage. *Toxoplasma gondii* (*T. gondii*) a protozoan parasite where cats are its definitive host. Many adverse pregnancy outcomes, such as spontaneous miscarriage or stillbirth, have been reported with toxoplasmosis in cat owners (Dar et al. 1997). The parasite is excreted in the cat's faeces, so pregnant females are advised not to change cats' litter box (Dubey et al. 2012).

Seropositivity for *T. gondii* is markedly associated with contacting cats or cleaning their litter boxes (El-Ridi et al. 1991). Moreover, living with domestic cats increases the risk of *T. gondii* infection by five-folds (El-Sebai, 1991).

Toxoplasma seropositivity in pregnant women was found to range between 22.9 and 58.2% (Engelhard et al. 2001; Fakhfakh et al. 2013; Giakoumelou et al. 2016). In Saudi Arabia, *T. gondii* seropositivity rate was 41% in Aseer, 54.4% in Makkah and 61.4% in Al Ahsa (Hay, 2004), 38% in Riyadh (Hughes et al. 2000; Kassa et al. 2020), and 39.4% in the Eastern Province (Kheirandish et al. 2019). The overall seroprevalence of toxoplasmosis among the Iranian women in reproductive age were 39.9% (Liu et al. 2020).

An Egyptian study demonstrated the histological signs of toxoplasmic placentitis, as well as the presence of the organism in the placenta of miscarried women (Macklon et al. 2002). Furthermore, *T. gondii* seroconversion rates in females with spontaneous or recurrent pregnancy was 24.2% in Qaseem – Saudi Arabia (Manicklal et al. 2013), and 30.6% in the United Arab Emirates (Mocanu et al. 2022). There is lack of information regarding the frequency of miscarriages and congenital disorders caused by *T. gondii*. In an Iranian case-control study; 240 women who had their first spontaneous abortion were compared with 240 women normally delivered without previous history of abortions, *T. gondii* IgM antibodies were significantly detected in 3.3% of the cases and 0.4% of controls ($P < 0.019$). While *T. gondii* IgG antibodies

were detected in 47.5% of cases and 46.3% of controls. Low *T. gondii* IgG avidity was detected in 87.5% of IgM-positive sera, indicating an acute infection (Mohammed et al. 2018).

CMV is the most common congenital viral infection that can globally affect up to 2% of pregnancies (Obeid, 2007). CMV sero negative mothers have 0.7–4.1% higher risk to get CMV infection and congenital CMV infection could affect 0.64% of all newborns (Borna et al. 2013). It was found that females with prior CMV infection had a lower live birth rate than those without prior CMV infection (Pereira et al. 2003). The placental inflammation with cytokines and growth factors released in amniotic fluid secondary to intrauterine CMV infection are the cause of pregnancy loss (Rasti et al. 2016).

The presence of rubella IgM antibodies typically indicates an acute infection. While the presence rubella IgG along with the absence of rubella IgM indicates immunity against the rubella virus. However, lack of both rubella IgG and IgM antibodies indicates a person's susceptibility to infection with higher risk of congenital rubella infection among pregnant women (Shawky & Soliman, 2001).

We demonstrated rubella IgM antibodies in 1% of studied cases. This agreed with the cross-sectional study conducted on 4328 pregnant women in Al Khobar City, Saudi Arabia which revealed positive rubella IgM antibodies in 1.21% of them (Shet, 2011).

The prevalence of rubella IgM antibodies in Ethiopia is 9.5%, Nigeria 9.2%, Sub-Saharan Africa 5%, and Turkey 2% (Shawky & Soliman, 2001; Singh, 1996). The variance in rubella IgM seroprevalence between studies owed to the differences in rubella virus prevalence and immunization policies between countries.

We detected only one case (1%) with of HSV-1 IgG infection. HSV-1 and HSV-2 are members of the human Herpesviridae family. They are dsDNA viruses that remain dormant in host cells and can be reactivated (Suzumori & Sugiura-Ogasawara, 2010). HSV has been recorded to potentially infect the decidua and/or placenta in about 6–14% of pregnancies with decidua more likely to be infected than placenta (Wang et al. 2019).

A 93.2% seroprevalence of HSV-1 IgG antibodies was detected two studies conducted in Al Khobar and Abha cities, Saudi Arabia. However, neither study reported HSV IgM positivity, a sign of a current infection (Wondimeneh et al. 2018; Zemene et al. 2012).

Limitations:

Our study's limitations were that it was only conducted in the city of Al Taif and that there were only 100 participants. The prevalence of TORCH infections among females with prior related miscarriages would be better assessed in a larger study involving hospitals from various regions of Saudi Arabia. Enhancing prenatal visits' health education should include information, education, and counselling about this illness. This knowledge could help

doctors advice their patients and make the best clinical choices for the mother.

Further studies are also needed to explore the effect of different levels of IgG and IgM avidity on pregnant and neonatal outcomes among patients with TORCH infections.

CONCLUSION

According to this study's findings, significant association between younger maternal age and miscarriage, TORCH infections are common among aborted women in Taif City (10% of cases), *T. gondii* is found in 50% of infected cases, and mixed infections are rare (2% of cases). The majority of seropositive cases had mixed inflammatory infiltrates in their POC, which was a good indicator of infectious causes of abortion. Therefore, enhancing prenatal visits' health education should include information, education, and counselling about this condition. Pet animals were a risk factor for an infectious cause of abortion. Doctors could use this information to counsel patients and choose the best clinical options for the mother.

Supplementary materials

The supplementary material / supporting for this article can be found online and downloaded at: <https://www.isisn.org/article/10.3390/antiox12081524/s1>,

Author contributions

Conceptualization, A.S.A. and E.O.S.; methodology, I.K.A., A.M.M., H.M.H. and A.A.M.; software, A.A.A.; validation, A.A.S. and A.A.; formal analysis, A.H.A.; investigation, A.M.H.; resources, E.O.S.; data curation, K.K.H.; writing-original draft preparation, I.K.A.; writing-review and editing, A.S.A. and A.N.M. and K.O.M. ; visualization, H.M.H.; supervision, H.M.H. and A.A.; project administration A.S.A.; funding acquisition, E.O.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was approved by the Bioethical Committee of the KFMC number (H-02-T-123).

Informed Consent Statement

Informed written consent was obtained from each patient.

Data Availability Statement

All of the data is included in the article/Supplementary Material.

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Conflict of interest

The authors declare no conflict of interest.

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