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ASSOCIATION BETWEEN TORCH INFECTION AND DIFFERENT SOCIO-DEMOGRAPHIC FACTORS WITH RECURRENT MISCARRIAGE

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ABSTRACT
Miscarriages are the most common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies in the general population. Recurrent miscarriage or recurrent pregnancy loss (RPL), defined as the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive. It has been estimated that 1–2% of second-trimester pregnancies miscarry before 24 weeks of gestation. The aim of this study is to found if there is any association between different socio-demographic factors, Toxoplasmosis, CMV, Rubella infections and recurrent miscarriage. This prospective case-control study was carried out in the private clinic between January 2016 and July 2016. Hundred, apparently healthy pregnant women with history of recurrent miscarriages with gestational age 10-20 weeks were selected as target group. Their ages ranged between 20 and 40 years. Every woman interviewed separately and asked number of questions designed in a questionnaire paper including full history, examination and information of different socio-demographic factors also blood sample were obtained from women for investigation to detect any infection with Toxoplasmosis, CMV, Rubella. Results showed the highest percent of recurrent miscarriage was occurred at the age group (21-30) years, (47%) also in the weeks of gestation < 10 weeks (78%). Nullipara, housewives, those lived in Urban region had higher percentage of recurrent pregnancy loss. (65%) of pregnant women with history of recurrent miscarriage completed her pregnancy while (35%) end with miscarriage, (99%) of woman with recurrent miscarriage who enrolled in this study not had any infection with Toxoplasmosis, CMV, or Rubella. It concluded that although the diagnosis of RPL can be quite devastating, it can be helpful for the physician and patient to keep in mind the relatively high likelihood that the next pregnancy will be successful.

KEYWORD: TORCH, Recurrent Misscarrage.

INTRODUCTION
Miscarriages are the most common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies in the general population. The exact frequency of miscarriages is, however, unknown as miscarriages frequently occur before the woman is aware of her pregnancy. It is estimated that more pregnancies are lost spontaneously than are actually carried to term (Rai and Regan, 2006; Stephenson and Kutteh, 2007).

Miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. It should be noted that advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation (RCOG, 2011).

Recurrent miscarriage or recurrent pregnancy loss (RPL), defined as the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive (Stirrat, 1990). It has been estimated that 1–2% of second-trimester pregnancies miscarry before 24 weeks of gestation (Wyatt, 2005).

Recent evidence indicates that two or more, not necessarily consecutive, miscarriages constitute recurrent miscarriage (Nielsen, 2010).

Well-established risk factors for miscarriage include increased maternal age, (Nybo, 2000; De La, 2002) history of miscarriage and infertility, (Hakim, 1995; Axmon, 2005) although the interaction between age, parity, infertility and previous pregnancy loss is complex and still not entirely understood. Several behavioral and social risk factors have been reported as increasing the

risk of miscarriage, but most remain controversial or unconfirmed. Alcohol consumption, smoking (Rasch, 2003; Wisborg, 2003) and caffeine intake are the main examples, and controversy remains because few studies have examined these associations in the context of nausea, known to reduce the risk of miscarriage, (Wen, 2001; Jarnfelt, 1983), and the etiology of RPL is varied, and includes maternal or paternal chromosomal aberrations, uterine anatomic abnormalities, endocrine disorders, infections, and reproductive autoimmune defects. However, the etiology is undetermined in 40–60% of women with recurrent abortion (Stray, 1984; Griebel, 2005). About half of the concepts of RPL have an abnormal karyotype (Stern, 1996), even though the risk for a spontaneous abortion in a subsequent pregnancy is increased when a normal embryonic karyotype is found in abortus material (Morton, 1987). Infection of the uterine lining or endometrium with slow growing bacteria has also been associated with pregnancy loss in 5–10% of women with RPL. Certain infectious agents have been identified more frequently in cultures from women who have had a spontaneous pregnancy loss; these include *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Chlamydia*. Other less frequent pathogens include *Toxoplasma gondii*, Rubella, HSV, Measles, CMV, Coxsackie virus and *Listeria monocytogenes*, though none have convincingly. At all any severe maternal infection which leads to bacteraemia or viraemia can cause miscarriage. TORCH {toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV)}, that can cause illness in pregnant women and may cause birth defects in their newborns. These entire infectious agents induce a shift of immune response during pregnancy from Th2 to Th1 and apoptosis which can be observed clinically as an abortion process (Campbell, 2000).

Aim of study: If there is any association between different socio-demographic factors and recurrent miscarriage also if there is association between RPL and infection with CMV, Toxoplasmosis and Rubella in pregnant women in diyala province.

Aim of thesis

Large number of studies examined the risk factors of miscarriage, there have been few studies that have examined interactions between these risk factors. Interactions may increase risks of miscarriage that might provide new targets for interventions to reduce the risk of miscarriage, so our hypothesis to identify.

1. If there is any association between different socio-demographic factors and recurrent miscarriage.
2. If there is association between RPL and infection with CMV, Toxoplasmosis and Rubella in pregnant women in diyala province. Subjects and methods.

Study design: Prospective case- control study, it was conducted to determine the association between different risk factors and recurrent abortion. This study was carried out in the private clinic between January 2016 and July 2016.

Study population: hundred, apparently healthy pregnant women with history of recurrent miscarriages with gestational age 10-20 weeks were selected as target group. Their ages ranged between 20 and 40 years. Gestational age was estimated from the date of last menstrual cycle and 1st trimester US that used CRL for determination weeks of gestation or two 2nd trimester US.

Inclusion criteria

Women who were admitted to private clinic because of miscarriage (the most recent pregnancy).

Three or more recurrent miscarriage (whether primary or secondary) before 20 weeks gestation.

Exclusion Criteria: Uterine abnormalities: Fibroid, congenital anomalies, incompetent internal OS, and uterine hypoplasia (from detected investigations as ultrasound and hysterosalpingography, and uterine sound).

In all cases full history and complete physical examinations including body weight, height and body mass index were done. Ultrasound examination was done to exclude anatomical causes in the uterus and calculating weeks of gestation.

Study Instruments and testing

The study instruments will be an interviewer administered questionnaire and a medical records abstraction form. The questionnaire was developed based on other study questionnaires and the internationally published literature in this field. This instrument was further pretested and adapted as needed for the current study. Questions about smoking, coffee drinking and alcohol consumption were adapted from study questionnaires used by the Center for Health Services Research and Development (CHSR) at the American University of Armenia. The questionnaire includes questions about participants' socio-demographic characteristics (maternal/paternal age, employment, marital status and family income) and questions about risk factors for miscarriage. Medical record abstraction forms were based on the internationally published literature in the field and adapted for acquiring the required data for the proposed study. Data about uterine defects and infections will be obtained. The blood samples will also be used for further analysis to identify infections and that are also risk factors for miscarriage. Five ml blood samples were obtained by vein puncture from all studied women after cleaning the skin with samples were stored in plastic tubes and left to clot undisturbed for about 1/2 hr at room temperature min at 3000 r.p.m. and then the serum was transferred into other tubes(10). After the serum samples were collected, they were stored at –20 C until they were tested. all serum samples were screened for the presence IgM antibodies

against Toxoplasma gondii, Cytomegalovirus and Rubella virus by using (mini VIDAS kits : Vitek Immuno Diagnostic Assay System) for Biomerieux company). The tests were performed according to manufactures instruction by added 200 micro liter of serum to sample well in test strip and the instrument worked automatic, all the samples were showing optical density above cut off value considered positive (cut off value of anti –toxoplasma Ab IgM > 0.65, cut off value of anti CMV Ab IgM > 0.90, cut off value of anti Rubella Ab IgM > 1.20.

There are 11 questions and the main domains of the questionnaire are

- Socio-demographic questions – maternal and paternal age, family income, marital and employment status.
- History of the previous pregnancies and their sequence
- Number of abortions

Statistical analysis: Descriptive statistical analysis including tables, graphs, frequency and percentages.

RESULTS

The aim of this study is to determine if there is any association between different socio-demographic parameters like age, weeks of gestation, occupation BMI, and others with recurrent miscarriage and also if infection with CMV or Toxoplasmosis and Rubella lead to recurrent miscarriage. The study group consisted of 100 women with a history of two or more recurrent first trimester spontaneous abortions and also early 2nd trimester miscarriage. The study is prospective cross sectional study, Descriptive statistical analysis of each parameter was performed.

Recurrent miscarriage and different socio-demographic factors.

Age and weeks of gestation of the studied group: The highest percent of recurrent miscarriage was occurred at the age group (21-30) years, whereas the lowest one was at the age of(<20)years (47%, 11%) respectively, also the highest percent of recurrent miscarriage was observed in the weeks of gestation < 10 weeks (78%) while the lowest percent with the weeks of gestation > 20 weeks (2%). As shown in table 3.1.

Occupation of the studied group: It was observed that housewife had higher percentage of miscarriage(52%) compared with employer and educated (31%, 17%) respectively as shown in table 3.1.

BMI of the studied group: BMI (26-30) had highest percent of recurrent miscarriage (50%) while BMI of > or equal to 31 had lowest percent(17%). Table 3.1.

Parity of Studied Group: Nullipara showed to have highest percent of recurrent miscarriage (47%) followed by para 1 (42%) and lastly multipara (31%). Table 3.1.

Residency of Studied Group: Table 3.1 showed that woman lived in urban area had higher percentage of recurrent miscarriage (60%) while those lived in rural area had lowest percent (40%).

Table 3.1: Socio-demographic characteristics among pregnant women with recurrent miscarriage.

Parameters	Number=100	Percentage 100%
Age stratum		
>20 years	11	11%
21-30 years	47	47%
31-40 years	42	42%
Weeks of gestation		
<10 weeks	78	78%
10-20 weeks	20	20%
>20 weeks	2	2%
Occupation		
Housewife	52	52%
Employer	31	31%
Educated	17	17%
BMI		
< or equal to 25	33	33%
26-30	50	50%
>or equal to 31	17	17%
Parity		
Nullipara	47	47%
Para1	42	42%
Multipara	31	31%
Residency		
Rural	40	40%
rban	60	60%

Recurrent miscarriage and pregnancy outcome and ANC.

ANC in Studied Group: (31%) of pregnant woman with recurrent miscarriage who enrolled in the study had regular ANC while majority had irregular ANC (48%) on the other hand (21%) had no ANC at all. Table 3.2 pregnancy outcome in studied group.

Table 3.2 showed that (65%) of pregnant women with history of recurrent miscarriage completed her pregnancy while (35%) end with miscarriage.

Table 3.2: Distribution of patient with recurrent abortion according to pregnancy outcome and ANC.

Parameters	Number	Percentage
ANC		
Regular	31	31%
Irregular	48	48%
No ANC	21	21%
Pregnancy outcome	65	65%
Completed	35	35%
End with miscarriage		

3.3. Occupation of husband of pregnant women with recurrent miscarriage: Regarding the occupation of husband of pregnant women with history of recurrent miscarriage this study showed that wives of employers had lowest percent of recurrent miscarriage (25%) followed by wives of military (31%) and others occupations had percent of (44%) as shown in figure 3.1.

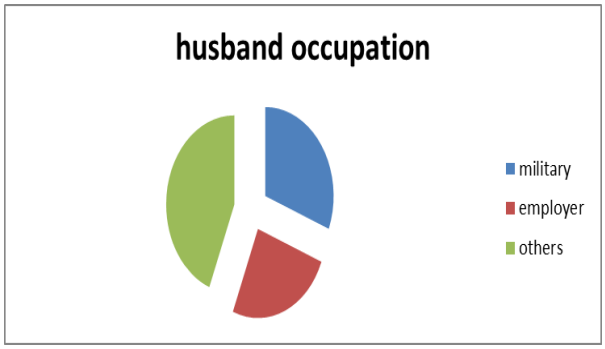

Fig. 3.1: Distribution of pregnant women with recurrent miscarriage according to husband occupation recurrent miscarriage and Toxoplasmosis, CMV, Rubella infections.

This study observed that (1%) of pregnant women had +ve IgM for toxoplasmosis also the same percent for IgM of CMV and Rubella IgM while (99%) of pregnant women were –ve for this antibodies as shown in figure 3.2.

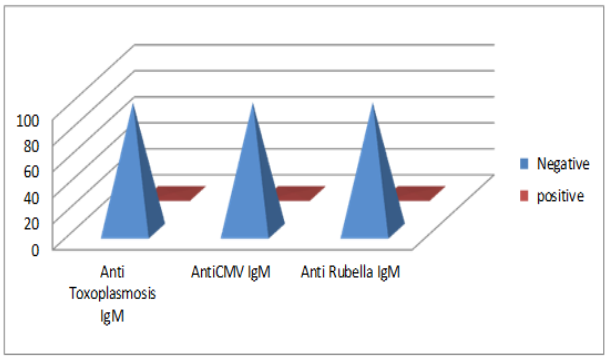

Fig. 3.2: Distribution of patient with recurrent miscarriage according to CMV, Toxoplasmosis, Rubella infections.

DISCUSSION

In this thesis, I investigated several risk factors that may be contributed to the etiology of recurrent miscarriage these included numbers of socio-demographic factors like age of pregnant women, parity ,occupation of female and her husband, BMI, residency, weeks of gestation, also if the pregnant women complaining from any medical diseases that may be responsible for recurrent miscarriage. Also all women were investigated for infection with Toxoplasmosis, CMV, Rubella to find if any one of them may cause recurrent miscarriage Regarding the different socio-demographic factors that investigated in this study we will discuss each item separately.

In this study higher recurrent pregnancy percent found in age group (21-30 years) and this not in agree with (Nybo, 2000) who found that the majority of cases of RPL were with age 42 years old. On the other hand most of cases with RPL occur in the early 1st trimester in this study may be because most of cases that evaluated in the period of study was in there 1st trimester or may be due to other causes that not evaluated in this study.

Occupational factors in spontaneous RPL were studied in current study and it was found that housewife had the highest percentage followed by employer woman this in concordance with (McDonald, et al., 1986) who observed that only heavy lifting and other strenuous physical activity were risks of spontaneous miscarriage also this study observed that there is lower percentage of recurrent miscarriage associated with educational woman this in agree with (Apgar and Churgay, 1993) who demonstrated that no association was found between education level of pregnant woman and miscarriage.

Overweight in this study showed highest percent of RPL while obese woman had lowest percent this may be related to new trend in our society that pass towered decreasing weight before pregnancy to decrease the rate of complications in pregnancy, this not in agreement with (Winnie, 2012) in which his study concluded that overweight did not demonstrate increase risk of miscarriage while higher percentage found in underweight pregnant.

Concerns have been raised regarding a possible association between residential and occupational electromagnetic field exposure and adverse reproductive effects. Nevertheless, there is little evidence for a strong association between spontaneous abortion and use of a video display terminal by a woman during pregnancy (Shaw and Croen, 1993), this looks agree with this study as we found that more RPL observed in woman lived in urban area than in rural one.

Nulliparity in this group found to had higher percentage of RPL compared with para1 and multipara this not in agree with (Guzel, et al., 2015) who observed that high parity associated with higher percent of RPL this may be because of limited number and time of collection of data in this study may be due to increase rate of infertility in our province that made nulipara woman to consult a doctor and to be discovered more than multipara.

In this study unexpectedly we observed that woman with no ANC had lowest risk of recurrent pregnancy loss and higher percentage with woman with irregular ANC this may be due to deficiency in recording real number of miscarriage in women with irregular and with no ANC that made large number of cases of miscarriage passed unnoticed, this not in agreement with (Stray, 1984) how concluded that women receiving specific antenatal counseling and psychological support had higher

pregnancy success rate compared with woman who had no specific ANC.

Majority of cases in this study had successful pregnancy outcome while lower percentage end with miscarriage, this in concordance with (Clifford,1997) with his large study demonstrates the excellent outcome of pregnancy after unexplained recurrent first trimester miscarriage that can be achieved in a dedicated clinic with supportive care alone.

In this study occupation of husband found to be a risk factor for recurrent miscarriage this in agree with (Parazzini *et al*., 1991; Edmonds *et al*., 1982) there data have suggested that male factors may influence early embryo loss: the occupation of the male partner, have been shown to influence the number, motility and morphological features of spermatozoa.

In this study through investigations that performed to all pregnant women with history of recurrent miscarriage to detect infection with CMV by measuring IgM it was found that just one case among 100 women enrolled in the study had infection with CMV this not agree with (Szkaradkiewicz et al, 1997) found more frequent seropositivity and higher levels of antibodies in women with RPL than controls and suggested that abortion might have resulted from fetal infection due to reactivation of chronic CMV infection in the course of pregnancy, but agree with other studies with using polymerase chain reaction method did not find CMV in gestational tissue of women with RPL(Cook, et al.,1993; Sifakis, et al.,1998; van, et al., 1994).

Regarding toxoplasmosis infection in this study also there was only one case infected this agree with (Qublan, et al., 2002) who concluded that There was no significant difference in the rate of habitual abortion between seropositive and seronegative women, on the other hand Rubella also reported in one case in this study, and no study found to demonstrate any relation between Rubella and RPL.

We conclude

1. Recurrent miscarriage is a complex condition, in which almost half of all patients have no associated risk factor.
2. Although the diagnosis of RPL can be quite devastating, it can be helpful for the physician and patient to keep in mind the relatively high likelihood that the next pregnancy will be successful.
3. Occupation of mother and father are not nor the education level of the mother effect in the rate of recurrent miscarriage.
4. Toxoplasmosis, CMV, Rubella not a risk of recurrent pregnancy loss in diyala province We recommend.

1. Appropriate investigations should be carried out to elicit any treatable cause for recurrent miscarriages.
2. All patients with recurrent miscarriages should receive sympathetic supports and close welfare.
3. Hospitals should improve their ways of records and documentation.
4. More prospective studies are required to identify the other causes that responsible on increase rate of recurrent miscarriage.

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