Association between Spontaneous Abortion and Human Papilloma Virus Infection in Mosul Province, Iraq

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ABSTRACT

Background: In pregnant women or in their partners, Human Papilloma Virus infection can be considered as a risk of preterm birth, abortions and virus transmission to the newborn.
Objectives: To find association between Human Papilloma Virus infection and spontaneous abortion and to detect the associated risk factors.
Methods: A case-control study that was conducted in Obstetrics and Gynecology Department of Al-Khansaa Teaching Hospital in duration of one year from Jun 2017 to May 2018. It included 60 pregnant women with spontaneous abortion (case group), and 60 pregnant women ended with viable full term pregnancy (Control group). Age < 18 years, chronic medical disease during pregnancy or multiple pregnancy, premature rupture of membrane or preterm or post term labor, history of previous three or more recurrent abortions were excluded. Human Papilloma Virus test was done by performing polymerase chain reaction test from a sample had been taken from each pregnant woman.
Results: The majority did not have Human Papilloma Virus infection (88.3%), while 11.7% had. Human Papilloma Virus infection presented in higher rate in women who had abortion that occurred in the 1st trimester (20.6%). Significant higher proportion of study patients with Human Papilloma Virus infection were ended with abortion (78.6%, P=0.022). Human Papilloma Virus infection was significantly seen among patients with previous history of abortion and in patients who currently use oral contraceptive pills (25.6%, P=0.001 and 20.5%, P=0.022 respectively).
Conclusion: Human Papilloma Virus prevalence is higher in pregnancy with spontaneous abortion compared to women experience a normal full term pregnancy. Previous history of abortion and current use of oral contraceptive pills were modifiable risk factors associated with Human Papilloma Virus infection.

Keywords: Human papilloma virus, Pregnancy, Abortion, Mosul, Iraq.

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Abortion is defined as the spontaneous loss of a pregnancy during the first 24 weeks of gestation. Early abortion is defined as pregnancy loss during the 1st trimester of pregnancy (less than 12 weeks of gestation) and occurs in up to one in five pregnancies. Late abortion occurs during the 2nd trimester (12–24 weeks of gestation) and is less common, occurring in 1-2% of pregnancies. Stillbirth is defined as fetal death from the 25th week of gestation onwards[1,2]. Considerable physiological and psychological implications with significant health care costs for the patient can be occurred due to abortion that happens in one in five pregnancies[3].

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There is evidence that 15% of early abortions and up to 66% of late abortions were caused by potentially preventable infections[4]. Pregnancy had proven to be a state of mild immunosuppression due to the drop in the number of natural killer cells, possibly making pregnant women more vulnerable to infections, as Human Papillomavirus (HPV). Various immunological theories have been discussed to explain the possibility for pregnancy and the survival of the fetus[5]. Intrauterine infection by bacteria is well established as a pathway leading to spontaneous abortion and spontaneous preterm birth, much less is known about viral infection and adverse pregnancy outcome[6]. HPV, which is known as a well-established cause for cervical cancer, does

though constitute a candidate. HPV infections are common, but about 90% of all infections can be cleared within less than two years by unknown mechanisms[7,8]. Pregnancy is known to be an independent risk factor for HPV infection[9]. There is some evidence that elevated steroid hormone levels during pregnancy influence the increase of HPV virus replication by interacting with hormone response elements in the viral genome, thereby giving another possible explanation for the higher incidence of HPV infection during pregnancy [10]. The finding that HPV DNA was detected more frequently in spontaneous abortions compared to voluntary abortions led to the consideration that HPV may be involved in the pathophysiology of early pregnancy loss[11]. Despite licensure of HPV vaccines in more than half of the world's countries, the global HPV prevalence was estimated at 12% in 2012[12]. Most recent data indicate that 14 million people are newly infected each year in the USA, with a total of 79 million people currently affected. The overall cost burden of preventing and treating HPV-associated disease in 2010 was estimated to be $8.0 billion[13,14]. Although little information is available regarding the association between HPV infection and pregnancy outcome, HPV has been reported to be more prevalent in spontaneous abortions than in elective terminations of pregnancy[9]. Therefore, it is of great interest to examine whether or not there is an association between HPV infection and spontaneous abortion by doing comparison between spontaneous abortion and full term pregnancy by investigating HPV within the cervix.

Methods

This is a case-control study that was conducted in Obstetrics and Gynecology Department of Al-Khansaa Teaching Hospital in duration of one year from Jun 2017 to May 2018. It included 60 pregnant women experiencing spontaneous abortion (case group), and 60 healthy pregnant women ended with viable full term pregnancy (control group). Women aged < 18 years, those with any chronic medical disease during pregnancy or multiple pregnancy, pregnant women with PROM or with preterm or post term labor, or those with a history of previous three or more recurrent abortions were excluded from this study. Data collection was done by a questionnaire gathering information on certain socio-demographic variables, certain risk factors of HPV infection (smoking, duration of marriage, number of marriages, and history of OCP ingestion), past obstetrical history, and certain information about current abortion. HPV test was done by performing PCR test from a sample had been taken from each pregnant woman by using cyto-brush from the cervical transformation zone rotated three times in counter clockwise direction, and then the brush removed from the canal and immersed into a fixative jar containing one ml of DNAzole (Invitrogen), and then placed in the refrigerator at -2 degree centigrade. Verbal permission was obtained from each patient prior to collecting data, and all information's were anonymous. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.

Results

The mean age of study patients was 27.2 ± 4.22 years; 65% were multigravida and 70% were living in urban areas. About two thirds of them (64.2%) didn't had a history of previous miscarriage and most of them were non-smokers (86.7%). The majority presented with her first marriage (80%) and 60% were married for less than five years. The highest proportion of study patients didn't use OCP (63.3%), (Table 1).

The majority of study patients didn't have HPV infection (106 patients, 88.3%), while 14 patients (11.7%) had HPV infection. Regarding those with positive HPV infection, 11 of them ended with abortion while the other three were delivered a viable full term baby. 18.3% of those who were ended with abortion had HPV infection, and the association between pregnancy

outcome and HPV infection was statistically significant (P=0.022). In case group (Patients with abortion), 56.7% of them had abortion in the first trimester and 43.3% had abortion in the second trimester.

Concerning HPV infection in relation to time of abortion, in this study, the highest prevalence of HPV infection presented in women who had abortion that occurred in the first trimester (63.7%), while the prevalence of HPV in the second trimester was (36.3%), (Table 2).

The association between HPV infection and certain characteristics is shown in table (3). We noticed that the highest proportion of HPV infection was significantly seen among patients with previous history of abortion and in patients who currently use OCP (25.6%, P=0.001 and 20.5%, P=0.022, respectively).

Table 1: Distribution of study patients by certain characteristics.

Variable	Case Group n= 60 (%)	Control Group n= 60 (%)	Total n= 120 (%)
Age (Years)			
< 25	27 (45.0)	41 (68.3)	68 (56.7)
25 - 34	19 (31.7)	13 (21.7)	32 (26.7)
≥ 35	14 (23.3)	6 (10.0)	20 (16.7)
Parity			
Prim gravida	14 (23.3)	28 (46.7)	42 (35.0)
Multigravida	46 (76.7)	32 (53.3)	78 (65.0)
Residence			
Urban	32 (53.3)	52 (86.7)	84 (70.0)
Rural	28 (46.7)	8 (13.3)	36 (30.0)
History of previous abortion			
YES	19 (31.7)	24 (40.0)	43 (35.8)
NO	41 (68.3)	36 (60.0)	77 (64.2)
Smoking			
YES	12 (20.0)	4 (6.5)	16 (13.3)
NO	48 (80.0)	56 (93.5)	104 (86.7)
Number of marriages			
one	44 (73.4)	52 (86.7)	96 (80.0)
More than one	16 (26.6)	8 (13.3)	24 (20.0)
Duration of Marriage (Years)			
< 5	25 (41.7)	47 (78.3)	72 (60.0)
≥ 5	35 (58.3)	13 (21.7)	48 (40.0)
Current OCP use			
YES	25 (41.7)	19 (31.7)	44 (36.7)
NO	35 (58.3)	41 (68.3)	76 (63.3)

Table 2: Association between pregnancy outcome and HPV infection.

Variable	Study Group		Total (%) N= 120	P - value
	Case (%) N= 60	Control (%) N= 60		
HPV infection				
Yes	11 (18.3)	3 (5.0)	14 (11.7)	0.022
No	49 (81.7)	57 (95.0)	106 (88.3)	
Time of Miscarriage				
First trimester	34 (56.7)	-	-	-
Second trimester	26 (43.3)	-	-	-
Time of HPV infection	n= 11			
First trimester	7 (63.7)	-	-	-
Second trimester	4 (36.3)	-	-	-

Table 3: The association between HPV infection and certain characteristics.

Variable	HPV infection		Total (%) n= 120	P- value
	Positive (%) n= 14	Negative (%) n= 106		
Age Group (Years)				
< 25	7 (10.3)	61 (89.7)	68 (56.7)	0.28
25 – 34	6 (18.8)	26 (81.3)	32 (26.7)	
≥ 35	1 (5)	19 (95)	20 (16.7)	
Parity				
Prim gravida	4 (9.5)	38 (90.5)	42 (35.0)	0.591
Multi gravida	10 (12.8)	68 (87.2)	78 (65.0)	
Residence				
Urban	8 (9.5)	76 (90.5)	84 (70.0)	0.264
Rural	6 (16.7)	30 (83.3)	36 (30.0)	
History of previous abortion				
YES	11 (25.6)	32 (74.4)	43 (35.8)	0.001
NO	3 (3.9)	74 (96.1)	77 (64.2)	
Number of marriages				
One	9 (9.4)	87 (90.6)	96 (80.0)	0.117
More than one	5 (20.8)	19 (79.2)	24 (20.0)	
Duration of marriage (Years)				
< 5	7 (9.7)	65 (90.3)	72 (60.0)	0.416
≥ 5	7 (14.6)	41 (85.4)	48 (40.0)	
Smoking				
YES	4 (25)	12 (75)	16 (13.3)	0.074
NO	10 (9.6)	94 (90.4)	104 (86.7)	
Current OCP use				
YES	9 (20.5)	35 (79.5)	44 (36.7)	0.022
NO	5 (6.6)	71 (93.4)	76 (63.3)	

Discussion

Recent evidence suggested that HPV infection may affect fertility and alter the efficacy of assisted reproductive technologies[15]. Beyond the geographical location, the time point of sample collection in pregnancy as well as the HPV detection methods used may influence the results on HPV prevalence[5]. Multiple studies indicate that viral infection can impair trophoblast function, potentially contributing to pregnancy loss or abnormal implantation[16]. HPV detection rates range widely from six to 65% and the results are controversial[10]. Therefore, of great interest to examine how widespread HPV infection among pregnant women and whether or not there is an association between HPV infection and spontaneous abortion, since nowadays there exist a successful vaccination to prevent infection and disease caused by infection with HPV 16, 18, thus there might be a chance to minimize the risk for pregnancy complication through vaccination. In this study, the prevalence of HPV infection was higher in patients with abortion (18.3%) than in normal full term pregnancies (5%), study patients with HPV infection were already had abortion and the association between pregnancy outcome and HPV infection was statistically significant (P=0.022). HPV infection prevalence was reported in a quantitative analysis when 14 470 pregnant women were analyzed and they found that the HPV infection prevalence in women delivered viable full term baby was 35.5% and 29.6% in population from Latin America and USA respectively, while the Asian population showed that the cervical HPV infection prevalence varied between 10.1% and 36.2%. European population showed that the HPV infection prevalence varied between 2.2% and 36.6%, with a summary estimate of 11%[5]. The time of samples collection during pregnancy is thought to have an influence on HPV prevalence. Agreement with this result was found in a study conducted in USA, 2008 and proved that trophoblasts transfected with plasmids harboring HPV16 genome undergo apoptosis at rates three to six times higher than trophoblasts transfected with empty plasmids. This could be responsible for dysfunctions in placenta, reduction of embryo ability to invade the uterine wall and finally lead to abortions in the earlier stages of pregnancy[17]. Different result was found in a studies conducted in Mexico, 2013[18] and Poland, 2011[19] when reported that HPV prevalence was higher in women experiencing spontaneous abortion than HPV prevalence in the control group but the difference did not reach the statistical significance. In this analysis, we noticed that HPV infection was significantly higher among women with positive previous history of abortions than those without (25.6% versus 3.9%, P=0.001) and this result agreed with a study conducted in Morocco in 2007-2008[20], in contrary to a result found by a study conducted in Italy 2013[21] when showed that HPV prevalence was higher in the group of women without a history of recurrent abortions. Also, this study found that HPV infection was significantly higher among OCP current users (20.5%, P=0.022). A possible explanation for this association might be due to the fact which proved by a number of hypotheses when reported that the use of OCP is associated with an increased incidence of cervical ectropion, which means that the site where HPV infection preferentially induces neoplastic lesions. Estrogen and progesterone may also affect cervical cells directly, increasing cell proliferation and stimulating transcription of HPVs[22]. Similar finding was seen in a study conducted in USA 2002.

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