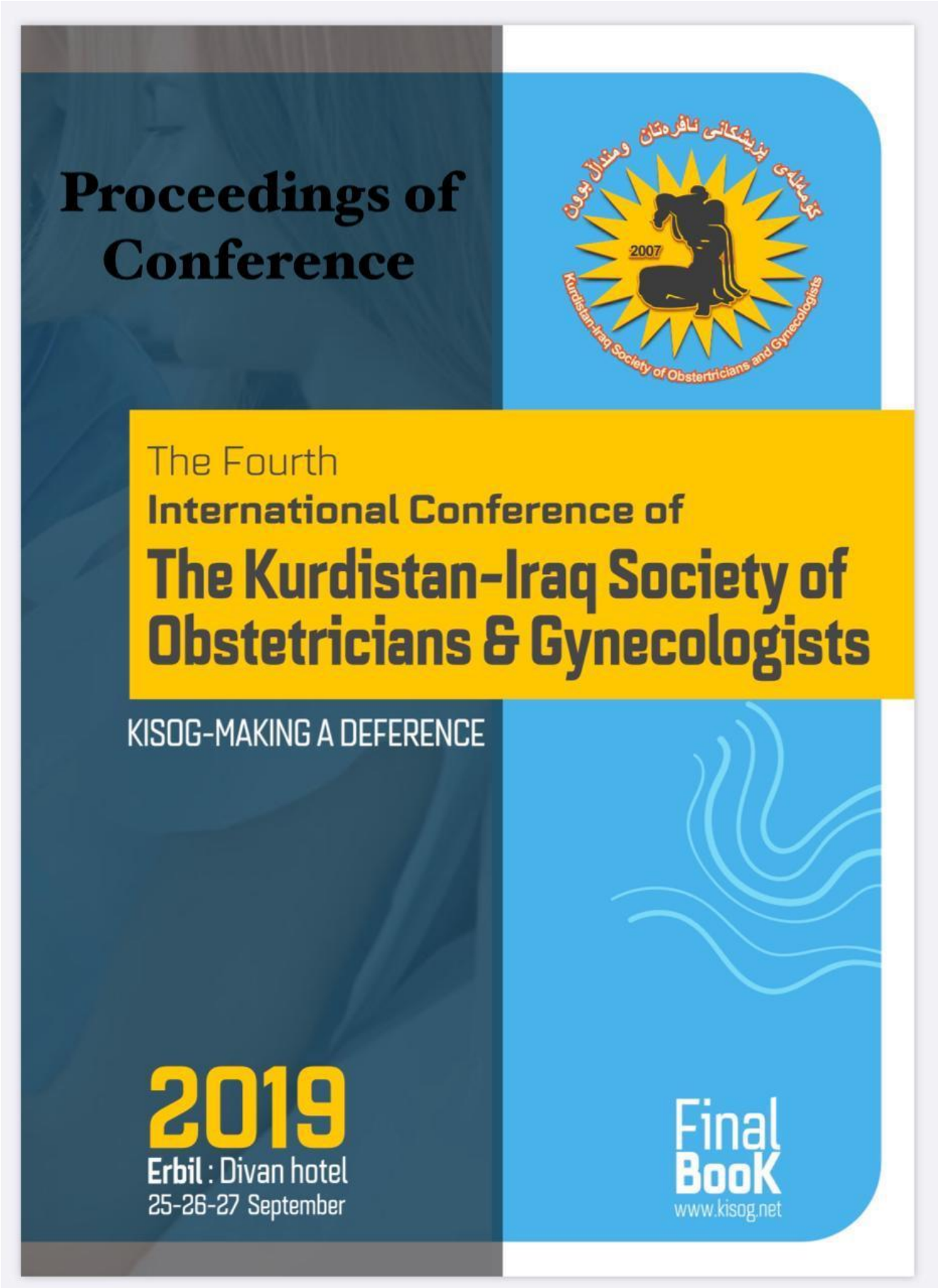
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Association of women infertility and smoking

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Abstract

Background and objectives: Infertility is a frequently observed reproductive failure and remains a global health problem and establishing a major psycho-social problem in many families and communities. Smoking is harmful to the ovaries, this damage is dependent upon the amount and length of time a woman smokes

Methods: A cross sectional study conducted at the Maternity Teaching Hospital Fertility Center (MTHFC) in Erbil city, Iraq from the period of 1stMay 2017 to 30th June 2018. Involved 400 infertile women were compared according to smoking status (337 non-smoker and 63 smokers) using a questionnaire after formal consent and recording the demographic characters. Anti-mullerian hormone (AMH), basal follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estrogen (E2) were measured for all of them with basal antral follicular count (AFC) by transvaginal ultrasound.

Results: Among the study population, anti-mullerian hormone (AMH) and antral follicular count as marker of ovarian reserve were reduced in smokers compared with non-smokers. Women who smoked had significantly higher FSH and estrogen (E2) levels. No significant difference was found in LH levels according to smoking status. The impact of smoking on AMH, FSH and AFC values was not dose dependent based on cigarettes per day showed (P value 0.467, 0.066 and 0.076 respectively.

Conclusions: Cigarette smoking is associated with ovarian reserve alteration in infertile women and affecting the reproductive pathway as reflected by decrease AFC and Anti-mullerian hormone (AMH). Every female smoker should be encouraged to stop smoking to prevent the damage caused by cigarette smoking and preserve their own fertility.

Keywords: Infertility, smoking, ovarian reserve, anti-mullerian hormone

Introduction

The World Health Organization (WHO) defines infertility as a disease of the reproductive system and a couple is considered infertile if they cannot conceive After 12 months of unprotected intercourse [1]. Infertility is divided into primary those never conceived in the past and who have regular unprotected intercourse for at least one year and secondary those who conceived in the past and who have regular unprotected intercourse for at least one year [2].

The level and causes of infertility vary widely, both among and within countries [3] .The incidence of and causes of infertility between populations mainly due to their dietary and life-style, environmental, occupational factors and infectious diseases [4].

Female infertility varies widely by geographic location around the world. In 2010, there was an estimated 48.5 million infertile couples worldwide, and from 1990 to 2010 there was little change in levels of infertility in most of the world [5].

Cigarette smoke contains about 4000 compounds belonging to a variety of chemical classes known to be toxic, including polycyclic aromatic hydrocarbons (PAH) [e.g. benzo (a) pyrene (BaP), acenapthelene, phenanthrene and pyrene], nitrosamines, heavy metals [e.g. cadmium (Cd) and cobalt], alkaloids (nicotine), aromatic amines and so forth [6, 7].These compounds have different properties and probably different targets on the human reproductive system. Some damage is irreversible, but stopping smoking can prevent further damage [8.] Smokers are 60% more likely to be infertile than non-smokers [9] .WHO (2015), estimated that prevalence of smoking among women in Iraq is 2.9% [10.]

Smoking is harmful to the ovaries, this damage is dependent upon the length of time a woman smokes or is exposed to a smoke-filled environment. Nicotine and other chemicals in cigarettes interfere with the body's ability to create estrogen, a hormone that regulates folliculogenesis and

ovulation, so cigarette smoking interferes with folliculogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and the uterine myometrium [11] .

Smokers present an abnormal endocrine profile characterized by higher testosterone level and higher level of FSH [12,13.] Several authors have observed that smoke compounds disrupt steroidogenesis, leading to impairment of E_2 synthesis [14, 15.]

Ovarian reserve seems to be lower in smokers [16.] Evaluation of anti-Mullerian hormone (AMH) in smokers on day 3 of the menstrual cycle and found that AMH was significantly lower in smokers.

The hypothesis that the fallopian tube could be considered as a target of cigarette smoke was raised after observation of an increased rate of ectopic pregnancies following exposure to smoke with an increased risk with increasing number of cigarettes smoked and with active smoking [17, 18]. Many studies have reported higher risks of multiple symptoms, including premenstrual tension, heavy periods, severe pain, and frequent and irregular periods among smokers, especially heavy smokers [19, 20.] Other studies reported increased risks of short and/or irregular cycles among smokers, with some dose-response relationships observed (the more the exposure the more the symptom) [21, 22].To authors knowledge till now there is no research has been devoted in Maternity Teaching Hospital Fertility Center (MTHFC) to determine the risk factors that are causally related to infertility which can be prevented to decrease this frequently observed reproductive failure.Aim of this study is to examine the link between cigarette smoking and risk of infertility in women in reproductive age.

The objectives of this study is to:

1-Determine the adverse effects of active smoking on delayed conception and decreasing fertility.

2-Find out that smoking promoting irregular cycles.

3-Determine to which extent smoking influences ovarian reserve, as measured by AMH levels.

Materials and methods

A prospective cross sectional study carried out at the Maternity Teaching Hospital Fertility Center (MTHFC), it is the main referral center for infertility and Gynecologic outpatient clinic in Erbil city, Kurdistan Region , Iraq from the period of 1stMay 2016 to 30th June 2017.

Study sample females with a history of infertility who attended the fertility center. The cases compared for different factors and each of them divided into smoker and nonsmoker groups.

The definition of smokers in this study were those women currently and formerly smoking only cigarettes and they divided according to the number of cigarette sticks per day into <10, 10-19 and ≥ 20 /day and duration of smoking considered in years, and the preferred definition of non-smoker those who had never smoked before.

Women with the following criteria included in the study:

1. Ages 18-39 years.

2. History of infertility: Is diagnosed after 12 months or more of being unable to achieve a successful pregnancy, earlier evaluation and treatment may be justified based on medical history and physical findings and warranted after 6 months for women over age 35 years [23] .

3. Unexplained infertility

4 .No evidence of hair suitism and endocrine dysfunction

While exclusion criteria:

1. Alcoholics

2. Patients diagnosed with organic cause of infertility, tubal blockage whether iatrogenic or known pathological problem.

3. Those with iatrogenic oophorectomy and premature ovarian failure.

This study carried out after approvement by the Scientific commitee and the agreement of the principle of maternity teaching hospital and the head of department of the MTHFC .

An informed consent obtained from all the patients who agree to participate in the study by direct interview by a special self-administered designed questionnaire at base line included questions on reproductive health and socio-demographic characters and blood sample is taken for hormones 3-4 ml at second to fourth days of cycle, the following hormonal investigations performed for all infertile women, including serum FSH, LH, Estradiol (E2) and AMH (anti-mullerian hormone). The blood centrifuged at the 3500 rpm for 10 min, and the serum was stored in 1.5ml polypropylene tubes at 2-8 ℃ if the assay performed within 24 hr., but for longer storage were kept frozen at -20℃. All the sample analyzed in the same laboratory of the MTHFC except for AMH have done in a laboratory outside the hospital as the reagents for this test is not available in the hospital laboratory.

Transvaginal ultrasound examinations have done for all patients by a single operator, by endovaginal probe. The antral follicle count (AFC) measurement performed on days 3 and 5 of menstrual cycle of both ovaries.

Statistical analysis done using SPSS 22 (Statistical Package of Social Science version 22).The data presented in frequency distributions. T-test used to compare means and the Chi-square for categorical variables to check relationship between women fertility and socio-demographical variables and P values of 0.05% or less considered significant.

Results

A total of 500 patients with infertility participated in the current study. Their age ranged from 20 to 39, frequency, age distribution and demographic characters are showed in Table 1 and Figure 1.

Table 1: Distribution of sample by demographic characters

		F	%
Age	<25	48	12.0%
	25-29	83	20.8%
	30-34	143	35.8%
	≥35	126	31.5%
Education	Illiterate	104	26.0%
	Read and Write	172	43.0%
	primary and secondary	85	21.3%
	college and high education	39	9.8%
BMI	<18.5	49	12.3%
	18.5-24.9	265	66.3%
	25 -29.9	72	18.0%
	≥30	14	3.5%

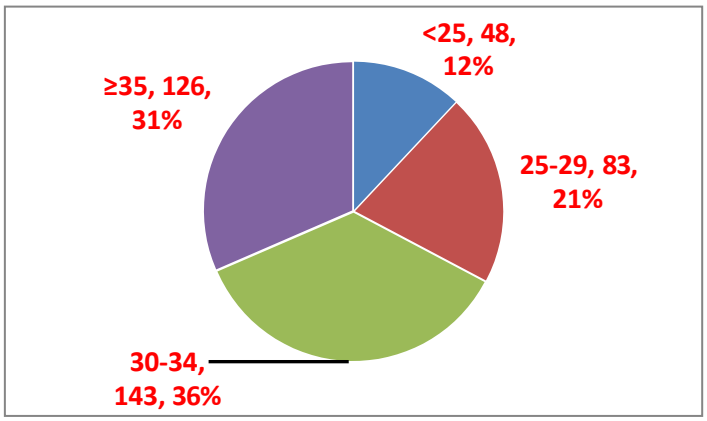

Figure 1: Age distribution among infertile patients (By number and frequency)

From table 2 we can see a significant association of BMI among smoker and non-smoker (P< 0.001), and there is significant association between smoker and non-smoker regarding cycle pattern (P< 0.001).

Table 2: Association of smoking with BMI and cycle pattern

		Smoker					
		Yes		**No**			
		No.	**%**	**No.**	**%**	**Total**	**(P-value)**
BMI	<18.5	16	4.0%	33	8.3%	49	**< 0.001**
	18.5-24.9	42	10.5%	223	55.8%	265	
	25 -29.9	5	1.3%	67	16.8%	72	
	≥30	0	0.0%	14	3.5%	14	
Cycle pattern	Regular	26	6.5%	244	61.0%	270	**<0.001**
	Irregular	37	9.3%	93	23.3%	130	

Table 3 shows that there is significant difference between the mean of AMH (ng/mL), FSH(mIU/mL), estrogen(ng/mL) and AFC by ultrasound of smoker and non-smoker patients (P<0.001),but there is no significant difference between the mean of LH (mIU/mL) of patients (smoker and non-smoker) (P> 0.01).

Table 3: Mean ±SD of hormones (AMH, LH, FSH and Estrogen) and AFC of smoker and non-smoker

	Smoker	N	Mean ± SD	t-test(p-value)
AMH (ng/mL)	Yes	63	2.10 ±1.51	4.720
	No	337	2.95 ±1.27	(p<0.001)
LH (mIU/mL)	Yes	63	7.15 ±1.74	1.312
	No	337	6.80 ±1.97	(p>0.01)
FSH (mIU/mL)	Yes	63	11.52 ±5.18	9.817
	No	337	6.86 ±3.04	(p<0.001)
Estrogen (ng/mL)	Yes	63	36.97 ±16.31	7.342
	No	337	51.08 ±13.54	(p<0.001)
AFC by US	Yes	63	8.17 ±4.57	7.342
	No	337	12.092 ±3.74	(p<0.001)

Table 4 shows that there is a no significant difference between the mean of AMH (ng/ml), FSH and AFC among the (No. of cig. smoking per day-groups) P= 0.467, P= 0.066, P= 0.076 respectively.

Table 4: Comparing mean of AMH, FSH and AFC in relation to the number of cigarette smoking

		N	Mean	Std. Deviation	(Anova)P value
AMH (ng/ml)	<10	6	1.23	0.60	0.467
	10-19	31	2.09	1.74	
	≥20	16	1.98	1.37	
	Total	63	1.96	1.55	
FSH(mIU/mL)	<10	6	15.53	4.60	0.066
	10-19	31	11.53	4.89	
	≥20	16	9.69	5.67	
	Total	63	11.42	5.29	
AFC by US	<10	6	6.67	3.67	0.076
	10-19	31	8.81	4.74	
	≥20	16	6.00	2.48	
	Total	63	7.72	4.21	

Discussion

Infertility is a frequently observed reproductive failure and remains a global health problem and establishing a major psycho-social problems in many families and communities, although the etiology of a proportion of female infertility remains idiopathic recent studies suggested a role for environmental and life style factors in this condition.

The consequence of diminished ovarian reserve are serious not only because of infertility but also act on general health of females by affecting the endocrine functions. One of the limitation of the study is that the female smokers are rare in Kurdistan region.

The mean age of the women seeking infertility services in the current study was 31.4 which is similar to that in the study done in Alexandria in Egypt in 2006 [24]. Regarding BMI in the smoker and non- smoker in contrast the prevalence of obesity among Turkish women was 32.4% whereas the prevalence of overweight was 50.4 % [25]. Similarly study from China, reported that prevalence of overweight in women aged 20 to 45 years of age was 19.2 % and that of obesity 1.5%, respectively [26], the finding in this study is similar to that reported in China. This may be

related to dietary habit, activity and life style modifications and because this may be a center for IVF treatment so they tried all the lines for treatment including weight reduction.

Similarly many studies reported higher risks of menstrual irregularities among smokers [20] ,and this may be related to the effect of smoking compounds on the hormone functions at different stages while in contrast another study found little difference in cycle length among smokers compared with non-smokers [27].

AMH is considered a marker of ovarian reserve and there is clear evidence that smoking may directly accelerate ovarian follicular depletion [11] , as seen in this study, However contradictory results have been reported on the relationship between smoking and AMH, with some authors [28] reporting reduced AMH levels in smokers versus nonsmokers and another study reporting similar values in both groups of women[29].

Smoking alter metabolic pathway for many other steroid hormones including estradiol, follicular stimulating hormone (FSH) and luteinizing hormone (LH), this study showed significant difference between smoker and non- smoker group regarding FSH women who smoked had significantly higher serum FSH concentrations than their non-smoker which is consistant with the study done by Cooper [30] but inconsistent with the study done by Dafopoulos [31] .While estradiol is decreased in this study on the contrary of the study done by Donatella [32] there is no significant difference between both groups.

In the present study we observed that smokers had fewer antral follicles than never smokers. This result led us to hypothesize that cigarette smoking could affect ovarian reserve by accelerating follicular atresia the same result found by Donattella [32] and by several other studies.

In the present study has not observed significant difference in early follicular-phase LH concentrations between smokers and non-smokers. Our results differ from those of Whitcomb [33], who found significantly higher serum levels of LH at menses in smokers while in our study is nearly the same, this differences might be due to timing of sample collection, mean age of woman included in the study, dose response relation ship and duration of smoking.

While compairing dose effect of smoking with FSH, AMH and AFC gives no significant response in contrast to the report of the study of Donattella [32] , found that intensity of smoking was negatively correlated to AFC and positively correlated to FSH levels, suggesting a proportional deleterious effect of smoking components on oocytes pool.

Cigarette smoke may interfere with steroid hormone release and different pathway of metabolism resulting in changes in circulating hormone concentrations. Although Confounding factors may distort the association between smoking and infertility (e.g. age, alcohol, coffee consumption and education) there was a significantly increased risk of infertility by affecting the endocrine functions and ovarian reserve in women who smoked however may not be a causal.

Conclusion

Those women suffering from infertility and intrested in having children need to know that continuing to smoke may adversely affect the success of therapy and worsening of the condition by affecting the endocrine function, ovarian reserve and response ovarian stimulation should try to stop smoking. Cigarette smoke compound affect all stages of reproductive functions. Further studies are required for better understanding the deleterious effects of cigarette smoke compounds on the reproduction to provide a better health care and help to reduce cigarette smoking

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Conflicts of interest

The author report no conflicts of interest

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