



The Effect of Reproductive Factors on Coronary Artery Disease in Women

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Abstract

Introduction: There is a sex discrepancy in cardiovascular physiology. In this study, we aimed to investigate the effect of female reproductive factors on coronary artery disease (CAD) beyond the known CAD risk factors.

Methods: In a case-control study, women referred to Tehran Heart Center for coronary artery angiography from 2012 to 2014 were enrolled. Of these, 80 premenopausal and 100 postmenopausal females with CAD in angiography were randomly selected as cases and 80 premenopausal and 100 postmenopausal females without CAD in angiography were selected as controls. A questionnaire including reproductive history and known CAD risk factors was filled for every subject. Analysis was performed separately for pre and postmenopausal women and a final adjustment for coronary artery disease risk factors was done.

Results: Among reproductive factors, oligomenorrhea (OR= 6.72) was a significant risk factor for CAD in premenopausal women and history of oral contraceptive (OCP) use had a protective effect on CAD in pre and postmenopausal woman (OR= 0.24 and 0.20, respectively).

Conclusions: Since oligomenorrhea has a strong association with insulin resistance and diabetes, a conventional risk factor of CAD, women with oligomenorrhea should be treated not only for cyclic irregularity but also for prevention of CAD.

INTRODUCTION

Cardiovascular disease is the most common cause of death-worldwide. Incidence of coronary artery disease (CAD) in premenopausal women is lower than men at the same age. There are a lot of evidence about sex differences in the molecular and cellular physiology of the heart and blood vessels [1]. Female hormones, mainly estrogens, modify blood lipids and blood pressure and the levels vary during pregnancy [2]. Moreover, pregnancy is a state that leads to insulin resistance, undesirable lipid profile and elevated

coagulation factors [3]. It has been reported that some of these changes continue several years after pregnancy [3]. So, number of pregnancies and age at first pregnancy may affect cardiovascular health status as well as hormonal level. Menstrual cycle irregularity has been shown to be a sign of insulin resistance [4]. Moreover, polycystic ovarian syndrome (PCOS), the most common cause of oligomenorrhea, has strong association with conventional CAD risk factors such as insulin resistance, diabetes, hypertension and

dyslipidemia [5]. In addition to pregnancy, reproductive history and menstrual cycle irregularity, hormonal medicines such as oral contraceptives (OCP) probably have some effects on cardiovascular status because of alteration in hormonal level in circulation. In this study, we attempted to investigate the effect of reproductive and hormonal factors on coronary artery disease beyond the known CAD risk factors.

METHODS

In this case-control study, women who referred to Tehran Heart Center for coronary artery angiography from 2012 to 2014 were included. Women with prior history of hysterectomy were excluded. Of these, 80 premenopausal and 100 postmenopausal females with CAD in angiography, were randomly selected as cases and 80 premenopausal and 100 postmenopausal females without CAD in angiography were selected as controls. Coronary artery disease was defined as luminal stenosis $\geq 50\%$ in at least one pericardial coronary artery. A questionnaire including demographic data, reproductive history and known CAD risk factors, was filled for all participants. Demographic data involved age, education level, job status and body mass index (BMI). Reproductive factors were included the number of pregnancies, number of children, number of abortions, age at first pregnancy, age at menarche, oligomenorrhea, menopausal status, age of menopause, type of menopause, OCP use, duration of OCP use, hormonal replacement therapy (HRT), and duration of HRT.

Traditional CAD risk factors, including diabetes (DM), hypertension (HTN), hyperlipidemia (HLP), cigarette smoking (CS) and family history of CAD were also evaluated. It is certified that all ethical considerations, i.e., applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Informed written consent was obtained from all participants and the Ethical Committee of Tehran University of Medical Sciences approved this study. The study protocol conforms to the ethical guidelines of the 2008

Declaration of Helsinki [6]. Our gathered data were confidential and no extra cost was constrained on our participants. Analysis was carried out separately for pre and postmenopausal women. Independent samples t-test was used for comparison of numerical variables as well as Pearson chi-square and Fisher's exact test for categorical data. Final adjustment for confounding factors including conventional CAD risk factors (HTN, diabetes, FH, age) was carried out by multiple logistic regression models. The statistical significance level was set at a two-tailed type I error of 0.05. All statistical analyses were performed using SPSS version 15.

RESULTS

As is shown in Table 1 and 2, univariate analysis in premenopausal women determined that increasing age and number of children besides decreasing age at first pregnancy among the numerical data as well as oligomenorrhea, being house-wife, low education, having no partner, DM, HTN and family history of CAD among categorical data were associated with CAD. However after adjusting all variables for CAD, only three characteristics remained significant (Table 3); DM with odds ratio (OR) of 6.32, HTN with OR of 9.01 and oligomenorrhea with OR of 6.72.

Among numerical variables in postmenopausal women in univariate analysis, increasing age and number of children besides decreasing age at first pregnancy, age of menopause and duration of OCP use were associated with CAD (Table 1). There was also a relation between CAD and oligomenorrhea, being house-wife, having no history of OCP use, DM and family history of CAD among categorical variables in postmenopausal women (Table 2). After adjusting all variables for CAD, the subsequent items were significantly correlated (Table 4): increasing age with OR of 1.36, DM with OR of 5.18 and family history of CAD with OR of 8.33.

Also, history of OCP use with OR of 0.24 and 0.20, respectively in pre and postmenopausal women was a protective factor against CAD. In addition, increase in age of menopause with OR of 0.80 had protective effect on CAD (Table 4).

Table 1: Demographic Numerical Variables of Premenopausal and Postmenopausal Women

Variable	Premenopausal women			Postmenopausal women		
	CAD, n=80, mean \pm SD	No CAD, n=80, mean \pm SD	Pvalue	CAD, n=100, mean \pm SD	No CAD, n=100, mean \pm SD	Pvalue
Age (years)	46.01 \pm 6.02	43.6 \pm 6.6	0.02*	61.6 \pm 5.1	55.08 \pm 4.9	<0.001*
Number of pregnancies	3.6 \pm 2.6	3.1 \pm 1.09	0.10	6.01 \pm 2.4	5.4 \pm 2.5	0.09
Number of children	2.9 \pm 1.9	2.4 \pm 1.02	0.04*	5.08 \pm 2.2	3.9 \pm 1.6	<0.001*
Number of abortions	0.6 \pm 0.4	0.7 \pm 0.7	0.70	1 \pm 0.2	1.08 \pm 0.4	0.60
Age at first pregnancy (years)	19.2 \pm 4.5	22.3 \pm 6.6	0.001*	17.6 \pm 2.09	18.7 \pm 4.05	0.01*
Age at menarche (years)	12.8 \pm 1.1	12.4 \pm 2.2	0.21	12.9 \pm 1.1	12.8 \pm 1.3	0.30
Duration of OCP use (months)	55.6 \pm 38.7	49 \pm 36.3	0.50	26.6 \pm 8.6	37.08 \pm 12	0.002*
BMI (kg/m ²)	29.7 \pm 7.1	28.2 \pm 2.8	0.08	28.8 \pm 4.9	30.04 \pm 6.1	0.10
Menopausal age (years)	-	-	-	45.4 \pm 4.8	50.9 \pm 5.3	<0.001

*P<0.05 significant

Table 2: Demographic Categorical Variables of Premenopausal and Postmenopausal Women

Variable	Premenopausal women				Postmenopausal women			
	CAD, n=80, mean ± SD	No CAD, n=80, mean ± SD	Pvalue	Unadjusted OR (95%CI)	CAD, n=100, mean ± SD	No CAD, n=100, mean ± SD	Pvalue	Unadjusted OR (95%CI)
Oligomenorrhea	28(35%)	4(5%)	<0.001*	10.2 (3.3-30.9)	20(20%)	5(5%)	0.001*	4.7 (1.7-13.2)
OCP use	21(26.3%)	23(28.8%)	0.70	-	17(17%)	75(75%)	<0.001*	0.06 (0.03-0.1)
House wife	59(73.8%)	25(31.3%)	<0.001*	6.1 (3.1-12.2)	89(89%)	74(74%)	<0.001*	2.8 (1.3-6.1)
Education (≤diploma)	40(50%)	20(25%)	0.001*	3 (1.5-5.8)	85(85%)	80(80%)	0.30	-
Marital status (unmarried)	8(10%)	1(1.3%)	0.03*	8.7 (1.07-7)	1(1%)	5(5%)	0.20	-
DM	44(55%)	12(15%)	<0.001*	6.9 (3.2-14.7)	65(65%)	40(40%)	<0.001*	2.7 (1.5-4.9)
HTN	48(60%)	16(20%)	<0.001*	6 (2.9-12.1)	70(70%)	60(60%)	0.10	-
HLP	52(65%)	44(55%)	0.10	-	80(80%)	75(75%)	0.30	-
C/S	4(5%)	4(5%)	10	-	5(5%)	1(1%)	0.20	-
FH	52(65%)	28(35%)	<0.001*	3.4 (1.8-6.6)	60(60%)	20(20%)	<0.001*	6 (3.1-11.2)
HRT	-	-	-	-	5(5.9%)	10(10.5%)	0.20	-
Surgical menopause	-	-	-	-	15(15%)	25(25%)	0.07	-

DM: Diabetes Mellitus, HLP: Hyperlipidemia, HTN: Hypertension, C/S: Caesarean Section, FH: Family History, HRT: Hormone Replacement Therapy

*P<0.05 significant

Table 3: Adjusted Odds Ratio in Premenopausal Women

Variable	P value	Adjusted OR (95%CI)
Diabetes	<0.001	6.32 (2.68-14.89)
Hypertension	<0.001	9.01 (3.01-26.93)
Oligomenorrhea	0.002	6.72 (1.96-23.03)
OCP	0.024	0.24 (0.07-0.82)

Table 4: Adjusted Odds ratio in Postmenopausal Women

Variable	P value	Adjusted OR (95%CI)
Age	<0.001	1.36 (1.21-1.53)
Menopausal Age	<0.001	0.80 (0.71-0.89)
OCP	0.002	0.20 (0.07-0.55)
Diabetes	0.002	5.18 (1.82-14.72)
Family history of CAD	<0.001	8.33 (2.96-23.45)

DISCUSSION

This study shows that diabetes is the most important coronary artery disease risk factor in women (adjusted OR in premenopausal age = 6.32, adjusted in postmenopausal age = 5.18) that is consistent with results of The Women's Ischemia Syndrome Evaluation (WISE) study in 2003 [7]. It has been approved that diabetic women have more menstrual irregularity, lower blood estrogen levels, and higher androgen levels than non-diabetic [7]. Moreover, it has been established that hypoestrogenemia in female is accompanied by a diminution of normal vasodilatation and even vasoconstriction in response to stress [7]. It seems that one of the most important harmful effects of diabetes on female that leads to CAD comes from the ability of diabetes to change hormonal level. So, diabetes -not only influences on cardiovascular status with a direct effect on vascular system, but also in an indirect way by changing hormonal levels. That is why diabetes is the most significant risk factor for CAD in women. Our study results after adjustment for confounders did not

confirmed age at first birth as a risk factor for CAD. This finding is similar to findings of Colditz et al. [8] study while contrasts with the results of Kharazmi et al. [9] and Cooper et al. [10] studies, which confirmed increased risk in women with lower and higher maternal age at first birth, respectively. However, Hardy et al.'s study showed that lower age at first birth is associated with higher CAD risk factors in both genders [11]. The main advantage of Hardy et al.'s study over other studies was prospective data collection during reproductive years instead of recalling in the later life [11]. In another recent study by Pirkle et al. in Canada, no significant association was found between low maternal age at first birth and CAD [12].

In our study, after adjustment of results for confounding factors there was no significant association between number of children and CAD as it was observed in earliest Hardy et al.'s study [13]. Both Hardy et al.'s studies concluded that any association between CAD risk factors and number of children or parental age at

first birth is a result of family lifestyle and behaviors rather than biological effect of pregnancy in women [11, 13]. The association between parity and CAD was also confirmed by later studies by Parikh et al. and Pirkle et al. [12, 14] while Jacobsen et al. did not find any association between parity and total, ischemic heart disease or stroke mortality [15]. Oligomenorrhea with odds ratio of 6.72 was another reproductive risk factor associated with CAD in premenopausal but not postmenopausal women in our study. Menstrual irregularity is one of the predictors of future diabetes and then coronary artery disease [4]. To the best of our knowledge, Polycystic ovarian syndrome (PCOS) is the most common cause of menstrual irregularity, specifically oligomenorrhea is associated with metabolic disorders and subsequent CAD. Thus, this correlation between oligomenorrhea and CAD is rational. A study by Wang et al. in 2011 showed a non-significant increased risk of CAD in women with menstrual irregularity which after adjustment for BMI changed to nonsignificant [16] which in our study remained significant (Table 3).

Age at menopause was another reproductive factor significantly associated with CAD in postmenopausal women in our study. Similar to ours, He et al.'s study showed significant association between age at menopause and CAD in rural Chinese women with odds ratio of 1.02 which is higher than our study (0.80) [17]. In fact in our study, higher age at menopause has protective effect on CAD (Table 4). Present study did not find any significant association between age at menarche and CAD in women while CVD mortality was associated inversely with age at menarche in non-smoker women in China [18]. Wu et al.'s study found that younger age at menarche and menopause are associated with higher risk of total mortality and mortality from stroke, respectively [19].

Canoy et al.'s cohort showed significantly increased risk of CAD both in early and late ages at menarche [20]. Another study in China also found a significant association between higher ages at menarche and menopause and lower risk of CVD [21]. In this study, there was an adverse relation between OCP use and CAD in pre and postmenopausal women and OCP was a protective factor against CAD. This has been confirmed by other studies. Kaplan et al [22] have demonstrated that contraceptive hormone treatment inhibits the acceleration of atherosclerosis in female monkeys. BairyMerz et al. [23] also reported that past oral contraceptive use was associated with an approximately 2.5 lower CAD severity and Stampfer et al. [24] verified a lower RR (0.8) in OCP users for CAD. Greater flow mediated dilation in OCP users may be cause of such protection against CAD [25].

CONCLUSIONS

In animal studies it has been found that OCP blocked the neuroendocrine stress response in primate [24].

This capability protects cardiovascular system from the adverse effect of stressors. In addition to this benefit, OCP correct menstrual irregularity that may be leads to diabetes and CAD. Therefore, OCP could be an appropriate choice for treatment of menstrual irregularity. The main limitation of our study is recall bias that is probable in both groups of women and it should be considered in interpretation of results. Diabetes is the most important risk factor for CAD in both pre and postmenopausal women, so that female with diabetes must be strictly under treatment. Among reproductive factors, after adjusting all known CAD risk factors and reproductive factors for CAD, only oligomenorrhea in premenopausal women and age at menopause in postmenopausal women were associated with CAD. Since, oligomenorrhea could lead to diabetes and had subsequent CAD risk, all women with cyclic irregularity should be treated to prevent from later CAD. Also, OCP has a protective effect on cardiovascular disease both in pre and postmenopausal women, therefore could be an appropriate choice for treatment of these patients.

ETHICAL CONSIDERATION

The present study was approved by the research ethics committee of Tehran University of Medical Sciences.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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AUTHORS' CONTRIBUTION

Soodabeh Darvish: Collected the data and wrote the paper

Saeed Sadeghian: Conceived of the presented idea

Azizeh Ghaseminejad: Developed the theory and performed the computations

Reza Mohebi: Performed the analysis

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