INTRODUCTION

The incidence of cardiovascular disease (CVD) and mortality reaches to a significantly higher level in older women, which may be related to menopausal transition: estradiol depletion or relative androgen excess, which promotes plaque stability and clot formation, increasing the risk of myocardial diseases. Many randomized clinical trials have suggested that estrogen and progesterin, used as contraceptive or Hormone Replacement Therapy (HRT), does not confer cardiac protection and may increase the risk of Coronary Heart Disease (CHD) in healthy women. The most frequent major adverse effect of hormonal contraceptives is shown to be an increased risk of CVD including Myocardial Infarction (MI), Venous Thromboembolism (VTE), and cerebrovascular strokes. World Health Organization's (WHO's) international multi-center case control studies, during late 1990's, on the risks of CVD, enforced the importance of providing adequate information to current and prospective contraceptive users about cardiovascular risks associated with contraceptives and their interaction with smoking, obesity and other risk factors. The studies, carried out by WHO, revealed evidence of increased risk of MI with Oral Contraceptives (OC) containing higher doses of estrogen than those commonly prescribed nowadays, which are of low doses in women with known cardiovascular risk factors, which include increasing age, smoking, obesity, family history of high serum cholesterol level, hypertension and/or heart disease.

The relationship between Blood Pressure (BP) and risk of cardiovascular event is continuous, consistent and independent of other risk factors. Resting smooth muscle sympathetic nerve activity and sympathetic baroreflex sensitivity were found to be greater in midluteal phase (high hormone) as compared to early follicular (low hormone) phase, as estrogen enhances baroreflex activity and progesterone reduces it. Estrogen can directly or indirectly alter peripheral vascular tone by enhancing basic nitric oxide release and both estrogen and progesterone increase circulating blood volume.

The electrocardiographic changes recorded in women during different phases of normal menstrual cycle and after menopause revealed many differences as...
compared to men, which may be due to different sex hormones, difference in expression and function of ion channels in activation of autonomic nervous system.\textsuperscript{11,12} ECG findings revealed women to have a faster baseline heart rate, a shorter sinus node refractory time.\textsuperscript{13}

The use of oral and injectable contraceptives is on the rise in Pakistani population whom various hormonal preparations are prescribed without initial recording of weight, blood pressure and a proper cardiovascular check up. It is pertinent to study the effects of these preparations as unlike other commonly prescribed medicines, contraceptives are taken by healthy women for longer periods of time.

The aim of present study was to evaluate the effect of contraceptive hormonal administration on ECG, BP and BMI in the local female population with different environmental, socioeconomic and cultural background.

\section*{MATERIALS AND METHODS}

It was an observational study conducted at the National Institute of Fertility Research Centre, Jinnah Postgraduate Medical Centre, Karachi, from July 1997 to 1999. Sixty-four women aged between 20-35 years, belonging to low-income group, having almost similar dietary pattern, environmental conditions and life style, volunteered for the study. Forty-four of them were using oral and injectable contraceptives for varying periods of duration (1.5 - 6 years) and compared with 20 age matched controls.

Subjects were categorized in three groups: (i) Women not taking any form of contraceptives served as controls (n=20); (ii) Women using oral contraceptive tablets OC users, estrogen users and progesterone (n=22) and iii) Women using injectable contraceptives IC users, progesterone only.

A structured questionnaire was administered to obtain information on personal details, occupational, medical and social histories, use of tobacco in any form, use of salt and oil/ghee in diet, and exercise. Their weight, height and blood pressure were measured. Heart rate, rhythm, P-R interval, QT interval and ST segment changes were evaluated by ECG.

Body weight was measured on weighing scale without shoes, and standing body height was measured without shoes to the nearest 0.5, with shoulders in a relaxed position and arms hanging freely. BMI was measured as body weight in kilogram divided by the square of the body height in meters.

\textit{BMI} = \textit{Weight (kg)} / \textit{Height (m})^2

Based on international obesity task force convened by the World Health Organization, a subject with BMI of \textless{} 25 has normal weight, between 25.0 - 29.9 kg/m\textsuperscript{2}, is defined as overweight. A BMI of more than 30.0 kg / m\textsuperscript{2} is defined as obese.\textsuperscript{14}

Blood pressure was measured with the subject seated comfortably in a chair with the back supported and arms rested at heart level. Measurements were taken using mercury sphygmomanometer applied on the right arm of the participant, after at least five minutes of rest. First and fifth Korotkoff's sounds were recorded for systolic and diastolic readings respectively. Two readings separated by two minutes were averaged. If they differ by more than 5 mmHg, one additional reading was obtained and then averaged. Subjects were also asked regarding family history of hypertension or heart disease, past history of hypertension during any pregnancy (including pre-eclampsia or eclampsia), or ever using any anti- hypertensive treatment and whether their blood pressure was checked before starting OC and IC.

All participants were studied using the 12 lead standard ECG machine, which measured the heart rate and durations of PR intervals and QRS complexes, coded the interpretation of different waves, which was further confirmed by a cardiologist.

Written consent was obtained from all volunteers.

The data was analyzed in three groups; OC and IC users and controls. The group means and standard deviations were determined for various parameters and compared. Analysis of different variables was performed using test of significance ‘t’ test with \textit{p} value < 0.05 as the significant level.

\section*{RESULTS}

In this cross-sectional study, the effects of contraceptives were evaluated on BMI, blood pressure and ECG parameters in 44 young married women (age 20-35 years), using contraceptives under study for 1.5 - 6 years and compared with 20 control subjects. Their marriage duration was between 2.5 - 15 years, with at least 4 - 6 living children, and exhibiting regular menstrual pattern. The data is presented as mean ± standard deviation in Table I. There was no history of smoking, which excluded a very important risk factor, use of excess salt and oil in diet, and none of them ever performed regular exercise.

The subjects classified according to the type of contraceptive and their BMI revealed 50%, 27% and 27% each belonged to overweight category in control, OC and IC users respectively. There was insignificant difference of BMI in subjects using contraceptives (OC= 23.1 ± 3.2; IC= 22.9 ± 4.7) as compared to controls (24.2 ± 4.0). However, the subjects who were married for more than 10 years, and were using contraceptives for more than 3 years, had a tendency to become overweight.

The systolic and diastolic blood pressure in control group was within normal range, except for one subject with blood pressure of 140/90 mmHg. In subjects using
OC, 22% subjects showed systolic reading of 130-140 mmHg, whereas the diastolic BP was observed over 90 mmHg only in 13% of OC users. On the contrary, in IC users, systolic BP was higher than 120 mmHg in 13% subjects, whereas diastolic BP >90 mmHg was observed only in 9% subjects. The statistical analysis showed no significant difference between BP values of normal and overweight subjects. The study revealed significant correlation between BMI and heart rate (p <0.05) of OC users (Figure 1). In IC users, BMI was significantly correlated with both systolic (p < 0.01) and diastolic (p < 0.05) blood pressures as compared to controls. In these subjects there was no history of hypertension in the past or in family or during any pregnancy.

The ECG findings were normal in control group. Although 40% subjects using contraceptives showed altered ECG changes, most of them were normally observed during menstrual cycle. These included sinus tachycardia, supraventricular tachycardia and right ventricular conduction delay. Significant observations among contraceptive users were left ventricular hypertrophy, right axis deviation, right atrial enlargement and lateral and inferior wall ischemia (9%). There was no significant difference of any variable between controls and contraceptive users (both types). However, on comparing the control values with either OC or injectable users, it was found that BMI and systolic BP (p < 0.05) values were significant in injectable users as compared to controls (Figure 2a and 2c). There was no statistical difference of any variable between subjects of two types of contraceptive users.

**DISCUSSION**

In the present study, the effects of OC and IC were evaluated on BMI, BP and ECG patterns on females aged between 20 – 35 years. This age limit was ideal...
because women in this group were sexually active, perfect and regular users; also increasing age is itself a risk factor and WHO cautions the women above 35 years of age to refrain from using these preparations, particularly if they are smokers. The contraceptives mostly used by Pakistani women are oral tablet (containing both estrogen and progesterone) and injectables (progestin only) belonging to second-generation group.

This study did not show any significant effect on BMI in contraceptive users, which is consistent with previous reports which failed to correlate an increase in body weight or body composition during short-term treatment period. However, when age, parity, income, socioeconomic condition and duration of use were matched, it was revealed that subjects in age group > 30 years, and duration of contraceptive use > 3 years had a tendency to gain weight (27% each in OC and IC groups). These subjects also had altered lipid profiles, blood glucose level and fibrinogen titer as reported previously. Many women perceive that OC pills cause weight gain (the progesterone and androgens may affect appetite), but actual studies of currently available formulations demonstrate little or no change in weight. On the contrary, a study in USA showed a constant weight gain averaging 0.33kg/month in injectable users. Not all women gain weight but some who have a tendency to abnormal glucose metabolism are the ones to watch for.

In this study, the systolic and diastolic BP were slightly increased in a few subjects using either of the two contraceptives; however, most of them generally remained unaffected. The systolic BP in 22% (OC) and 13% (IC) subjects was in pre-hypertensive phase whereas diastolic BP was 90 mmHg in 13% OC and 9% IC users respectively. Previously, a study reported mild HT in many and significant HT in 5% of those who used OC. Another study on effect of long-term use of injectable contraceptives did not reveal an unfavourable effect on weight and BP; but in our study, injectable users have significant correlation between BMI and systolic and diastolic pressures. These effects probably result from capacity of both estrogen and progestin to facilitate retention of sodium and water secondary to rise in plasma renin activity and subsequent formation of angiotensin.

Previous studies revealed a small proportion of OC users (5%) appeared to have the risk of developing HT with prolonged OC use. In some of them, HT was coincidental; in most of the others, it subsided after cessation of OC use; in rare cases, it has been noted to progress to malignant HT. Normally, the systolic BP is higher throughout the menstrual cycle in women who take OC, than in ovulatory women as synthetic estrogen and progestin tend to elevate BP, while naturally occurring hormones lower it or have no effects. In a study from United States of America (USA), blood pressure did not change subsequently in either ovulatory women or OC users throughout the menstrual cycle. In another study published in USA, there were insignificant changes in the systolic and diastolic BP values recorded at follow-up; only one injectable user developed systemic HT (160/100 mmHg) after six months of use. Unfortunately, no data regarding effect of contraceptives on weight gain or BP is available in Pakistani female population.

The risk of HT with the use of hormonal contraceptives has been observed to increase with age and with increasing duration of use, being greatest in women above 35 years of age. A study revealed a mean increase of 4 mmHg for systolic pressure and 2 mmHg for diastolic pressure in women using third generation contraceptives. Smoking may also be responsible for the higher incidence of HT among OC users, as evidenced by two studies (both included smokers), which showed an increased risk of MI among current contraceptive users with a history of high blood pressure, compared to current users without a history. The subjects in our study were all non-smokers who did not use tobacco in any form, which excluded a very important risk factor.

Relationship between the use of low dose OC and MI was studied in a population-based case-control study which found that with respect to MI, low dose OC can be used safely by women who lack risk factors for CHD. There was no significant difference between second and third generation products; the excess risk of venous thromboembolism associated with the use of third generation products may be balanced by the reduced risk of MI associated with same product.

Alteration in ECG profiles, found among 40% of contraceptive users in the current study, were mostly those normally recorded during different phases of menstrual cycle; although a few cases of other disorders were also observed e.g. inferior wall ischemia, atrial and ventricular hypertrophy, right axis deviation and ventricular conduction delay, which were important pathological findings, as the subjects were asymptomatic and had no previous history of heart disease. It was observed that in OC users, increase in BMI was significantly correlated with tachycardia (p < 0.05).

Data is sparse regarding the prevalence, incidence and independent prognostic value of minor and/or major ECG abnormalities in asymptomatic women receiving contraceptives or hormone replacement therapy. In Pakistan, the data regarding ECG changes in contraceptive users is not widely available. Suspicious ECG findings in women, using OC were reported for the first time in 1980, though only in 10% of patients. A recent publication on ECG abnormalities in women...
participating in Women’s Health Indicative Study revealed that the trial was stopped in 2002, as there was a significant increase in CHD and mortality, as evidenced by wide QRS/T angles, QT prolongation and reduced heart rate variability.\(^3\)\(^{30}\) Previously, a study reported resting and exercise electrocardiographic abnormalities were associated with sex hormone used by women, and a higher prevalence of pathological ECG changes in postmenopausal women receiving hormone replacement therapy.\(^3\)\(^{31}\)

ECG study, following short-term Norplant use (12 months), although reported no significant changes either in BP, heart rate, rhythm and cardiac axis, but reported significantly prolonged PR and QT intervals; however, progesterone containing replacement therapy was associated with increased heart rate and an attenuation of heart rate variability in postmenopausal women.\(^3\)\(^{32}\) Whereas, hormone replacement therapy with estrogen beneficially modulates autonomic tone and BP regulation in postmenopausal women, the impact of concomitant treatment with progestin remains unclear, as progestin has anti-estrogenic effect.\(^3\)\(^{27}\)

**CONCLUSION**

From the data gathered, it is concluded that women aged < 30 years and using contraceptives for > 3 years had a tendency to gain weight as well as developed mild increase in BP. Results become significant in the prospect that no such study was done before to find correlation between different cardiovascular risk factors in Pakistani female population using oral and injectable contraceptives, with quite different dietary, environmental and lifestyle behaviours from western population.

**REFERENCES**


