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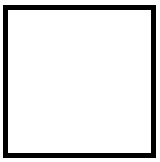

# Myocardial ischaemia in postmenopausal women in Kathmandu valley and role of hormone replacement therapy for its prevention

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## ABSTRACT

**This is a retrospective study of coronary heart disease (CHD) in postmenopausal women in one calendar year. The study included 186 consecutive women admitted in two government and one private hospitals in Kathmandu having CCU/ICU beds; the women were diagnosed with this disease in one calendar year. The epidemiology and risks factors and role of 'hormone replacement therapy' for its prevention are discussed. In most of the developed countries, the set standard was that barring any contraindication, all postmenopausal women with acute myocardial infarction should be prescribed hormone replacement therapy before being discharged from hospital. The evidence base of this standard derives from more than 30 epidemiological and clinical studies and a large body of biological data. However in this study, 'hormone replacement therapy' in postmenopausal women with myocardial infarction has not received much attention. Professionals caring for women, who have had myocardial infarction, need to consider hormone replacement therapy as a secondary prophylaxis of myocardial infarction. Gynaecologists should liaise with colleagues in other specialties to ensure that information on the non gynaecological benefits of hormone replacement therapy is widely disseminated.**

*Keywords: Postmenopausal women; myocardial infarction; risk factors; hormone replacement.*

## INTRODUCTION

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Coronary heart disease (CHD) is the major cause of death in postmenopausal women in developed countries and is increasing in developing countries, and current evidence indicates that this is due to a loss of the protective effects of endogenous oestrogen on the cardio-vascular system. The extent and poor prognosis of myocardial infarction in women have only been recently identified. As shown in the Framingham study[1], women are more likely than men to die after myocardial infarction with both medical and surgical therapies. The in-hospital mortality rate among women who undergo coronary artery surgery is substantially higher than those among men.[2-7] It is uncertain whether this excess mortality reflects the older age, smaller body size or more frequent and severe co-existing illness of women when symptomatic coronary disease occurs. Ischaemic heart disease (IHD) is more dependent on age in women than in men; women are usually 10 years older than men when any coronary manifestation first appear.[8] With the aging of the population more women than men now die of coronary heart disease each year unless women take preventive measures throughout their life. Most primary preventive efforts have focused on the major modifiable determinants of risks eg., cigarette smoking, an elevated blood's cholesterol level, hypertension, obesity, diabetes and sedentary life style. Recently attention has been directed towards the possible benefits of oestrogen replacement therapy in postmenopausal women.[9]

Cigarette smoking is directly responsible for 21% of all mortality of CHD and is inversely related to education.[10] The relative risk of infarction in ex- smoker decreases rapidly as have been demonstrated in observational studies both case control[9] and cohort[10]. Total plasma cholesterol and low density liproprotein (LDL-C) levels are important risk factor for CHD in women[11,12]. Various studies HERS[13] 4S[14] CARE[11] showed reduced death or subsequent infarction by 46% in women and 26% in men by lowering cholesterol and LDL-C level after myocardial infarction. Prospective observational studies have shown that high blood pressure is positively and independently associated with the risk of strokes, myocardial infarction and mortality from all vascular causes.[15,16] Diabetes is a far greater risk factor for women than men; women over 45 years are twice as likely as men to develop diabetes.[17] Diabetes has an adverse effect on the in-hospital and long-term prognosis after myocardial infarction, much more worse in women. More women than men who undergo myocardial revascularization procedures are diabetic, which probably contributes to the less favourable outcome in women. Physical inactivity is a highly prevalent and independent risk factor in women. Moderate leisure time activity reduces the risk on myocardial infarction by half. Despite this benefit, few women are referred to exercise rehabilitation after coronary event.[18,19] Obesity is well-established cause of diabetes mellitus, hypertension and lipid abnormalities.[9] In a cohort study by American Cancer Society[20] and Farmingham Heart study[21], 40% of the coronary events were attributable to being overweight. The cardiovascular risks of obesity were amplified by other coronary risk factors.[22]

'Hormone replacement therapy' after menopause is a promising approach to the primary and secondary prevention of coronary heart disease in women.[23-25] The importance of primary prevention is highlighted by the fact that about a quarter of new cases of coronary heart disease present as sudden death.[26] Secondary prevention should be approached with the same vigour as primary prevention because morbidity and mortality for IHD have considerable social and financial implication for individuals as well as communities. The protective effects of oestrogen are its favourable effects on serum lipid profile, reducing total cholesterol and LDL levels and increasing HDL levels.[11-14] Oestrogen causes inhibition of endothelial hyperplasia and atherosclerosis through endothelial nitric acid synthatase (eNos)[27,28] as well as the enhanced production of prostacyclin within the arterial endothelial cells which induces vasodilating effect and a consequent fall in blood pressure.[29] The meta - analysis of over 30 epidemiological studies suggest a reduction of approximately 50% in the risk of CHD in healthy post-menopausal women taking oral oestrogen.[9,23-35] While it is possible that selection bias account for a significant proportion of the cardio protection observed in healthy post menopausal women using hormone replacement therapy, an even more substantial benefits in women with documented coronary disease, is associated with significant reduction in risk of mortality (table I). The effectiveness of HRT in primary and secondary prevention of CHD has recently been confirmed in the Nurse's Health Study[30,31], and Finish National Register data.[27] In the Leisure World Study[25,32], the relative risk of suffering a fatal infarction by those with previous infarction or angina and who had used oestrogen replacement therapy was 0.4 compared with never users with a similar history. In a cohort of women with cardiovascular disease followed-up for an average of 8.5 years, oestrogen replacement therapy was associated with a 79% reduction in cardiovascular death rate.[25,33] A 10-year follow-up of women with severe coronary artery stenosis showed that the survival rate for oestrogen users and never users were 98% and 60% respectively.[25,34] In a case-control study of post menopausal women, who underwent elective percutaneous transluminal coronary angioplasty, HRT was associated with improved long-term outcome.[25,35] Most of these studies were conducted in the United States, where a conjugated equine oestrogen preparation taken orally without a progestion, has been the most commonly used regime. Recent observational studies[36,37] suggest that oestrogen/progestin regimens (recommended to prevent oestrogen-induced endometrial cancer) have a cardioprotective effects similar to unopposed oestrogen.

The evidence is largely from observational studies rather than random – allocation trial, due to difficulties in instituting the later. Nevertheless, the magnitude of benefit demonstrated by all observational studies and in view of the rising life expectancy in women, these notions imply that 'hormone replacement therapy' should at long last received the recognition it deserves as one of the finest available tools for fighting aging.

**Table I:** Benefits of oestrogen replacement therapy in postmenopausal women with coronory artery disease.

| *Author* | *Samples size* | *Outcome measures* | *Users* | *Non-users* |
|---|---|---|---|---|
| Sullivan *et al* [33] | 2268 | 10-year survival rate (%) | 97 | 60* |
| Henderson *et al* [32] | 8841 | relative risk of repeat/fatal myocardial infarction | 0.4 | 1 |
| Bush *et al* [34] | 2270 | cardiovascular death rate (per 1000 persons-year) n | 13.8 | 66.3 ⇓ |
| Rosano *et al* [40] | 11 | exercise tolerance | – | - |
| O'Keefe *et al* [35] | 337 | 7-yrs survival rate (%) | 93 | 75 ♥ |
| | | CVS event rate | 12 | 35 |
| *P=0.007; ♥ P=0.001; ⇓ 79% reduction | | | | |

## METHOD

All female in-patients with a diagnosis of CHD/myocardial Ischaemia/Angina Pectoris in two big government hospitals (Bir Hospital and TUTH) and one private hospital (Medicare Hospital and Research Centre) in Kathmandu, the capital city of Nepal, between 14th April 1998 and 14th 1999, were identified through the record book of CCU/ICU wards. The case notes of 186 consecutive women were analyzed and searched for data relating to the diagnosis of myocardial infarction and ischaemia, medical history, presence or absence of risk factors and history of use of hormone (current/Past) and evidence of HRT prescribed before discharge. Out of 186 case notes, 8 cases were premenopausal, therefore excluded from the study.

The diagnosis of acute myocardial infarction was diagnosed if the patient had any two of the followings:

- characteristic history of substernal pain of recent onset lasting longer than 30 minutes, elevated cardiac enzymes (creatinine kinase, aspartate transaminase, lactate dihydrogenase);
- electrocardiographic evidence of an infarct (pathological Q-waves and/or ST elevation of >1 mm in standard lead I/aVL and/or ST elevating >2 mm in precordial levels V1-6 followed by T-wave inversion. There were 355 CHD/myocardial infarction/AP cases in male during this study period giving the ratio of male to female as 2:1 ratio.

## RESULT

The mean age of the women was 65 years, the youngest was 45 years and the oldest was 89 years. Of the 186, 8 cases were premenopausal therefore excluded from further analysis. Table I shows the distribution of patients agewise.

**Table I:** Distribution of patients by age

| *<50* | *50-80* | *80+* | *Total* |
|---|---|---|---|

| *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
|---|---|---|---|---|---|---|---|
| 20 | (11.2%) | 140 | (78.6%) | 18 | (10.2%) | 178 | (100%) |

The maximum number of patients, about 79%, were in the age group of 50-80 years of age. The presenting symptoms are shown in Table II.

The characteristic substernal pain with radiating nature was seen in 135 cases (76.9%) followed by shortness of breath (50%), giddiness (41%), sweating (45%), palpitation (12%) and fainting (16%). The majority of the patients had a combination of two or more of the above symptoms.

The duration of illness before admission to ccu/icu is shown in table III. The duration varies from just under 3 hours to as long as 2 weeks.

It is seen that as much as 45% of the patients came to hospital very late. About 15% of the women came to hospital as late as 2 weeks or more. Acute myocardial infarction was diagnosed in 123 cases (69%) using the above mentioned criteria for diagnosis and is shown in table IV.

The following risk factors were identified: previous ischaemic heart disease, smoking, hypertension, diabetes mellitus and the combination of risk factors. Obesity was mentioned only in seven case notes. Family history of IHD was recorded in two case notes. Lipid profile was done in 12 cases only. The pattern of risk factors is shown in table V.

**Table II:** Main presenting symptoms on admission.

| *Chest pain* | | *SOB* | | *Giddiness* | | *Sweating* | | *Palpitation* | | *Fainting* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
| 135 | (76.9%) | 88 | (50%) | 41 | (23%) | 45 | (25.2%) | 12 | (6.7%) | 16 | (9.1%) |

**Table III:** Duration of illness before admission.

| *< 3 hours* | | *Up to 24 hours* | | *< 1 week* | | *> 1 week* | | *Total* | |
|---|---|---|---|---|---|---|---|---|---|
| *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
| 26 | (14.6%) | 70 | (39.5%) | 56 | (31.4%) | 26 | (14.5%) | 178 | (100%) |

**Table IV:** Disease pattern identification.

| *CHD/AP* | | *Myocardial infarction* | | *Total* | |
|---|---|---|---|---|---|
| *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
| 55 | (30.9%) | 123 | (69.1%) | 178 | (100%) |

**Table V:** Presence of risk factors.

| *Hypertension* | | *Smoking* | | *Diabetes* | | *Previous IHD* | | *Obesity* | | *Hyperlipidemia* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
| 92 | (51.7%) | 61 | (34.2%) | 35 | (19.6%) | 28 | (15.7%) | 7 | (4%) | 12 | (7%) |

The family history of CHD was mentioned only in two cases, and 13 (7.3%) patients had more than one risk factor. The common form of risk factors were hypertension and/or diabetes, smoking, obesity and previous CHD. Seventeen women (13.8%) of myocardial infarction died during the index admission and 161 cases were discharged home. Three women were readmitted with a repeated myocardial infarction during the study period and all recovered well and discharged home. There were no cases of undiagnosed vaginal bleeding or deep vein thrombosis or liver disease or cancer that would contraindicate HRT. None of the women had ever used HRT, and none of them was prescribed HRT at the time of discharge. In view of recent concern about the risk of deep vein thrombosis with HRT, it maybe considered the best practice to prescribe hormones after the woman has fully mobilized. However, no recommendation was made to use HRT at discharge or later at follow-up.

## DISCUSSION

Acute myocardial infarction occurs frequently in women, manifests about 10 years later than in men and is associated with a high rate of mortality with both medical and surgical therapies. With the aging of the population, more women than men now die of coronary heart disease each year unless women take preventive measures throughout their life. Reduction in the risk of CHD is important for women of all ages, notably, by means of change in diet for weight control[9,20-22], fat restriction and cholesterol reduction[11-14], smoking prevention and cessation[9,10] control of blood pressure[15,16], and diabetes[17], regular exercise[18,19] with moderate alcohol consumption – all appear to reduce the risk of the first myocardial infraction substantially. CHD runs in families[38] and blood relatives of patient, with premature coronary disease, are themselves at increased risk of developing the disease; yet two third of patients did not know whether their family has been advised to be screened for coronary risk factors. Because risk factors for coronary heart disease are highly prevalent in women, physicians should educate their women patients that CHD can be prevented or altered by behavioural strategies.

Epidemiological data indicating that HRT is protective against repeat/fatal myocardial infarction have been available for at least 10 years.[25] Post menopausal oestrogen therapy not only inhibits progression of coronary artery atherosclerosis but also affects coronary artery reactivity and cardiovascular haemodyamics.[28] In addition to the long-term benefit, there is some evidence that oestrogen is beneficial in the acute management of myocardial ischaemia.[40] On the basis of best available data, the American College of Physicians recommended the use of HRT by

women who have CHD or who are at increased risk of CHD.[14] This recommendation has been reaffirmed by the American Heart Association. Recent observation studies[36,37] suggest that oestrogen and progestin regimens (recommended to prevent oestrogen induced hyperplasia and cancer) have a cardioprotective effect similar to unopposed oestrogen. Current hormone users regardless of whether they use oestrogen alone or with progestin tended to have a better risk profile than women who had never used hormones.[31] In the women who used oestrogen with progestin, there was also a marked decrease in the risk of major coronary disease.[31] Unfortunately, clinical practice in Nepal is yet to be informed accordingly. There was no mention of 'hormone replacement therapy' in the management of patients after their first myocardial infarction. Following this review, ways of modifying current practice to meet the set standard is to be discussed with the physicians involved with the CHD treatment. This includes liaison between medical and gynecological colleagues and routine referral of the women to the menopausal clinic when discharged from the hospital. Obstetricians and gynaecologists are in a good position to play an active role in the prevention of cardiovascular disease because their professional activities are often geared towards screening and preventing reproductive diseases in relatively healthy women. Gynaecologists should assume the responsibility of disseminating information on 'hormone replacement therapy' to colleagues of other specialities. Provision of hormone replacement therapy in high risk women is an important element. Myocardial infarction is more likely to be fatal in women than in men, and women are more likely than men to suffer reinfarction during their first year after the initial events. It is recommended that coronary care units nationwide liaise with local gynaecologist to provide 'hormone replacement therapy' for women who have had a myocardial infarction. The recently reported association between 'hormone replacement therapy' and an increased risk of venous thromboembolism[43,44] should not preclude its use in women for whom the benefit exceed the risks eg., oesteoporotic fracture and coronary heart disease and the probable modest increase in breast cancer. The best strategy is probably to avoid HRT in first degree relatives of cancer patients, prescribe shorter interval for endometrial cancer screening in HRT users.[27]

## CONCLUSION

In view of rapid urbanization, industrialization and changed life-style, CHD is emerging as a great public health problem in developing countries especially in urban population. This study is mainly concentrated on CHD/MI in postmenopausal women, and male to female ratio is at 2:1 ratio. The magnitude of the problem can well be imagined from this study in Kathmandu by the number of new CHD likely to occur in elderly female population yearly. The prevalence of CHD and MI in south East Asia is at 0.08% and 0.02% respectively.[41] In the Kathmandu valley including suburbs with approximate population of 700000, the prevalence rate of CHD in adult population is at 0.07% and MI in

postmenopausal women is at 0.01% as shown by this study, which is similar to S/E Asian population. The only solution to deal with the global coronary catastrophe which is world no. 1 public health enemy, is by primary prevention. The risk factor control has greater potential for lowering CHD morbidity and mortality than medical intervention detected at high risk candidates or those who already have disease. The magnitude of the CHD is higher in women especially in those who are hypertensive. The more intensive evaluation of chest pain in women must be evaluated and the role of postmenopausal hormone treatment must be assessed in improving the long-term outcome of women with coronary heart disease.

The community-based epidemiological and supportive research as a regional basis with diversity of socio-cultural patterns, dietary habits and living-styles are essential to define total burden of CHD, determines risk factor level, monitor disease trends in various population and evaluate intervention efforts.

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