Does Hypertension Predispose to Dysfunctional Uterine Bleeding? A Report of Three Cases

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Abstract
Three peri-menopausal mildly hypertensive women aged 38, 38 and 47 years and who were all multipara, presented with dysfunctional uterine bleeding. They were treated with nifedipine 20mg 8 hourly for the first three months and subsequently with 20mg of nifedipine retard daily and haematinics. The body mass indexes were 23, 19 and 19.7 respectively. Over an eighteen month period it was observed that they had a wide pulse pressure and the dysfunctional uterine bleeding abated. The changing events surrounding peri-menopause and blood pressure is reviewed

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Introduction

Speroff *et al*[1] defined dysfunctional uterine bleeding (DUB) as a variety of bleeding manifestations of anovulatory cycles categorized as oestrogen breakthrough bleeding, oestrogen withdrawal bleeding and progesterone breakthrough bleeding. In each instance the manner in which the endometrium deviated from the norm is depicted and specific steroid therapy is recommended to counter the difficulties each situation presents.

This mode of clinical management has been in regular use for many years, and failure to control vaginal bleeding with this therapy despite appropriate application and utilization excludes the diagnosis of DUB. When this occurs, attention is directed to pathologic entity within the reproductive tract as the cause of abnormal bleeding. This applies to the anovulatory extremes of reproductive life. In the menopausal transition, however, it has been estimated that menstrual irregularity occurs in more than half of all women[2]. Bleeding can be irregular, heavy or prolonged. This is attributed to a decrease in the number of normally functioning follicles reflected by a rise in follicle stimulating hormone (FSH)[3]. In other words there is a fall in the normal levels of estrogens. Other known causes of bleeding like pregnancy, endometrial hyperplasia, cancer, use of oral contraceptives, obesity, androgen excess, thyroid enlargement and clotting disorders should be excluded when DUB is suspected. Patients who have constant, non-cycling oestrogen levels that stimulate endometrial growth without periodic shedding will have their endometrium outgrowing its blood supply and have DUB. This is due to the fact that the tissue breaks and sloughs from the uterus. Subsequent healing of the endometrium is irregular and dyssynchronous. Thus, chronic stimulation from elevated levels of oestrogen will lead to episodes of frequent, heavy bleeding. Chronic stimulation by low levels of oestrogen on the other hand will result in infrequent, light dysfunctional uterine bleeding. Dysfunctional bleeding can also occur in ovulating women without recognizable pelvic pathology. Added to this is the fact that patients with DUB are treated with hormonal therapy under the presumption of endocrinological causes of abnormal bleeding. We did observe that some of these women in perimenopause were also hypertensive.

Material and Methods

After explanation and obtaining their consent, three peri-menopausal, hypertensive women with dysfunctional uterine bleeding (DUB) were monitored for eighteen months. The age, parity, blood pressure, height and weight were recorded during the first visits. The menstrual histories were recorded. Noted were the number and degree of soaking of pads used per day, number of days of flow and the presence or absence of clots. Thyroid enlargement was excluded by clinical palpation. Investigations carried out included complete blood count, thyroid stimulating hormone (TSH) estimation, clotting time, vaginal ultrasonography describing the uterine contour, endometrial thickness and ovarian follicular size. Endometrial curettage was done to exclude to exclude endometrial cancer in each case. They were treated with 20 mg nifedipine (Schein Pharmaceutical Canada Inc.77 Belfield Rd, Etobicoke ON, Canada M9W 1G6) 8-hourly for the first three months and subsequently with 20mg of nifedipine retard daily, fersolate 200mg daily, folic acid 5mg daily and vitamin C 100mg daily. They were counselled on low salt diet and weight loss.

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Results

The ages of Mrs. MO, GA, and AF were 38, 38 and 47 respectively. Their parities were P2002, P4004, and P5004. The recorded blood pressures fluctuated between 140/90 and 100/70 for Mrs. MO; 150/80 and 110/70 for Mrs. GA; and 140/90 for Mrs. AF Their body mass index (wt. kg/height[m]^2) was calculated as 23, 19, and 19.7 respectively. Table I summarizes the rest of the results. During the periods of their treatment with nifedipine, the uterine bleeding abated.

Discussion

The noted increase in the pulse pressure, apparent increase in pulse pressure in one of our three patients and the response to the anti-hypertensive therapy suggest that hypertension is associated with perimenopausal bleeding.

In the cardiovascular system, the microcirculation of each organ is organized specifically to secure that organ's needs. In general, each artery entering an organ divide six to eight times before the arteries become small enough to be called arterioles having internal diameters that measure less than 20μm. These arterioles branch further a few more times before reaching diameters of 5 to 9 μm where they supply blood to the capillaries. The capillary wall is composed of unicellular layer of endothelial cells and is surrounded by a basement membrane on the outside. The total thickness of the wall is only about 0.5 micrometer. The internal diameter of the capillary is 4 to 9 μm, barely enough for a red cell and other blood cells to squeeze through. Endothelial dysfunction and changes in arterial wall morphology, including thickening of the tunica intima, excess synthesis of collagen matrix (fibroblastic intimal thickening) and permanent or dynamic deposition of lipids (fatty streaks) already occur in childhood or adolescence.[4]

This endothelial function deteriorates with aging in both men and women; but there is evidence that their aging change is accelerated in women following the withdrawal of ovarian hormones. Taddei et al[4] investigated endothelium dependent vasodilatation in normotensive and hypertensive 37 men and 36 women respectively by injecting intrabrachial acetylcholine and measuring the effects of blood flow. Prior to age 40 in men and 49 in women, the age related decline in response to acetylcholine was more rapid in men than women while after this age the rate of decline slowed in men and accelerated in women. This finding, at an age typical of the onset of menopause in women is highly suggestive of a process related to sex hormone and their effects on vascular endothelial function.

Table 1: Biodata and Response to Treatment in the Three Patients

Name	MO	GA	AF
Age	38	38	47
Parity	2, 2 alive	4, 4 alive	5, 4 alive
Blood pressure	100/70 to 140/90	110/70 to 150/80	110/90 to 130/90
Body mass index(wt. kg/Ht(m)^2	23	19	19.7
Uterine bleeding:			
Regular heavy& prolonged	No	No	No
Irregular, heavy & prolonged	Yes	Yes	Yes
Thyroid enlargement	No	No	No
Complete blood count	Normal	Normal	Normal
Clotting time	6 mins	7mins	6.5 mins
Ultrasonography:			
Uterine contour	Pear shaped	Pear shaped	Pear shaped
Endometrial thickness	2mm	2mm	2.5mm
Ovarian structure	cysts<3mm	cysts<3mm	cysts < 3mm
Endometrial sampling	proliferative	endometritis proliferative	simple endometrial hyperplasia
Treatment:	Nifedipine	Nifedipine D & C	Nifedipine D&C
Response:	Good	Good	Good

Spieker *et al*[5] also observed that the vascular endothelium synthesizes and releases a spectrum of vasoactive substances like nitric oxide (NO) and endothelin (ET). In hypertension, the delicate balance of endothelium-derived factors is disturbed. ET acts as the natural counterpart to endothelium-derived NO, which exerts vasodilating, anti-thrombotic, and anti-proliferative effects, and inhibits leukocyte adhesion to the vascular wall Besides its blood pressure rising effect also in man, ET vascular and myocardial hypertrophy which are independent risk factors for cardiovascular for cardiovascular morbidity and mortality. The derangement of endothelial function in hypertension is likely to be caused in part by genetic factors, but also due to elevated blood pressure itself. Due to its position between blood pressure and smooth muscle cells responsible for peripheral resistance, the endothelium is thought to be target and mediator of arterial hypertension. Endothelial dysfunction in hypertension is crucial both for the development of the disease process in the vasculature and an important therapeutic target.

Recently it has been recognized that women develop high blood pressure particularly systolic hypertension at an increased rate as they age; and that this age-related blood pressure is exaggerated by the menopause.[6] This is also a time that there is a fall in the oestrogen levels. Hypertension is one of the most prevalent and powerful contributors to atherosclerotic cardiovascular disease. Oestrogen deficiency has been linked to the rapid increase in cardiovascular disease in women who have undergone natural or surgical menopause.[7] Initiation and early progression of atherosclerosis rely on conventional risk factors such as hyperlipidaemia, smoking, severe alcohol consumption, chronic infections and hypertension.[8] These factors are not uncommon.

The role of ovarian hormones and their withdrawal in the pathogenesis of hypertension may have a variety of mechanisms and may contribute to the wide pulse pressure and high prevalence of isolated systolic hypertension in older women.[9, 10] This wide pulse pressure we observed in our three patients. There is evidence that oestrogen affects systemic arterial compliance.[11] Oestrogen affects the expression of the rennin-angiotensin system and the level of plasma catecholamine both of which play important roles in the pathogenesis of essential hypertension[12]. With the plaque deposition from childhood and adolescence, plaque extension is effectively compensated for by a focal widening of the vessel thereby preventing the development of lumen obstruction. For stenosis to emerge, conventional plaque must convert to complicated plaques characterized by plaque rupture and consecutive athero-thrombosis. This process usually starts with small to medium-sized plaques. According to pathological observations, fissuring of atherosclerotic lesions is a frequent event while the formation of the overlying large thrombi is definitely rare.[13] This may explain the uterine bleeding seen in our 3 patients.

It is, therefore, conceivable that oestrogen withdrawal may lead to increase in pulse pressure and loss of endometrial compliance due to plaque deposition. With the resulting increased pulse pressure and compensatory vasodilatation, rupture of the plaques and diminished thrombi formation ensues and endometrial bleeding results. This is worth further investigation.

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