Increased pregnancy loss in young women with aortoiliac disease.Atherosclerosis 2002

Rosendaal, F.R.

ELSEVIER

Atherosclerosis 164 (2002) 121–127

ATHEROSCLEROSIS

www elsevier com/locate/atherosclerosis

Increased pregnancy loss in young women with aortoiliac disease

Maurice A.A.J. van den Bosch [a,b], Willem P.Th.M. Mali [b], Daisy G.M. Bloemenkamp [a,b], Bert C. Eikelboom [c], Jeanet M. Kemmeren [a], Bea C. Tanis [d], Ale Algra [a], Frits R. Rosendaal [e], Yolanda van der Graaf [a,*]

[a] *Julius Center for Health Sciences and Primary Care Room D 01 335 University Medical Center Utrecht, P O Box 85500 3508 GA Utrecht The Netherlands*

[b] *Department of Radiology Image Sciences Institute University Medical Center Utrecht, Utrecht The Netherlands*

[c] *Department of Vascular Surgery University Medical Center Utrecht Utrecht The Netherlands*

[d] *Department of Hematology Leiden University Medical Center Leiden The Netherlands*

[e] *Department of Clinical Epidemiology Leiden University Medical Center, Leiden The Netherlands*

Received 8 October 2001, received in revised form 17 January 2002, accepted 1 February 2002

Abstract

Background During clinical evaluation of young women with peripheral arterial occlusive disease, we were surprised by the high prevalence of pregnancy loss in women with segmental stenosis confined to the aortoiliac segment We wondered if increased occurrence of miscarriage is the result of high expression of vascular and obstetrical risk factors in these patients, or if it is related to localization of disease In a case-control study designed to investigate risk factors for peripheral arterial occlusive disease in young women, we assessed the risk of miscarriage in these patients according to level of obstruction *Methods* A total of 202 female patients, aged 18–49 years and 466 healthy control women from a population based case-control study, donated venous blood samples and filled out a structured questionnaire concerning classical cardiovascular risk factors and obstetrical history In all patients, diagnosis of peripheral arterial occlusive disease was confirmed by intra-arterial angiography Patients were classified into two groups those with and those without stenosis of the aortoiliac segment (aortoiliac disease) *Results* In 77 of the 202 patients (38%) with peripheral arterial occlusive disease, the obstruction was confined to the aortoiliac segment The occurrence of miscarriage was high (42%) in young women with aortoiliac disease Compared to healthy controls, the risk of miscarriage increased 3-fold (OR 3 1, 95% CI 1 8–5 6) in these patients Adjustment for obstetrical and vascular risk factors did not affect the risk estimate *Conclusion* This is the first study that identifies aortoiliac disease as a risk factor for pregnancy loss in young women The risk of miscarriage is increased 3-fold in women with aortoiliac disease The presence of vascular and obstetrical risk factors did not affect the strength of the association Pregnancy loss could be the first sign of insufficient aortic circulation in these patients

Keywords Peripheral arterial occlusive disease, Localization, Risk factors, Pregnancy loss, Young women

1. Introduction

Peripheral arterial occlusive disease is a disease of advanced age It usually develops at several levels within the arteries, but may also be restricted to a single localized region within a vessel [1,2] Results of previous studies indicated that younger patients had more isolated aortoiliac involvement than older patients who had a more diffuse disease [3–8] Most of these young patients with aortoiliac disease are women and present with a characteristic pattern of one segmental stenosis that is confined to the distal part of the abdominal aorta [5]

During the last few years, we had selected a group of young women with peripheral arterial occlusive disease for risk factor assessment During data analysis, we were surprised to discover that the majority of young women with peripheral arterial occlusive disease confined to the aortoiliac segment appeared to have a remarkable

* Corresponding author Tel +31-30-250-9351, fax +31-30-250-5485

E-mail address y vandergraaf@jc azu nl (Y van der Graaf)

0021-9150/02/$ - see front matter
PII S0021-9150(02)00045-X

history of miscarriages, whereas female patients with more diffuse disease affecting the distal vessels did not report these problems

Miscarriage, defined as pregnancy loss before 22 weeks' gestation, is not uncommon About 10–15% of clinically recognized pregnancies end in miscarriage [9,10] The clinical and environmental causes of miscarriage have been extensively studied Several risk factors have been unraveled including smoking, alcohol use, social class, hyperhomocysteinemia, hypertension, antiphospholipid antibodies and diabetes Genetic causes of miscarriage, including chromosomal abnormalities, comprise only 5% of causes of pregnancy loss Most losses due to chromosome abnormalities occur before 7 weeks' gestation and pass by unnoticed [11–13] Also, vascular abnormalities resulting in impaired uterine perfusion have been linked to pregnancy loss and fetal growth restriction [14–17]

Most of the identified obstetrical risk factors appeared to have a remarkable similarity to those of peripheral arterial occlusive disease In fact, smoking, hypertension, hyperhomocysteinemia and diabetes are the most prominent risk factors for manifestation of vascular disease at a young age [1] One might therefore wonder if increased occurrence of miscarriage in young women with aortoiliac disease is the consequence of a selective expression of vascular (and obstetrical) risk factors in these patients, or the result of unfavorable localization of the disease, i e abdominal aorta, resulting in reduced flow during pregnancy in these patients

In this study, the group of young women with peripheral arterial occlusive disease was included We assessed the risk of miscarriage in these patients according to level of obstruction

2. Patients and methods

2 1 Patients and control women

The data were obtained from the Risk of Arterial Thrombosis In relation with Oral contraceptive use (RATIO) study, a population-based case-control study in The Netherlands on oral contraceptives and peripheral arterial occlusive disease Patients were women aged 18–49 years without a history of preexistent cardiovascular disease, who had been admitted to one of the five collaborating hospitals, between January 1990 and December 1999, with initial symptoms of intermittent claudication Peripheral arterial occlusive disease was considered if a patient presented typical symptoms of intermittent claudication (cramping pain of the calves or buttocks during exercise) or with rest pain, non-healing ulcers or gangrene In all patients, peripheral arterial occlusive disease was confirmed by intra-arterial angiography The angiograms were reviewed by two radiologists A stenotic lesion of $>50\%$ was considered diagnostic for peripheral arterial occlusive disease Patients with a stenotic lesion of 50% or more were included for analyses

Control women were identified by random digit dialing (RDD) [18] In this method, random phone numbers were dialed and households were ascertained for eligible individuals (female, aged 18–49 year) who were subsequently asked to participate This method resulted in the selection of control women who were approximately (5-year strata) the same age as the patients and who lived in the service areas of the participating hospitals There were two phases of data collection In the first phase, patients and control women filled out a first structured questionnaire concerning classical cardiovascular risk factors In the second phase (June 1998 to May 2000), they were approached again, blood samples were drawn and participants filled out a second questionnaire that included questions on their obstetrical history Of the 220 patients and 629 control women who filled out the first questionnaire and also donated venous blood samples, 202 patients and 466 controls filled out the second structured questionnaire and were included for analyses

All participants gave informed consent for the study which was approved by the ethics committees of the participating hospitals

2 2 Atherosclerotic and obstetrical risk factors

Patients and control women filled out the same structured questionnaires, comprising of questions on demographic characteristics, medication use and cardiovascular risk factors, as well as risk factors for miscarriages, i e smoking, body mass index (BMI), alcohol use, history of hypertension, history of diabetes mellitus, history of hypercholesterolemia and family history of cardiovascular diseases The second questionnaire covered various aspects of obstetric history, including family planning, pregnancies, parity, gestation, birth weights and abortions Miscarriage was defined according to the commonly used World Health Organization definition as pregnancy loss before 22 weeks' gestation [9] We categorized smokers as current, former or never BMI was calculated as body weight (kg) divided by height squared (m^2) Obesity was defined as body mass index $\geq 27\,3$ kg/m^2 Alcohol use was categorized as never or ever use The socio-economic status was defined as the highest level of education attended by the participant primary school, secondary school or higher education/university A positive family history of cardiovascular disease was defined as the occurrence of a cardiovascular disease (myocardial infarction, stroke or peripheral arterial occlusive disease) before 60 years of age in one or both parents

Subsequently, all participants had their blood pressure measured and donated venous blood samples Blood pressure was measured semi-automatically (Omron*M1* OMRON Healthcare GmbH, Hamburg, Germany) at one point in time Serum and plasma were stored at −80 °C until processed Plasma and serum were analyzed for plasma total homocysteine level and biochemical parameters, including glucose, serum total cholesterol, triglycerides and the lipid fractions A positive history of diabetes mellitus was defined by the use of glucose lowering medication or a (non-fasting) serum glucose ≥11 0 mmol/l A positive history of hypercholesterolemia was defined by the use of cholesterol lowering medication or a serum total cholesterol ≥5 0 mmol/l A positive history of hypertension was defined by use of antihypertensive drugs or a systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg Analysis of plasma total homocysteine levels was performed, independent of knowledge of case-control status, by high-pressure liquid chromatography (HPLC) Values for plasma total homocysteine (tHcy), expressed as homocysteine concentration in μmol/l, included the sum of free and bound forms of homocysteine, homocysteine and homocysteine–cysteine mixed disulfide Hyperhomocysteinemia was defined as plasma total homocysteine values exceeding the 90th percentile of the control range

2 3 *Localization of peripheral arterial occlusive disease*

Based on the angiogram, patients with peripheral arterial occlusive disease were classified into two groups [7,8] The first group (with aortoiliac disease) consisted of patients with at least one obstruction within the arterial segments above the inguinal ligament, i e distal abdominal aorta, common iliac artery, internal or external iliac artery The second group (without aortoiliac disease) consisted of patients without any obstruction above the inguinal ligament, which implies at least one obstruction in one of the following arteries femoral artery, popliteal artery, anterior and posterior tibial artery or peroneal artery

2 4 *Statistical analysis*

Means or proportions of cardiovascular and obstetrical risk factors were calculated for both patient groups and control women We evaluated the strength of the association between miscarriage and peripheral arterial occlusive disease according to localization of arterial obstruction We calculated odds ratios as estimates of the relative risk of miscarriage in patients with aortoiliac disease and patients without aortoiliac disease Odds ratios and 95% confidence intervals were assessed by unconditional logistic regression models Because the age at first pregnancy, the number of pregnant women and the mean number of pregnancies per pregnant woman affects the number of miscarriages, primary adjustment for these variables was made In addition, multivariate adjustment was made for potential confounding factors, smoking (never, former, current), alcohol use (yes/no), education level (primary/secondary/higher education), hypertension (yes/no), hypercholesterolemia (yes/no), diabetes mellitus (yes/no) and hyperhomocysteinemia (yes/no)

3. Results

In 77 of the 202 patients (38%) with peripheral arterial occlusive disease, the obstruction was confined to the aortoiliac segment Table 1 summarizes the characteristics of both patient groups and 466 control women Patients were slightly older, had a higher body mass index and lower level of education than controls Also, the traditional risk factors for peripheral arterial occlusive disease and pregnancy loss, including current smoking, alcohol use, education level, hypertension, hypercholesterolemia, diabetes mellitus and hyperhomocysteinemia, were all more prevalent in patients

If both groups of patients were compared, patients with aortoiliac disease had a lower level of education, were all current or former smokers and more frequently suffered from hypercholesterolemia, whereas patients without aortoiliac stenosis were more likely to have a history of hypertension, diabetes mellitus or hyperhomocysteinemia

Table 2 shows the obstetrical history of both patient groups and control women Patients with aortoiliac disease were more often pregnant than patients without aortoiliac localization and healthy controls 94% of aortoiliac patients compared with 81% of patients without aortoiliac disease and 84% of healthy controls The occurrence of miscarriage was very high in patients with aortoiliac disease, 42% of all pregnant patients had suffered at least one miscarriage In the two other groups, these percentages were much lower 11% in the patients without aortoiliac localization and 21% in the healthy controls group Fetal growth was also most restricted in aortoiliac patients, the mean birth weight per live birth being significantly lower in aortoiliac patients 2872 g compared with 3119 g in the other patient group and 3403 g in healthy controls ($P < 0$ 01)

Table 3 presents the odds ratios for miscarriage in patients with aortoiliac localization and patients without, relative to healthy controls Because the age at first pregnancy, the number of pregnant women and the mean number of pregnancies per pregnant women affects the number of miscarriages, primary adjustment for these variables was made The risk of miscarriage was increased in patients with aortoiliac disease, odds ratio 3 1 (95% CI 1 8–5 6), whereas the risk in patients

Table 1
Characteristics of subgroups of patients and control women

	Patients with aortoiliac disease ($N = 77$)	Patients without aortoiliac disease ($N = 125$)	Control women ($N = 466$)
Age (years)	43 6 (7 2)	43 9 (5 9)	45 5 (8 1)
Body mass index (kg m^{-2})	25 5 (4 8)	26 9 (6 4)	24 9 (4 2)
Education (%)			
Primary school or less	20 (27)	22 (18)	41 (9)
Secondary school	50 (67)	87 (73)	306 (66)
Higher education or university	5 (6)	11 (9)	116 (25)
Cigarette smoking (%)			
Current	56 (73)	65 (52)	153 (33)
Former	21 (27)	50 (40)	156 (33)
Never	–	9 (7)	157 (34)
Alcohol use (%)			
No use	28 (36)	43 (34)	96 (21)
Any use	49 (64)	82 (66)	365 (79)
Systolic blood pressure (mmHg)	137 (19)	143 (25)	130 (19)
Diastolic blood pressure (mmHg)	83 (11)	86 (12)	83 (11)
Hypertension[†] (%)	40 (52)	77 (62)	112 (24)
Cholesterol (mmol/l)	5 9 (1 6)	5 6 (1 2)	5 4 (1 1)
Hypercholesterolemia[‡] (%)	71 (92)	105 (84)	278 (60)
Glucose (mmol/l)	6 2 (2 8)	6 3 (4 2)	4 0 (1 4)
Diabetes mellitus[¶] (%)	8 (10)	18 (14)	4 (1)
Plasma total homocysteine (μmol/l)	12 3 (3 6)	13 7 (5 6)	12 2 (3 3)
Hyperhomocysteinemia (%)	12 (16)	33 (26)	44 (10)
Family history of cardiovascular disease (%)	51 (66)	74 (59)	173 (37)

Data are mean (S D) unless otherwise indicated
[†] Hypertension was defined as the use of antihypertensiva and/or systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 90 mmHg
[‡] Hypercholesterolemia was defined as use of lipid lowering drugs and/or cholesterol plasma concentration ≥ 5 0 mmol/l
[¶] Diabetes mellitus was defined as use of blood glucose lowering medication and/or (non-fasting) glucose plasma concentration ≥ 11 0 mmol/l

Table 2
Obstetrical history in patients with and without aortoiliac localization and healthy controls

	Patients with aortoiliac disease ($N = 77$)	Patients without aortoiliac disease ($N = 125$)	Controls ($N = 466$)
Ever pregnant			
Yes	72 (94)	102 (81)	390 (84)
No, on purpose	2 (2)	11 (9)	39 (8)
No, not on purpose	3 (4)	12 (10)	35 (8)
Total pregnancies	173 (100)	211 (100)	865 (100)
–Live births	129 (75)	190 (90)	736 (85)
–Miscarriage	44 (25)	21 (10)	129 (15)
Number of pregnancies per pregnant women	2 4 (0 8)	2 1 (0 7)	2 2 (0 6)
Number of pregnant women with at least one miscarriage*	32 (42)	13 (11)	97 (21)
Number of miscarriages in women with at least one miscarriage			
1	24 (75)	8 (61)	66 (68)
2	6 (19)	3 (24)	25 (26)
≥ 3	2 (6)	2 (15)	6 (6)
Birth weight per live birth	2872 (913)	3119 (1107)	3403 (742)

[*] Miscarriage is defined as self-reported pregnancy loss before 22 weeks gestation, if patients with aortoiliac disease were compared to controls a statistical significant P-value $< 0\ 05$ was found, if patients without aortoiliac disease were compared to controls a non-significant P-value of 0 11 was found

Table 3
Odds ratios (after adjustment for potential confounders) for miscarriage in female patients with and without aortoiliac localization, relative to healthy controls

Adjustment	Patients with aortoiliac disease OR (95% CI)*	Patients without aortoiliac disease OR (95% CI)*
1[a]	3.1 (1.8–5.6)	0.6 (0.3–1.1)
2[b]	2.8 (1.4–5.0)	0.5 (0.2–1.1)

[a] Adjusted for age at first pregnancy, number of pregnant women, number of pregnancies
[b] Adjusted for age at first pregnancy, number of pregnant women, number of pregnancies, SES, smoking, alcohol, hypertension, hypercholesterolemia, diabetes, hyperhomocysteinemia
* OR (95% CI) odds ratio and 95% confidence interval

without aortoiliac localization did not significantly differ from the risk in healthy controls; odds ratio 0.6 (95% CI 0.3–1.1). Additional adjustment for the presence of traditional atherosclerotic and obstetrical risk factors, i.e. education level, smoking, alcohol, hypertension, hypercholesterolemia, diabetes and hyperhomocysteinemia did not affect the risk estimates.

4. Discussion

4.1. Increased risk of miscarriage

The results of this study show that the occurrence of miscarriages is high (42%) in young women with aortoiliac disease. Compared to healthy controls, the risk of miscarriage is increased more than 3-fold (OR 3.1; 95% CI 1.8–5.6) in these patients. The difference in risk of miscarriage between women with peripheral arterial occlusive disease without aortoiliac localization and healthy controls did not reach statistical significance (OR 0.6; 95% CI 0.3–1.1).

4.2 Distribution of risk factors according localization

In this study, we compared patients with aortoiliac disease with healthy controls and patients with peripheral arterial occlusive disease but without aortoiliac localization. Because of this design, our results demonstrated that the occurrence of miscarriage was not related to the presence of atherosclerotic (as well as obstetrical) risk factors: prevalence of risk factors was high in both patient groups, while risk of miscarriage was only increased in patients with aortoiliac disease. This implies that the only explanation for increased pregnancy loss in patients with aortoiliac disease is the localization of obstruction.

The major characteristic associated with the presence of aortoiliac disease in young women was smoking status; 100% of all aortoiliac patients were former or current smokers. In addition, low education and hypercholesterolemia were major correlates of disease in these women. Compared with aortoiliac patients, diabetes mellitus, hyperhomocysteinemia and hypertension were the major risk factors in patients with peripheral arterial occlusive disease without aortoiliac localization. Several risk factors are also risk factors for miscarriage [9–12]. Although low education, hypertension, diabetes, hyperhomocysteinemia and advancing maternal age have been associated with increased miscarriage rates, smoking seems the most potentially confounding factor [19–21]. Smoking was defined in our study as a categorical variable (never/former/current). Adjustment for smoking did not affect the odds ratios of miscarriage (Table 3), this makes confounding unlikely. However, residual confounding (100% of the aortoiliac patients was former or current smoker) as cause of increased risk of miscarriage in these patients cannot be completely ruled out.

4.3 Comparison of the results with earlier reports

This is the first study that identifies aortoiliac disease as risk factor for pregnancy loss in young women. Literature with regard to pregnancy loss in young patients with peripheral arterial occlusive disease is scarce. In 1987, Drew et al. described a 22-year-old woman with occlusion of the abdominal aorta and a history of two spontaneous abortions [22]. They concluded that abortion in this young patient was the consequence of exposition to vascular risk factors including hypertension and increased antiphospholipid antibodies. Only a few more case reports focused on the combination of pregnancy loss and aortoiliac disease in young women [23,24]. Both studies presented young patients with a history of recurrent miscarriage. Besides hypertension and hypercholesterolemia, lupus anticoagulant and antibodies to cardiolipin were found to be positive in the women described.

They concluded that increased risk profile in combination with increased levels of antiphospholipid antibodies was the cause of pregnancy loss in these patients [23,24]. More recently, Gagne et al. investigated 24 female patients with aortoiliac disease [4]. They reported that 45% of the women with a history of pregnancy also had a history of spontaneous fetal loss. In contrast to the above mentioned case-reports, they found that none of the patients who suffered miscarriage had a history of systemic lupus erythematosus or other collagen vascular disease. An explanation for the increased prevalence of miscarriage in their patients was not provided. Our result of 42% miscarriage in patients with aortoiliac disease is in agreement with the 45% found by Gagne et al. Because of our study design, in which patients with aortoiliac disease were compared with patients with diffuse peripheral arterial occlusive disease without aortoiliac localization and healthy controls, we were

able to rule out any influence of risk factors and found localization of disease to be the only factor likely to be causally related to pregnancy loss.

As was hypothesized by Leriche in 1948, we believe that aortic calcification is a process of decades [25]. We therefore assume that atherosclerosis of the aortoiliac segment slowly progresses over many years, before it becomes clinically manifest in patients who are extensively exposed to vascular risk factors. Furthermore, it is known that pelvic viscera are supplied by the hypogastric divisions of the common iliac arteries. The anterior division of the hypogastric artery continues gradually into the uterine artery, which courses slightly forward and medially on the superior fascia of the levator ani muscle, to the lower margin of the broad ligament. At the level of the isthmus, the uterine artery gives off a descending cervical branch, which surrounds the cervix and anastomoses with branches of the vaginal artery. The main part of the uterine artery follows a tortuous course upward along the lateral margin of the uterus, giving off spiral branches to the anterior and posterior surfaces of the uterus [26]. The average doctor's delay (defined as the time between first onset of symptoms and date of angiography) was 8 years in patients with peripheral arterial occlusive disease. As a consequence it could be hypothesized that, because the uterine artery arises indirectly from the common iliac artery, impaired uterine flow during pregnancy could be the first sign of insufficient circulation in patients with aortoiliac disease. However, evidence to support this hypothesis, which implies that the aortoiliac lesions were large enough to significantly affect blood flow to the uterus in the patients at an age when they became pregnant, can only be provided by a novel prospective study. This study should focus on assessment of possible atherosclerotic lesions in the abdominal aorta of patients with recurrent miscarriage.

Our hypothesis of reduced placental flow as a consequence of atherosclerosis of the aortoiliac segment is supported by findings of several radiological studies that focused on the association of impaired uterine perfusion and early pregnancy loss in young women [15,27–29]. In 1995, Jaffe et al. determined the utility of color Doppler sonography of the uteroplacental circulation in 100 women to predict the outcome of first-trimester gestations. Abnormal color Doppler findings were associated with significantly higher prevalence of complicated pregnancies. Among women with abnormal Doppler findings, 12 (43%) of 28 pregnancies ended in miscarriage, whereas among women with normal findings only one (1.4%) of 72 women miscarried [27]. In 1998, Leible et al. studied the uterine perfusion pattern of both the right and left uterine arteries by transvaginal color Doppler ultrasonography in 318 pregnancies. Impaired uterine artery blood flow was associated with pregnancy loss before 20 weeks' gestation (OR 2.9; 95% CI 1.5–5.8) [15]. Although these studies reported an association between miscarriage and reduced flow, it is unknown if reduced flow is the cause or consequence of pregnancy loss in these patients. It has also been postulated that circulatory abnormalities associated with early miscarriage could also be the cause of intrauterine growth retardation [29]. In agreement with this fact, we found a trend of decreased birth weight in patients with aortoiliac disease.

4.4. Aspects of the design of the study

In this study, information with regard to obstetrical history was collected by means of a structured questionnaire, which has its drawbacks typically related to this method. Not all miscarriages are diagnosed and even the diagnosed ones may be forgotten or unreported for other reasons. Reliance on participant memory for information on miscarriage could have led to recall bias. Interviews are an alternative but are expensive and obstetric problems are frequently underreported. Anonymous questionnaires may be preferable in this setting. However, studies evaluating different methods of ascertaining obstetrical history concluded that the miscarriage rate using patient recall (questionnaires) agrees closely with investigations based on hCG levels [11]. Another drawback is the time interval between occurrence of miscarriage and assessment of risk factors in patients and control women. However, it seems unlikely that risk profiles change throughout the years. Only after the diagnosis of peripheral arterial occlusive disease has been made, reduction of controllable risk factors (i.e. smoking, lipids and hypertension) is started, resulting in a changed risk profile. All cases were included using intra-arterial contrast arteriograms. Based on the angiograms, patients were classified as those with and those without aortoiliac localization of disease. Because all arteriograms were blindly reviewed and scored by two radiologists and the presence of a typical distal aortic stenosis is highly reproducible, diagnostic bias is unlikely to have played an important role.

5. Conclusion

The results of this study showed that the risk of miscarriages was increased 3-fold in young women with aortoiliac disease. The strength of this association was not influenced by the presence of vascular or obstetrical risk factors. Although the mechanisms behind early pregnancy failure are many and complex, we found localization of stenosis to be the only factor likely to be causally related to increased occurrence of miscarriage in these patients. We believe aortoiliac calcification to be a process that exists for years before it becomes clinically

manifest Only patients who are extensively exposed to vascular risk factors are prone to develop symptomatic peripheral arterial occlusive disease Pregnancy loss could be the first sign of insufficient aortic circulation in these patients Further research, focusing on imaging of the abdominal aorta in young women with recurrent pregnancy loss, should be considered to detect subclinical peripheral arterial occlusive disease in these patients

References

[1] De Bakey ME, Crawford ES, Garrett HE, et al Occlusive disease of the lower extremities in patients 16 to 37 years of age Ann Surg 1964,159 873–90

[2] Hansen ME, Valentine RJ, McIntire DD, Meyers SI, Chervu A, Clagett GP Age-related differences in the distribution of peripheral atherosclerosis when is atherosclerosis truly premature? Surgery 1995,118 834–9

[3] Levy PJ, Hornung CA, Haynes JL, Rush DS Lower extremity ischemia in adults younger than forty years of age a community-wide survey of premature atherosclerotic arterial disease J Vasc Surg 1994,19 873–81

[4] Gagne PJ, Vitti MJ, Fink LM, et al Young women with advanced aortoiliac occlusive disease new insights Ann Vasc Surg 1996,10 546–57

[5] Cronenwett JL, Davis JT, Gooch JB, Garret HE Aortoiliac occlusive disease in women Surgery 1980,88 775–84

[6] Costantino MJ, Smith RB, Perdue GD Segmental aortic occlusion an unusual lesion found in menopausal women Arch Surg 1979,114 317–8

[7] Friedman SA, Holling HE, Roberts B Etiologic factors in aortoiliac and femoropopliteal vascular disease the Leriche syndrome New Engl J Med 1964,271 1382–5

[8] Bauwens F, Duprez D, Van Wassenhove A, Brusselmans F, Clement DL Localisation and risk factors of peripheral arterial occlusive disease in the female Int Angiol 1989,8 32–5

[9] Hemminki E, Forssas E Epidemiology of miscarriage and its relation to other reproductive events in Finland Am J Obstet Gynecol 1999,181 396–401

[10] Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al Incidence of early loss of pregnancy New Engl J Med 1988,19 189–94

[11] Katz VL, Kuller JA Recurrent miscarriage Am J Perinatol 1994,11 386–97

[12] Stirrat GM Recurrent miscarriage I definition and epidemiology Lancet 1990,336 673–5

[13] Modvig J, Schmidt L, Damsgaard MT Measurement of total risk of spontaneous abortion the virtue of conditional risk estimation Am J Epidemiol 1990,132 1021–38

[14] Hohlfeld J, Schneider M, Hein R, Barthels M, von der Lieth H, Rosenthal H, Lang W, Alexander K, et al Thrombosis of the terminal aorta, deep vein thrombosis, recurrent fetal loss, and antiphospholipid antibodies VASA 1996,25 194–9

[15] Leible S, Cumsille F, Walton R, Munoz H, Jankelevich J, Sepulveda W Discordant uterine artery velocity waveforms as a predictor of subsequent miscarriage in early viable pregnancies Am J Obstet Gynecol 1998,179 1587–93

[16] Cook V, Weeks J, Brown J, Bendon R Umbilical artery occlusion and fetoplacental thromboembolism Obstet Gynecol 1995,85 870–2

[17] Jauniaux J, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ Onset of maternal arterial blood flow and placental oxidative stress A possible factor in human early pregnancy failure Am J Pathol 2000,157 2111–212

[18] Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J Random digit dialing in selecting a population-based control group Am J Epidemiol 1984,120 825–33

[19] Welch GN, Loscalzo J Homocysteine and atherothrombosis New Engl J Med 1998,338 1042–50

[20] Goddijn-Wessel TAW, Wouters MGAJ, Van de Molen EF, Spuijbroek MDEH, Steegers-Theunissen RPM, Blom HJ, et al Hyperhomocysteinemia a risk factor for placental abruption or infarction Eur J Obstet Gynecol Reprod Biol 1996,66 23–9

[21] Steegers-Theunissen RPM, Broers GHJ, Blom HJ, Trijbels FJM, Eskes TKAB Hyperhomocysteinaemia and recurrent spontaneous abortion or abruptio placentae (letter) Lancet 1992,339 1122–3

[22] Drew P, Asherson RA, Zuk RJ, Goodwin FJ, Hughes GRV Aortic occlusion in systemic lupus erythematosus associated with antiphospholipid antibodies Ann Rheum Dis 1987,46 612–6

[23] Hohlfeld J, Schneider M, Hein R, et al Thrombosis of the terminal aorta, deep vein thrombosis, recurrent fetal loss, and antiphospholipid antibodies VASA 1996,25 194–9

[24] McGee GS, Pearce WH, Sharma L, Green D, Yao JST Antiphospholipid antibodies and arterial thrombosis Case reports and review of the literature Arch Surg 1992,127 342–6

[25] Leriche R, Morel A The syndrome of thrombotic obliteration of the aortic bifurcation Ann Surg 1948,127 193–206

[26] Netter FH The CIBA collection of medical illustrations In Reproductive system, vol II, 1st ed USA Colorpress, 1954 98–9

[27] Jaffe R, Dorgan A, Abramowicz JS Color Doppler imaging of the uteroplacental circulation in the first trimester value in predicting pregnancy failure or complication AJR 1995,164 1255–8

[28] Frates MC, Doubilet PM, Brown DL, et al Role of Doppler ultrasonography in the prediction of pregnancy outcome in women with recurrent spontaneous abortion J Ultrasound Med 1996,15 557–62

[29] Khong TY, De Wolf F, Robertson WB, Brosens I Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational-age infants Br J Obstet Gynaecol 1986,93 1049–59