Arch Gynecol Obstet (2013) 287:1081–1086
DOI 10.1007/s00404-012-2703-x

MATERNAL-FETAL MEDICINE

Association of parity with osteoprotegerin levels and atherosclerosis

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Received: 9 October 2012 / Accepted: 21 December 2012 / Published online: 4 January 2013

Abstract
Purpose Association of serum osteoprotegerin (OPG) levels and cardiovascular disorders has been shown previously. The aim of this observational study was to investigate the relationship between parity, OPG and carotid intima-media thickness (CIMT) in premenopausal women.
Methods A total of 128 women (mean age ± SD, 37.8 ± 4.7 years) were divided into three group according to parity [1–3 as group 1 ($n = 41$), 4–6 as group 2 ($n = 55$) and ≥7 as group 3 ($n = 32$)]. Serum OPG was measured and CIMT was evaluated.
Results Both serum OPG levels and CIMT tended to increase with advancing parity; OPG level was significantly higher in group 3 than in group 1 ($p = 0.013$) and CIMT was significantly higher in group 2 and group 3 than in group 1 ($p < 0.001$ for both). In correlation analyses, there were significant correlations between all three parameters.
Conclusions Our results revealed that there was an increased risk of cardiovascular disease in women with multiparity. Significant association of OPG with CIMT suggested that OPG might play a role in the pathogenesis of parity-induced atherosclerosis.

Keywords Parity · Carotid intima-media thickness · Osteoprotegerin

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Objective

Parity has been found to be associated with cardiovascular disease in some studies [1, 2] and claimed to be not associated in some others [3, 4]. Ultrasonographically determined carotid intima-media thickness (CIMT) is a valid, non-invasive surrogate marker of atherosclerotic disease and a strong predictor of future vascular events [5]. Positive correlation between increased CIMT and number of childbearing has been showed previously [6, 7].

Osteoprotegerin (OPG) is a soluble glycoprotein belonging to the tumor necrosis factor (TNF) receptor superfamily [8]. Receptor activator of nuclear factor κB (NF-κB) ligand (RANKL) is a key regulator of osteoclastogenesis which induces the differentiation of ostoeoclast [9]. OPG acts as a decoy receptor of the RANKL and

blocks the interaction between the RANKL with its receptor; OPG was originally discovered as an inhibitor of bone resorption [8, 9]. OPG is thought to play a crucial role in vascular homeostasis, as either deficiency or increased level of OPG effects vascular tree: OPG deficient mice develop medial calcification of the aorta and renal arteries in addition to severe osteoporosis [10], whereas high expression of OPG has been shown in atherosclerotic carotid plaques [11]. Elevated levels of serum OPG are associated with variety conditions of cardiovascular disease, e.g., future cardiovascular events in general population [12], cardiovascular mortality in elderly women [13], presence and severity of coronary artery disease [14, 15] and long-term mortality after acute coronary syndromes [16]. However, relation between OPG and parity has not been shown previously.

In this study, we aimed to investigate the levels of serum OPG in premenopausal women according to parity count and to compare our findings with CIMT as a valid predictor of atherosclerosis.

Materials and methods

Study population

The current study included 128 premenopausal women participants subsequently, who delivered at least one year ago and they stratified into three groups according to their parity count; from 1 to 3 as group 1 ($n = 41$), 4 to 6 as group 2 ($n = 55$) and ≥ 7 as group 3 ($n = 32$). Women with diabetes mellitus, ischemic heart disease, cerebrovascular disease, chronic liver and renal diseases, history of known osteoporosis, thyroid dysfunction, hypertension and histories of gestational diabetes, pregnancy-induced hypertension, preeclampsia and women smoking and/or using oral contraceptives were excluded. A physical examination was performed, and the height, weight, systolic and diastolic blood pressures and body mass index (BMI) were recorded. Informed consent for participation in the study was obtained from all women. The study protocol conforms to the principles of the Helsinki Declaration and was approved by the local Medical Ethics Committee.

Biochemical measurement

After an overnight fast, venous blood was collected, centrifuged and serum samples were stored at -80 °C until analysis. Serum samples were obtained in the postpartum second year (at least 1 year after the labor and during non-lactating period). Serum OPG levels were measured by enzyme linked immunosorbent assay (ELISA) method using a commercial kit (RayBiotech, Norcross, GA, USA). The intra- and inter-assay coefficients of variation (CV) were 10 % and 12 %, respectively. Results were given as pg/ml. Serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total-cholesterol (T-C), HDL-cholesterol (HDL-C), and triglyceride (TG) levels were determined by photometric method using commercial kits (Abbott, USA). LDL-cholesterol (LDL-C) was calculated by the Friedewald formula. Hemoglobin levels were measured by an automatic blood analyzer (Abbott, CELL-DYN Ruby, Hematology Analyser, USA).

Ultrasound measurement

All of the sonographic examinations were performed by the same examiner (HC) well-qualified in Doppler ultrasonographic evaluations with intra-observer variability of 3.2 % (and Intra- and interobserver variabilities for measuring CIMT were <5 and <10 %, respectively, for our laboratory) who was unaware of the subject's clinical status throughout the study to avoid observation bias. Each subject was studied in the morning hours (8:00 a.m. to 10:00 a.m.) after having abstained from alcohol, caffeine, tobacco and food for 8 h before the examination. None of the participants were using vasoactive drugs. Studies were performed in a quiet, temperature controlled room (20–25 °C). Images were obtained by high-resolution Doppler ultrasonography (Logiq 7 Pro; General Electric, Milwaukee, WI, USA) with a 12-MHz linear-array transducer.

Bilateral assessment of wall thickness was made in the common carotid artery (CCA). IMT was manually measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first line represents the lumen–intima interface, and the second line the collagen-containing upper layer of tunica adventitia. IMT measurement of both the right and left CCA was performed at three points on the far walls in each CCA from 2 cm proximal to the bifurcation of the CCA. The three locations were then averaged to produce the mean IMT for each side. The CIMT was reported as the average of right and left CCA. All ultrasonographic measurements were reviewed by another experienced radiologist (SY) who was blinded to both clinical and ultrasonographic characteristics.

Sample size

We used G power pocket program to detect our sample size. For power analysis and sample size calculation, we conducted a pilot study with 30 patients. According to this result, we found that for $\alpha = 0.05$ and $\beta = 0.80$ sample size must be 120 subjects.

Statistical analysis

All analyses were conducted using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentages. Analysis of normality of the continuous variables was performed with the Kolmogorov–Smirnov test. The OPG and CIMT were detected to be normally distributed. Comparison of categorical variables between the three groups was performed using the χ^2 test. Comparison of continuous variables between the three groups was performed using the one-way ANOVA with Bonferroni correction. The correlation between OPG, CIMT and continuous clinical and laboratory parameters was assessed by the Pearson correlation test. Regression analysis was employed to assess correlations between correlated parameters of CIMT, independent cardiovascular risk factors and CIMT. A two-tailed $p < 0.05$ was considered statistically significant.

Results

The mean age ± SD of the study participants was 37.8 ± 4.7 years, the mean BMI ± SD was 28.9 ± 5.2 kg/m^2 at enrollment. The mean number ± SD of pregnancies per woman was 4.9 ± 2.6 with a range of 1–12. After dividing the patients into three groups according to the number of births: the mean age, height, weight, BMI and systolic and diastolic blood pressures of the groups were similar. Hemoglobin levels and basal biochemical serum parameters also were not significantly different between the groups (Table 1). The percentages of abortions and miscarriages were the same in each group (12.0, 10.9 and 15.6 %, respectively; $p = 0.812$).

OPG and CIMT levels were detected to be increased from group 1 towards group 3 and reached significance level between group 1 and 3 ($p = 0.013$ and $p < 0.001$, respectively). Parity is found to be correlated with OPG level and CIMT ($r = 0.297$, $p = 0.001$; $r = 0.505$, $p < 0.001$, respectively). Furthermore, OPG level is also correlated with CIMT ($r = 0.277$, $p = 0.002$) (Fig. 1). In multivariate analysis, as CIMT-dependent variable and systolic blood pressure, LDL-C, smoking, weight, parity, and OPG levels independent variables, only parity and weight found to be independent predictors of CIMT (model $r^2 = 0.390$, $p < 0.001$) (Table 2).

Discussion

In this study involving premenopausal women with different parities, we evaluated the relationship between CIMT, an established risk factor of atherosclerosis, and OPG, whose relationship with vascular calcification was recently described. This is the first study to investigate the association between OPG, CIMT and parity. We detected increased OPG levels with advancing number of pregnancies and correlation with both CIMT and parity.

The positive association between parity and coronary heart disease (CHD) and CIMT has been assessed in a number of studies [1, 6, 7, 17]. There were physiologic

Table 1 Demographic and laboratory parameters of both groups

Parameters	Group 1 ($n = 41$)	Group 2 ($n = 55$)	Group 3 ($n = 32$)	p
Age (years)	37.1 ± 4.5	37.5 ± 4.8	39.3 ± 4.5	0.096
Height (cm)	161.4 ± 6.2	161.0 ± 7.2	159.9 ± 6.1	0.709
Weight (kg)	74.4 ± 13.9	75.5 ± 13.2	74.1 ± 12.6	0.918
BMI (kg/m^2)	28.5 ± 5.3	29.1 ± 5.4	29.0 ± 5.0	0.837
SBP (mmHg)	117.3 ± 12.9	122.7 ± 10.0	122.7 ± 10.9	0.064
DBP (mmHg)	71.9 ± 9.9	69.6 ± 7.9	69.5 ± 7.7	0.351
Glucose (mmol/L)	5.3 ± 0.8	5.2 ± 0.9	5.0 ± 0.5	0.284
Urea (mmol/L)	4.4 ± 1.0	4.5 ± 1.2	4.5 ± 1.2	0.939
Creatinine (mmol/L)	0.05 ± 0.02	0.05 ± 0.01	0.05 ± 0.02	0.577
AST (U/L)	19.6 ± 4.6	22.7 ± 11.8	19.4 ± 3.9	0.658
ALT (U/L)	20.6 ± 13.6	25.5 ± 19.2	19.1 ± 9.5	0.166
T-C (mmol/L)	4.7 ± 0.9	4.6 ± 0.9	4.6 ± 0.9	0.757
LDL-C (mmol/L)	2.9 ± 0.8	2.7 ± 0.8	2.6 ± 0.7	0.854
HDL-C (mmol/L)	1.1 ± 0.3	1.0 ± 0.2	1.2 ± 0.3	0.205
TG (mmol/L)	1.7 ± 1.2	1.8 ± 1.0	2.0 ± 1.1	0.219
Hgb (g/L)	129 ± 16	132 ± 13	128 ± 16	0.417
OPG (pg/mL)*	445.0 ± 244.0	558.0 ± 246.7	609.3 ± 219.7	0.011
CIMT (mm)**	0.43 ± 0.17	0.55 ± 0.11	0.62 ± 0.11	<0.001

Data are shown as mean ± SD

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *BMI* body mass index, *CIMT* carotid intima-media thickness, *HDL-C* high density lipoprotein cholesterol, *Hgb* hemoglobin, *LDL-C* low density lipoprotein cholesterol, *OPG* osteoprotegerin, *TG* triglyceride, *TC* total cholesterol

* $p = 0.013$ between group 1 and group 3

** $p < 0.001$ between group 1 and group 2, between group 1 and group 3

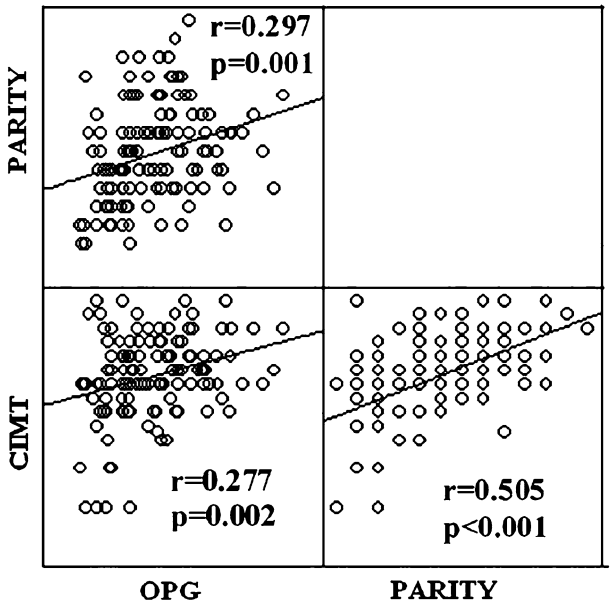

Fig. 1 Correlations of parity, osteoprotegerin and mean CIMT values. *CIMT* carotid intima-media thickness, OPG osteoprotegerin

Table 2 Multiple regression analysis with CIMT as the dependent variable

Parameters	β	p
Parity	0.003	<0.001
Weight	<0.001	0.006
OPG	0.082	0.444
SBP	0.058	0.584
Smoking	−0.167	0.094
LDL-C	−0.047	0.645

Multiple regression analysis was done with stepwise method

CIMT carotid intima-media thickness, *LDL-C* low density lipoprotein cholesterol, *OPG* osteoprotegerin

changes that influence the mediators in various cardiovascular pathways in normal pregnancy [7, 18, 19]. Since atherosclerosis is a progressive process, cumulative effect of these alterations over successive pregnancies may influence the progression of atherosclerosis [7, 19]. Skilton et al. [20] reported that there is a stronger association between CIMT and parity in younger women than in older women. In our study, women were young similar to study of Skilton, and we also found a strong association between CIMT and parity. Furthermore, elevated risk of atherosclerosis with the increased number of pregnancy has been shown previously [6, 7]. Increased insulin resistance and levels of lipids during pregnancy had directly effect on atherosclerosis [18]. OPG may have a role in the formation of vascular disease, in addition to its role in the bones. OPG is expressed in macro- and microvascular endothelial cells, as well as vascular smooth muscle cells and is able to increase endothelial and vascular smooth muscle cells survival. Dysfunction and death of vascular cells develop in the vessels affected by atherosclerosis [21]. Therefore, the ability of OPG to promote vascular cell survival suggests that OPG may be potentially protection mediator against the process of atherosclerosis [21]. For example, OPG deficient mice have severe vascular calcification as well as developing osteoporosis [10]. Moreover, increased levels of serum OPG were found to be associated with cardiovascular disorders in human studies [12, 14, 15, 22]. Furthermore, the association between OPG levels and left ventricular mass has been shown in general population and in hypertensive patients [23, 24].

There are limited studies of OPG in pregnant women. Both Naylor et al. [25] and Uemura et al. [26] demonstrated a progressive increase during pregnancy and a rapid postpartum decline in serum OPG levels. Hong et al. [27] showed a significant OPG increase in the third trimester of normal pregnancy. Moreover, increased OPG levels have been shown in preeclamptic women, especially in the postpartum period [28]. OPG was significantly higher in the group 3 which had high parity in our study. Although OPG has been shown to normalize in postpartum, our findings may be secondary to the cumulative effect of parities.

The positive correlation of OPG and CIMT was reported in few studies, such as in general population [29], in patients with type 2 diabetes mellitus [30], in healthy postmenopausal women [31] and in women with previous gestational diabetes mellitus [32]. OPG was showed significant positive correlations between parity and CIMT in our study. These results suggest us that women with multiparity have higher cardiovascular risk than those with less number of births and OPG involves through different mechanisms in endothelial dysfunction in multi-parity.

Several limitations of the present study should be considered. First of all, the study design is cross sectional; therefore findings of the present study should be evaluated in prospective population-based studies. As a second limitation, we have used CIMT—the surrogate marker of atherosclerosis—as the predictor of atherosclerosis. Assessing atherosclerosis in other arterial territories like coronary angiography, lower extremity duplex ultrasonography would add to the value of the manuscript; however, we could not have such an opportunity. Similarly, assessing insulin resistance would be valuable for this study; however, we could not also have opportunity to perform such an analysis. As another limitation, high parity may be related with low socioeconomic status, we did not take into account socioeconomic status of our patients [33]. We should also mention that the findings of this study on women with increased parities might not be generalized to Western populations with fairly decreased parities.

In conclusion, our result revealed that parity associated with increased risk of cardiovascular disease. Parity and weight were independent predictors of the elevated CIMT, as an established risk factor. Furthermore, OPG was correlated with CIMT and these results might suggest that OPG may have a role in the progression of parity-induced atherosclerosis.

Conflict of interest None.

References

1. Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, Stunkard AJ, D'Agostino RB (1993) Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J Med 328:1528–1533
2. Lawlor DA, Emberson JR, Ebrahim S, Whincup PH, Wannamethee SG, Walker M, Smith GD, British Women's Heart and Health Study, British Regional Heart Study (2003) Is the association between parity and coronary heart disease due to biological effects of pregnancy or adverse lifestyle risk factors associated with child-rearing? Findings from the British Women's Heart and Health Study and the British Regional Heart Study. Circulation 107:1260–1264
3. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH (1987) A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. Am J Epidemiol 126:861–870
4. Steenland K, Lally C, Thun M (1996) Parity and coronary heart disease among women in the American Cancer Society CPS II population. Epidemiology 7:641–643
5. Bots ML, Grobbee DE (2002) Intima media thickness as a surrogate marker for generalised atherosclerosis. Cardiovasc Drugs Ther 16:341–351
6. Kharazmi E, Moilanen L, Fallah M, Kaaja R, Kattainen A, Kähönen M, Jula A, Kesaniemi A, Luoto R (2007) Reproductive history and carotid intima-media thickness. Acta Obstet Gynecol Scand 86:995–1002
7. Skilton MR, Bonnet F, Begg LM, Juonala M, Kähönen M, Lehtimäki T, Viikari JS, Raitakari OT (2010) Childbearing, child-rearing, cardiovascular risk factors, and progression of carotid intima-media thickness: the Cardiovascular Risk in Young Finns study. Stroke 41:1332–1337
8. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Lüthy R, Nguyen HQ, Wooden S, Bennett L, Boone T, Shimamoto G, DeRose M, Elliott R, Colombero A, Tan HL, Trail G, Sullivan J, Davy E, Bucay N, Renshaw-Gegg L et al (1997) Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89:309–319
9. Schoppet M, Preissner KT, Hofbauer LC (2002) RANK ligand and osteoprotegerin: paracrine regulators of bone metabolism and vascular function. Arterioscler Thromb Vasc Biol 22:549–553
10. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS (1998) Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 12:1260–1268
11. Golledge J, McCann M, Mangan S, Lam A, Karan M (2004) Osteoprotegerin and osteopontin are expressed at high concentrations within symptomatic carotid atherosclerosis. Stroke 35:1636–1641
12. Kiechl S, Schett G, Wenning G, Redlich K, Oberhollenzer M, Mayr A, Santer P, Smolen J, Poewe W, Willeit J (2004) Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation 109:2175–2180
13. Browner WS, Lui LY, Cummings SR (2001) Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. J Clin Endocrinol Metab 86:631–637
14. Jono S, Ikari Y, Shioi A, Mori K, Miki T, Hara K, Nishizawa Y (2002) Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. Circulation 106:1192–1194
15. Anand DV, Lahiri A, Lim E, Hopkins D, Corder R (2006) The relationship between plasma osteoprotegerin levels and coronary artery calcification in uncomplicated type 2 diabetic subjects. J Am Coll Cardiol 47:1850–1857
16. Omland T, Ueland T, Jansson AM, Persson A, Karlsson T, Smith C, Herlitz J, Aukrust P, Hartford M, Caidahl K (2008) Circulating osteoprotegerin levels and long-term prognosis in patients with acute coronary syndromes. J Am Coll Cardiol 51:627–633
17. Green A, Beral V, Moser K (1988) Mortality in women in relation to their childbearing history. BMJ 297:391–395
18. Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF, Ingelsson E (2010) Parity and risk of later-life maternal cardiovascular disease. Am Heart J 159:215–221
19. Morris JM, Gopaul NK, Endresen MJ, Knight M, Linton EA, Dhir S, Anggård EE, Redman CW (1998) Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia. Br J Obstet Gynaecol 105:1195–1199
20. Skilton MR, Sérusclat A, Begg LM, Moulin P, Bonnet F (2009) Parity and carotid atherosclerosis in men and women: insights into the roles of childbearing and child-rearing. Stroke 40:1152–1157
21. Reid P, Holen I (2009) Pathophysiological roles of osteoprotegerin (OPG). Eur J Cell Biol 88:1–17
22. Abedin M, Omland T, Ueland T, Khera A, Aukrust P, Murphy SA, Jain T, Gruntmanis U, McGuire DK, de Lemos JA (2007) Relation of osteoprotegerin to coronary calcium and aortic plaque (from the Dallas Heart Study). Am J Cardiol 99:513–518
23. Omland T, Drazner MH, Ueland T, Abedin M, Murphy SA, Aukrust P, de Lemos JA (2007) Plasma osteoprotegerin levels in the general population: relation to indices of left ventricular structure and function. Hypertension 49:1392–1398
24. Noheria A, Mosley TH Jr, Kullo IJ (2010) Association of serum osteoprotegerin with left ventricular mass in African American adults with hypertension. Am J Hypertens 23:767–774
25. Naylor KE, Rogers A, Fraser RB, Hall V, Eastell R, Blumsohn A (2003) Serum osteoprotegerin as a determinant of bone metabolism in a longitudinal study of human pregnancy and lactation. J Clin Endocrinol Metab 88:5361–5365
26. Uemura H, Yasui T, Kiyokawa M, Kuwahara A, Ikawa H, Matsuzaki T, Maegawa M, Furumoto H, Irahara M (2002) Serum osteoprotegerin/osteoclastogenesis-inhibitory factor during pregnancy and lactation and the relationship with calcium-regulating hormones and bone turnover markers. J Endocrinol 174:353–359
27. Hong JS, Santolaya-Forgas J, Romero R, Espinoza J, Gonçalves LF, Kim YM, Edwin S, Yoon BH, Nien JK, Hassan S, Mazor M (2005) Maternal plasma osteoprotegerin concentration in normal pregnancy. Am J Obstet Gynecol 193:1011–1015
28. Vitoratos N, Lambrinoudaki I, Rizos D, Armeni E, Alexandrou A, Creatsas G (2011) Maternal circulating osteoprotegerin and soluble RANKL in pre-eclamptic women. Eur J Obstet Gynecol Reprod Biol 154(2):141–145
29. Vik A, Mathiesen EB, Brox J, Wilsgaard T, Njølstad I, Jørgensen L, Hansen JB (2010) Relation between serum osteoprotegerin and carotid intima media thickness in a general population—the Tromsø Study. J Thromb Haemost 8:2133–2139
30. Ishiyama M, Suzuki E, Katsuda J, Murase H, Tajima Y, Horikawa Y, Goto S, Fujita T, Takeda J (2009) Associations of

coronary artery calcification and carotid intima-media thickness with plasma concentrations of vascular calcification inhibitors in type 2 diabetic patients. Diabetes Res Clin Pract 85:189–196
31. Erdogan B, Aslan E, Bagis T, Gokcel A, Erkanli S, Bavbek M, Altinors N (2004) Intima-media thickness of the carotid arteries is related to serum osteoprotegerin levels in healthy postmenopausal women. Neurol Res 26:658–661
32. Akinci B, Demir T, Celtik A, Baris M, Yener S, Ozcan MA, Yuksel F, Secil M, Yesil S (2008) Serum osteoprotegerin is associated with carotid intima media thickness in women with previous gestational diabetes. Diabetes Res Clin Pract 82:172–178
33. Huber S, Bookstein FL, Fieder M (2010) Socioeconomic status, education, and reproduction in modern women: an evolutionary perspective. Am J Hum Biol 22:578–587