Original Article

Ectopic Fat Depots and Cardiometabolic Burden: A Possible Dangerous Liaison in Women Planning Assisted Reproduction

Michela Cirillo; M.Sc.[1,2], Maria Boddi; M.D. Ph.D.[1], Maria Elisabetta Coccia; M.D. Ph.D.[2,3], Monica Attanasio; M.Sc.[1], Cinzia Fatini; M.D. Ph.D.[1,2]

1 Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
2 Center for Assisted Reproductive Technology, Division of Obstetrics and Gynecology, Careggi University Hospital, Florence, Italy
3 Department of Clinical and Experimental Biomedical Sciences, University of Florence, Florence, Italy

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Abstract

Objective: We evaluated cardiometabolic burden in women planning assisted reproduction in order to identify subgroups at higher risk of pregnancy complications and cardiovascular disease.
Materials and methods: In this cross-sectional study we investigated 60 infertile women with BMI≥25 kg/m² referred to the Center for Assisted Reproduction. All women underwent metabolic, anthropometric parameters and ultrasound evaluation of ectopic fat depots.
Results: All women had waist ≥80 cm. We found that 93.3% of women had pathological subcutaneous, 58.3% visceral and 80% para-perirenal fat; all women had fatty liver. Visceral fat and severity of steatosis were significantly related to the presence of metabolic syndrome (OR =5.7; p=0.03). A significant negative correlation between low HDL-c and para-perirenal fat (p<0.0001), a significant positive correlation with fasting plasma glucose and para-perirenal fat (p=0.001) were found. We observed a significant positive correlation between visceral fat and hs-CRP (p=0.002), HOMA-IR (p=0.04) and triglycerides (p=0.002), a significant negative correlation with HDL-c (p=0.05).
Conclusion: This study by highlighting a clinically “dangerous liaison” between ectopic fat depots and metabolic/inflammatory markers, might permit to identify women with a worse metabolic phenotype and encourage lifestyle changes for improving their general and reproductive health together.

Keywords: Assisted Reproductive Techniques; Heart Disease Risk Factors; Obesity; Metabolic Syndrome; Women’s Health

Introduction

The historically lower risk of cardiovascular disease in young women in comparison to men has created a gender bias; beyond estrogens’ protection, atherosclerotic cardiovascular (CV) disease is still the major cause of mortality in women.

Therefore, atherosclerotic cardiovascular disease prevention remains undisputed and should be delivered to women by promoting healthier lifestyles

Correspondence:
Dr. Cinzia Fatini
Email: cinzia.fatini@unifi.it

and by modifying traditional, as well as emerging CV risk factors, such as hormonal status and negative pregnancy outcomes.

It is noteworthy that obesity is related to cardiometabolic disorders (1), as it represents a strong risk factor for heterogeneous conditions including insulin resistance, type 2 diabetes mellitus, metabolic syndrome (MetS), atherogenic dyslipidemia, hypertension and other cardiovascular diseases, as well as non-alcoholic fatty liver disease (NAFLD).

Recent insights suggest that besides obesity, fat distribution might be a better predictor of cardiovascular disease than obesity itself (2). In particular, ectopic fat depots with predominantly systemic effects, such as visceral and liver fat (3), which are often associated with insulin resistance, with atherogenic lipid profile and adverse metabolic phenotypes, independently of total adiposity (4,5), may contribute to increasing cardiometabolic risk. Moreover, accumulation of adipose tissue in ectopic sites such as para-perirenal and renal sinus fats, by inducing local effects, is possibly related to cardiovascular disease.

Obesity has become a worldwide epidemic, and apart from cardiovascular diseases, it negatively affects reproductive potential. Women with obesity are likely to have ovulatory dysfunction due to dysregulation of the hypothalamic-pituitary-ovarian axis (6), menstrual irregularities, infertility, and once pregnant, a wide range of obstetric and post-partum complications (7).

In the real world, increasing age of women in getting pregnant, physiological lowering in ovarian function, often associated with comorbidities, could explain the higher percentage of women undergoing assisted reproduction. Data from clinical studies demonstrated that women with overweight/obesity are less likely to achieve a clinical pregnancy after assisted reproduction compared to normal weight women (8). Moreover, women with overweight/obesity are prone to have lower clinical pregnancy rates, lower live birth rates and potential increased cardiovascular risk assisted reproduction-related, as compared with women of normal BMI (9). Recently, data from a study performed on women underwent ART provided evidence that weight gain is negatively associated with ART success, and in particular on probability of live birth following ART; this observation may support the benefits of preventing weight gain in female fertility (10). Actually, this topic remains the object of debate.

Preventive medicine and adequate treatments for preconception cardiovascular risk factors might contribute to control the added risk carried by assisted reproduction, while strategies and interventions aimed to change modifiable cardiovascular risk factors might improve pregnancy outcome and lifetime health.

The aim of the present study was to evaluate cardiometabolic burden in a model of women planning assisted reproduction, by investigating ectopic fat depots and their relationship with cardiometabolic risk factors, in order to identify subgroups of women at higher risk of pregnancy complications and cardiovascular disease.

Materials and methods

In this monocentric cross-sectional study, we investigated Caucasian infertile women with BMI ≥ 25 kg/m^2 planning assisted reproduction, at the Assisted Reproductive Technology Center, Division of Obstetrics and Gynecology, University Hospital, Careggi, Florence, Italy from February 2018 to November 2019.

The entire study population comprised 60 women with overweight/obesity, who were referred to the Internal Medicine Clinic at the Assisted Reproduction Center, in order to be framed for their cardiovascular risk profile and to better define preconceptional behaviors before Assisted Reproduction.

Information concerning cardiometabolic parameters derived from clinical reports and cardiovascular risk factors were investigated during the clinical evaluation.

According to the World Health Organization criteria, overweight was defined as BMI values ≥ 25 Kg/m^2, first grade obesity as BMI values ≥ 30 Kg/m^2 and <30 Kg/m^2, and second grade obesity as BMI ≥ 35 Kg/m^2.

All anthropometric parameters were also measured; waist circumference was measured midway between the inferior margin of the lowest rib and the iliac crest in the horizontal plane at the end of normal expiration; hip circumference was measured at the widest point over the buttocks. A value ≥ 80 cm was considered a marker of increased cardiovascular risk according to Alberti et al. (11); WHR was obtained by dividing the waist circumference by hip circumference, and a value >0.80 was considered a marker of increased cardiovascular risk. Dyslipidemia was defined according to ESC guidelines (12). MetS was defined according to the 2005 International Diabetes Federation criteria (11).

Ultrasound evaluation (US) of intra-abdominal (visceral) (VAT), subcutaneous (SAT), liver and para-perirenal fat were obtained. US-determined subcutaneous fat was defined as the distance between the skin and external face of linea alba, and visceral fat was defined as the distance between the internal face of linea alba and the anterior wall of the aorta. With the patient in the supine position, the probe was kept perpendicular to the skin 5 cm above the umbilical scar. Then longitudinal scanning was performed, and the probe was slowly moved laterally until the optimal position was found, at which the surface of the kidney was almost parallel to the skin. The thickness of fat (consisting of para- and perirenal fat) was measured from the inner side of the abdominal musculature to the surface of the kidney and designated ultrasound measure (UM) sonographic evaluation of visceral fat by measuring para- and perirenal fat. The average of the UM values on both sides was defined as the para- and perirenal ultrasound fat thickness (PUFT) (13).

The pressure exerted on the probe was as minimal as possible so that the fat layers were not compressed. NAFLD was defined according to Fatty Liver Indicator (14). Sonographer was blinded to any other aspect of the study.

Informed written consent for anonymous data analysis was obtained from all women. The investigation conforms to the principles outlined in the Declaration of Helsinki. The original study was approved by the Regional Ethical Committee (29 November 2016, CEAVC 10189, amendment 16 May 2018, 2018-017 CINECA 10189).

Statistical analysis: Statistical analysis was performed by using the SPSS (Statistical Package for Social Sciences, Chicago, USA) software for Windows (Version 25.0). Continuous variables were expressed as median, range; categorical variables were expressed as n, (%). Chi-square or Fisher's exact test were used to test for proportions of the categorical variables, as appropriate. Correlation analysis was measured by using Spearman's rho test. The association between ectopic fat depots and MetS was assessed by using logistic regression analysis. The odds ratio (OR) with 95% confidence interval (CI) was determined. A p-value <0.05 was considered to indicate statistical significance. Sample size calculation indicated that at least 52 subjects were sufficient to detect, with a statistical power of 80% (β) and a significance value of 0.05 (α), absolute differences in the prevalence of MetS (15), according to the presence of the ectopic fat depots investigated.

Receiver operating characteristic (ROC) curve was used to establish cut-off values for the diagnosis of visceral obesity based on waist circumference value (known to be more strongly associated with CT subcutaneous fat values) (16).

ROC curve analysis identified the cut-offs of 53 cm for US-determined visceral fat (specificity of 72.2%, sensitivity of 98.2%); for subcutaneous fat 20 cm (specificity 77.8%, sensitivity 84.2%); for Para-Perirenal Ultrasound Fat Thickness 20 cm (specificity 94.4%, sensitivity 73.7%).

Results

Demographical and clinical characteristics of the study population are reported in Table 1. The median age of our study population was 41 (24-49 yrs). The evaluation of traditional CV risk factors evidenced that 28 out of 60 women (46.7%) were overweight, and 32 (53.3%) were obese; as concern anthropometric parameters, all women had waist circumference ≥80 cm (100%); a high prevalence of dyslipidemia (76.7%), and smoking habit (15.6%), as well as impaired fasting glucose (20%), and hypertension (10%) were found. About 27% of women planning assisted reproduction had MetS, according to the IDF definition (11).

Table 1: Demographic and clinical characteristics of infertile women planning Assisted Reproduction

Variables	Infertile women (n=60)
Age, yrs[a]	41 (24-49)
BMI 25-29.99 Kg/m^2	28 (46.7)
BMI 30-34.99 Kg/m^2	24 (40)
BMI 35-39.99 Kg/m^2	8 (13.3)
WAIST circumference ≥ 80 cm	60 (100)
WHR > 0.8	48 (80)
Smoking habit (current), n (%)	10 (15.6)
Sedentary behaviour, n (%)	48 (80)
Dyslipidemia, n (%)	46 (76.7)
Hypertension, n (%)	6 (10)
Impaired fasting glucose, n (%)	12 (20)
Metabolic syndrome, n (%)	16 (26.7)
Family history of CV disease, n (%)	22 (36.7)
Migraine with aura, n (%)	6 (10)
POI, n (%)	2 (3.3)
PCOS, n (%)	10 (16.7)
History of negative pregnancy outcomes, n (%)	22 (36.7)
Anti-hypertensive treatment, n (%)	6 (10)

[a]Values are reported as median (range). WHR (Waist to Hip Ratio); POI (Premature Ovary Insufficiency); PCOS (Polycystic Ovary Syndrome); CV (cardiovascular).

As concerning traditional CV risk factors, evaluated according to overweight and obesity, we observed a higher, but not statistically significant prevalence of impaired fasting glucose in women with obesity than in women with overweight (25% vs. 14.3%), whereas no difference in the prevalence of both dyslipidemia and MetS was observed between women with overweight and women with obesity (75% vs. 78.1%; 28.6% vs. 25%, respectively). Hypertension was observed only in the group with obesity (18.8%). Values of waist circumference ≥80 cm, measure of visceral adiposity, were present in all women investigated, whereas WHR value >0.80 was present in 80% of infertile women; a significantly higher percentage of WHR value >0.80 was observed in women with obesity (93.8%), than that found in women with overweight (64.3%) (p=0.008). Biohumoral parameters are reported in Table 2. We observed elevated median levels of hs-CRP, total cholesterol and lipoprotein (a).

Table 2: Cardiometabolic parameters of infertile women planning Assisted Reproduction

Variables	Infertile women (n=60)
Total Cholesterol (mg/dl)	203 (144-269)
LDL-c (mg/dl)	130 (68-195)
HDL-c (mg/dl)	53.5 (31-85)
Triglycerides (mg/dl)	95 (68-306)
Lipoprotein (a) (mg/L)	383 (20-1750)
Fasting plasma glucose (mg/dl)	89 (70-119)
HbA1c (mmol/mol)	34 (23-39)
HOMA-IR	2.3 (0.7-9)
hs-CRP mg/L	5.3 (0.1-14)
AST IU/L	18 (8-45)
ALT IU/L	19 (7-48)
GGT IU/L	20 (12-33)
Creatinine mg/dl	0.7 (0.5-0.9)
Fibrinogen mg/dl	378 (238-597)

[a]Values are reported as median (range).
HOMA-IR (Homeostatic Model Assessment of Insulin Resistance); hs-CRP (high sensitive C Reactive Protein).

Ectopic fat depots and cardiometabolic burden

We investigated SAT, VAT, PUFT, and liver fat and we observed that 56 (93.3%) women had pathological SAT storage, 35 (58.3%) VAT, and 48 (80%) PUFT and all women (100%) had NAFLD, defined according to Fatty Liver Indicator. Forty-six (76.7%) women had moderate, and 14 (23.3%) severe NAFLD.

The univariable analysis showed that VAT and severity of steatosis were statistically significantly related to the presence of MetS (OR = 6; IC 95%, 1.41-25.38; p=0.02, respectively). At multivariable analysis, adjusted for age and traditional cardiovascular risk factors (family history of cardiovascular disease, smoking habit, dyslipidemia, BMI, hypertension), VAT and severity of steatosis remained significantly associated with MetS (OR = 5.7; IC 95%, 1.22-26.66; p=0.03). In Table 3 we reported the correlation between cardiometabolic parameters and ectopic fat depots; we observed a significant correlation between pathological VAT storage and hs-CRP, HOMA-IR and triglycerides (rho=0.45, p=0.002, rho=0.39, p=0.04; rho=0.43, p=0.002, respectively), and a significant negative correlation with HDL-c (rho= -0.28, p=0.05). Finally, we also found a significant negative correlation between low HDL-c values and PUFT (rho= -0.55, p<0.0001), and a significant positive correlation with fasting plasma glucose and both SAT and PUFT (rho=0.28, p0=0.05 and rho=0.45, p=0.001, respectively).

Discussion

This study supports the concept that obesity, conventionally defined by BMI ≥30 kg/m^2, seems to be not representative of the global cardiometabolic risk burden. Data from the literatures suggest that fat distribution might be a better predictor of cardiovascular disease than obesity itself (3,17); and the evaluation of amount and distribution of ectopic fat depots might help to clarify the heterogeneity of obesity phenotypes.

To date, in response to weight gain, both women and men have increased fatty acid release into blood; in particular, in women, a high concentration of triglycerides correlates more strongly with cardiovascular risk, even if the reason remains unknown (18).

Table 3: Correlation between cardiometabolic parameters and ectopic fat depots

Variables	HDL-c	LDL-c	Triglycerides	hs-CRP	HOMA-IR	Fasting plasma glucose
VAT	Rho -0.28 p=0.05	-	Rho 0.43 p=0.002	Rho 0.45 p=0.01	Rho 0.39 p=0.04	-
SAT	-	Rho 0.26 p=0.08	-	-	-	Rho 0.28 p=0.05
PUFT	Rho -0.55 p <0.0001	-	-	-	-	Rho 0.45 p=0.001

VAT (visceral adipose tissue); SAT (subcutaneous adipose tissue); PUFT (para-perirenal ultrasound fat thickness); hs-CRP (high sensitive C Reactive Protein); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

In our study, we observed a strong association between VAT, liver fat and the presence of MetS. This suggests that the severity of steatosis and visceral fat were more closely linked to the MetS components, in comparison to other ectopic fat depots, providing an opportunity to identify a subgroup of women with a higher future risk of vascular disease.

We also found a significant correlation between visceral adipose tissue and both increased triglycerides concentrations and HOMA-IR, as well as a decreased HDL-c. There are substantial experimental evidence that both higher levels of triglycerides and lower levels of HDL-c can be a consequence of insulin-resistance. Really, some mechanisms involving the activity of triglyceride lipases, have been proposed to account for this reduction in HDL-c as a consequence of insulin-resistance (19).

Metabolic syndrome, of which abdominal obesity is the main distinguishing feature, represents a constellation of metabolic abnormalities known as risk factors for cardiovascular disease. In order to explain the existing relationship between VAT and cardiometabolic risk, several mechanisms concerning lipolytic activity increased delivery of free fatty acids to the liver and consequently insulin-resistance, have been hypothesized. Furthermore, the liver, particularly susceptible to ectopic lipid accumulation, causally contribute to atherogenic dyslipidemia (high plasma triglyceride and reduced HDL-c) (20). Clinical data evidenced that visceral fat depot, by producing atherosclerotic cytokines, leads to low-grade systemic inflammation (1). Our findings demonstrated a significant correlation between VAT and hs-CRP, a predictor of cardiovascular risk (21) produced by the liver upon stimulation by inflammatory cytokines; hs-CRP is a downstream marker of the IL-1b–IL-6 pathway and its measurement may increase overall cardiovascular risk assessment. This datum is at variance with a recent study (22), which suggested that visceral body fat and subclinical atherosclerosis were not mediated by inflammation as measured by hs-CRP. This conflicting result might be related to the clinical characteristic of our study population, which comprised younger women without history of diabetes and cardiovascular disease, and in the absence of lipid-lowering or antithrombotic therapy, known to their pleiotropic effects.

At the best of our knowledge, no studies investigating PUFT in women with overweight/ obesity planning Assisted Reproduction are available. Our findings provided evidence of a significant correlation between para- perirenal fat and both lower HDL-C and increased fasting plasma glucose, parameters defining metabolic syndrome. These data are in keeping with those from Manno et al. (23), even if our population comprised only women, younger, and in preconception period.

PUFT represents an atypical visceral fat, possibly involved in regulating cardiovascular risk through mechanisms including neural, humoral and kidney-mediated regulation; noteworthy, PUFT is highly active in adipokines synthesis and abnormally involved in worsening glucose homeostasis (24).

A limitation of the study might be the lack of ultrasounds evaluation in normal weight women. This imaging method not represents routinely screening test in our clinical assisted reproduction setting, but is addressed only to women at higher risk for cardiovascular disease.

It is noteworthy that the distribution and contribution of metabolic syndrome components in defining cardiometabolic risk is specific to each population and that the relationship between lipid profiles and body fat distribution may vary by race/ethnicity in reproductive-age women. In our study all participants were Caucasians, and thus findings may not be generalizable to other racial and ethnic groups.

To date, there are direct implications of obesity on maternal health as well as obstetric and perinatal outcomes, in particular, in women undergoing assisted reproduction (25). Moreover, there is developing research indicating that in utero environmental factors during specific developmental periods (preconception, conception, and gestation), influence chronic disease susceptibility later in life (26).

Obesity is a reversible disorder, and strategies aimed to control this cardiovascular risk factor, might translate a “dysmetabolic” into a “healthy” vascular phenotype. The ideal timing for this virtuous transition is preconceptional period, as preconception care offers an opportunity for non-communicable disease prevention and health promotion among metabolically unhealthy women planning pregnancy after assisted reproduction, thus possibly improving their lifetime health.

Conclusion

This study performed in women with overweight and women with obesity planning assisted reproduction, might permit to identify, through ultrasounds evaluation of ectopic fat depots, women with a worse metabolic phenotype. Our study allowed us to assess a better clinical risk stratification, and to encourage lifestyle changes for improving their general health and reproductive health together. Our findings highlight a clinically "dangerous liaison" between ectopic fat depots, such as VAT and PUFT, and metabolic and inflammatory markers, possibly contributing to improving our knowledge concerning the cross-talking between ectopic fat depots, cellular pathways and cardiovascular health in women planning assisted reproduction. Due to the small number of women investigated, this study must be considered as a "pilot study", and further studies are required in order to reinforce the relevance of our findings.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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References

1. Lim S, Meigs JB. Ectopic fat and cardiometabolic and vascular risk. Int J Cardiol 2013; 169: 166-76.
2. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007; 116: 39–48.
3. Despres JP. Body Fat Distribution and Risk of Cardiovascular Disease: An Update. Circulation 2012; 126: 1301-13.
4. Ferrara D, Montecucco F, Dallegri F, Carbone F. Impact of Different Ectopic Fat Depots on Cardiovascular and Metabolic Diseases. J Cell Physio 2019; 234: 21630-41.
5. Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: The Framingham Heart Study. Hepatology 2010; 51: 1979–87.
6. Broughton DE, Moley KH. Obesity and Female Infertility: Potential Mediators of Obesity's Impact. Fertil Steril 2017; 107: 840-47.
7. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, Obstetric Complications and Cesarean Delivery Rate--A Population-Based Screening Study. Am J Obstet Gynecol 2004; 190: 1091-7.
8. Veleva Z, Tiitinen A, Vilska S, Hydén-Granskog C, Tomás C, Martikainen H, et al. High and Low BMI Increase the Risk of Miscarriage After IVF/ICSI and FET. Hum Reprod 2008; 23: 878-84.
9. Ciavattini A, Montik N, Clemente N, Santoni F, Moriconi L, Serri M, et al. Obesity and Ultrasound-Estimated Visceral Fat Deposits in Women Undergoing Assisted Reproductive Technology (ART) Procedures. Gynecol Endocrinol 2017; 33: 972-6.
10. Gaskins AJ, Arvizu M, Mínguez-Alarcón L, Dadd R, Souter I, Chavarro JE, et al. Substantial Weight Gain in Adulthood Is Associated with Lower Probability of Live Birth Following Assisted Reproduction. J Nutr 2021; 151: 649-56.
11. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366: 1059-62.
12. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European Heart Journal 2016; 37: 2999–3058.
13. Kawasaki S, Aoki K, Hasegawa O, Numata K, Tanaka K, Shibata N, et al. Sonographic Evaluation of Visceral Fat by Measuring Para- And Perirenal Fat. J Clin Ultrasound 2008; 36: 129-33.
14. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Targher G, et al. Ultrasonographic Fatty Liver Indicator Detects Mild Steatosis and Correlates with Metabolic/Histological Parameters in Various Liver Diseases. Metabolism 2017; 72: 57-65.
15. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome: A Randomized Trial. JAMA 2004; 292: 1440-6.
16. Ribeiro-Filho FF, Faria AN, Azjen S, Zanella MT, Ferreira SR. Methods of Estimation of Visceral Fat: Advantages of Ultrasonography. Obes Res 2003; 11: 1488-94.
17. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D,

Long MT. Visceral and Intrahepatic Fat Are Associated with Cardiometabolic Risk Factors Above Other Ectopic Fat Depots: The Framingham Heart Study. Am J Med 2018; 131: 684-92.e12.

18. Hokanson JE, Austin MA. Plasma Triglyceride Level Is a Risk Factor for Cardiovascular Disease Independent of High-Density Lipoprotein Cholesterol Level: A Meta-Analysis of Population-Based Prospective Studies. J Cardiovasc Risk 1996; 3: 213-9.
19. Robins SJ, Lyass A, Zachariah JP, Massaro JM, Vasan RS. Insulin resistance and the relationship of a dyslipidemia to coronary heart disease: The Framingham Heart Study. Arterioscler Thromb Vasc Biol 2011; 31: 1208–14.
20. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int J Mol Sci 2019; 20: 2358.
21. Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, et al. High-sensitivity C-reactive Protein and Cardiovascular Disease: A Resolute Belief or an Elusive Link? J Am Coll Cardiol 2013; 62: 397-408.
22. Christen T, Trompet S, Rensen PCN, Willems van Dijk K, Lamb HJ, Jukema JW, et al. The Role of Inflammation in the Association between Overall and Visceral Adiposity and Subclinical Atherosclerosis. Nutr Metab Cardiovasc Dis 2019; 29: 728-35.
23. Manno C, Campobasso N, Nardecchia A, Triggiani V, Zupo R, Gesualdo L, et al. Relationship of Para- And Perirenal Fat and Epicardial Fat with Metabolic Parameters in Overweight and Obese Subjects. Eat Weight Disord 2019; 24: 67-72.
24. Liu BX, Sun W, Kong XQ. Perirenal Fat: A Unique Fat Pad and Potential Target for Cardiovascular Disease. Angiology 2019;70: 584-93.
25. Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. Extremities of Body Mass Index and Their Association with Pregnancy Outcomes in Women Undergoing in Vitro Fertilization in the United States. Fertil Steril 2016; 106: 1742-50.
26. Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, et al. Developmental Origins of Health and Disease: Integrating Environmental Influences. Endocrinology 2015; 156: 3416-21.

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