

Lifestyle and Comorbidities: Do We Take Enough Care of Preconception Health in Assisted Reproduction?

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Abstract

Objective: The preconception period is largely neglected, whereas it represents an opportunity to identify and modify clinical and behavioral risks, particularly in infertile women characterized by an unfavorable vascular burden. The present study was performed to strengthen previous findings and to increase the awareness of clinicians who should envision a broader preconception approach in infertile women, beyond their reproductive health.

Materials and methods: In this cross-sectional study, we investigated 1003 Caucasian women, referred to the Internal Medicine Clinic at the Assisted Reproductive Technologies Center, Florence.

Results: A high prevalence of dyslipidemia (57.4%), overweight/obesity (29.1%) and, smoking habit (26.6%) were found. We provided evidence of unhealthy lifestyle habits, represented by a closer adherence to the Mediterranean diet in the 9.5% only and by a sedentary behavior in 73%. A significant correlation between the Mediterranean Diet score and both anthropometric and metabolic parameters was found. We also observed a lower score adherence with both metabolic syndrome and diabetes (for both $p=0.02$), but not with hypertension.

Conclusion: Before infertility treatment, the correction and the management of modifiable and non-modifiable cardiovascular risk factors are mandatory and represent the main goal for a safe pregnancy, and lifetime women's health.

Keywords: Preconception Care; Pregnancy Planning; Assisted Reproduction; Women's Health; Lifestyle; Cardiovascular Prevention

Introduction

The preconception period represents an opportunity to identify and modify clinical and behavioral risks in women undergoing Assisted Reproductive Technology (ART), to prevent cardiovascular disorders (1). Maternal clinical assessment should be planned before beginning infertility treatment,

through interventions aimed to obtain successful pregnancy outcomes and a healthy child (1). The period around conception is aimed to optimize gamete function and early placental development, to decrease the risk of pre-eclampsia, miscarriage, low birth weight, small for gestational age, stillbirth and neonatal death (2).

Older maternal age at the time of pregnancy, and the presence of comorbidities, such as obesity, in particular visceral obesity, dyslipidemia, hypertension, diabetes and metabolic syndrome, may

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affect cardiovascular women's health, and contribute to excessive rates of maternal short and long-term morbidity.

To date, fertility therapy in women undergoing ART, may act as a cardiometabolic stress by increasing risk of long-term adverse cardiovascular events following unsuccessful treatment (3). Fertility therapy failure may represent a sex specific cardiovascular risk factor useful to identify women who may benefit from a cardiovascular risk evaluation (3).

Diet and nutrition before pregnancy may affect maternal and perinatal outcomes by influencing Body Mass Index (BMI) or nutritional factors. Among dietary patterns, greater adherence to the Mediterranean diet seems to be associated with increased chances of a successful pregnancy for women undergoing ART (4), and reduced risk of pregnancy complications (5, 6). It has also been demonstrated that increased physical activity before pregnancy was associated with a reduction in the risk of negative pregnancy outcomes (7, 8).

The implementation of the preconception healthcare in natural pregnancy contributes to improving maternal outcomes (9) and fetal offspring (10), but the evidence about its role in women undergoing ART are few (11, 12).

The preconception period is largely neglected, whereas efforts to improve preconception health should be aimed at all women, in particular those planning ART, characterized by an unfavorable vascular burden, as previously documented (13).

In our study published in 2018, we reported preliminary data about the experience of the Internal Medicine Clinic at the Assisted Reproductive Technologies Center, Florence. After two years, we extended the present study to a larger sample to estimate if the prevalence of comorbidities in infertile women previously observed, was fully representative of the "real world" or was biased by the small number of women enrolled.

The present study was performed in order not only to strengthen our previous results but also to increase the awareness of clinicians who should envision a broader preconception approach in infertile women undergoing ART, beyond their reproductive health.

Materials and methods

This cross-sectional study represented an update two years later of our previous study (13), from November 2017 to September 2019, performed on Caucasian women at the Internal Medicine Clinic, at

the Assisted Reproductive Technologies Center, Division of Obstetrics and Gynecology, University Hospital, Careggi, Florence, Italy. The Internal Medicine Clinic consists of a multidisciplinary team of Internal Medicine and Nutrition experts, specifically focussed on the prevention of cardiovascular risk in women.

After performing infertility evaluation, gynecologists referred women with age more than 40 yrs and/or comorbidities, as well as a history of recurrent unexplained pregnancy loss and/or implantation failure to Internal Medicine Clinic before attempting ART. Information concerning cardiometabolic parameters derived from clinical reports and cardiovascular risk factors were investigated during the clinical evaluation. The entire study population comprised 1003 Caucasian women [median age 40 yrs, (range 25-49)].

According to the World Health Organization criteria, underweight was defined as BMI values <18.5 and overweight was defined as BMI values 25-29.99 Kg/m^2 , first grade obesity as BMI values 30-34.99 Kg/m^2 , second grade obesity as BMI 35-39.99 Kg/m^2 , and third grade obesity as BMI ≥ 40 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. The anthropometric measures were performed by the same operator. A value of ≥ 80 cm was considered a marker of increased cardiovascular risk according to Alberti KG. et al. (14); waist to hip ratio (WHR) was obtained by dividing the waist circumference by hip circumference, and a value >0.80 was considered a marker of increased cardiovascular risk (15). Dyslipidemia was defined according to the European Society of Cardiology (ESC) guidelines (16).

The women were considered to have hypertension if they had been diagnosed as hypertensives according to ESH/ESC guidelines ($\geq 140/90$ mmHg) or were taking antihypertensive drugs (17). Diabetes was defined in agreement with the American Diabetes Association (18); smokers were defined as current or recent (ex-smokers who stopped less than 5 years earlier) smokers. Metabolic Syndrome was defined according to the International Diabetes Federation (14). Diagnosis of migraine with aura had been performed by physicians according to the International Classification of Headache Disorders

3rd edition (19).

To better define cardiovascular risk profile, and based on the evidence linking preconception health, in particular nutritional status, to pregnancy and birth outcomes, information concerning physical activity and habitual food intake were added.

Physical activity grade was investigated and sedentary behavior was defined as absent or light (ie, either occasional walking or recreational activity only). Moreover, a validated 14-items Mediterranean Diet Assessment Tool was administered. The PREDIMED (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet) score represents the primary measure used in the PREDIMED trial (randomized, cardiovascular primary prevention trial) to appraise adherence of participants to the Mediterranean Diet. PREDIMED score consists of 14-items, which evaluated Mediterranean typically dietary pattern, based on foods such as vegetables, fruits, whole or minimally processed foods, fish, legumes, vegetable fat from olive oil and adverse dietary factors such as sugar-sweetened beverage, red and processed meat. Three categories of adherence to Mediterranean diet (≤ 5 low, 6-9 moderate, ≥ 10 high adherence points of the 14-item questionnaire) (20) were considered.

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 at the local Ethics Committee (Azienda Ospedaliera Universitaria Careggi, prot. 34044, 11292/OSS).

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 and range. Correlation analysis was measured by using Pearson's correlation test. A p-value <0.05 was considered to indicate statistical significance. The categorical variables were expressed as frequencies and percentages.

We calculated sample size referring to our previous study (13); sample size calculation indicated that at least 242 subjects were sufficient to detect, with a statistical power of 70% (β) and a significance value of 0.05 (α).

Results

In Table 1 we reported demographical and clinical characteristics of the study population.

Table 1: Clinical characteristics of study population

Variables	n = 1003
Age, years	40 (25-49)*
Age > 40 years	484 (48.3)
BMI <18.5 Kg/m ²	43 (4.3)
BMI 25-29.99 Kg/m ²	211 (21)
BMI 30-34.99 Kg/m ²	66 (6.6)
BMI 35-39.99 Kg/m ²	12 (1.2)
BMI ≥ 40 Kg/m ²	3 (0.3)
WAIST circumference, cm	87 (64-126)*
WAIST circumference ≥ 80 cm	631 (62.9)
WHR	0.81 (0.7-1.0)*
WHR > 0.80	530 (52.8)
Smoking habit (current)	267 (26.6)
Dyslipidemia	576 (57.4)
Hypertension	41 (4.1)
Diabetes	23 (2.3)
MetS	37 (3.7)
Sedentary behaviour	732 (73)
POI	84 (8.4)
Migraine with aura	51 (5.1)
Recurrent spontaneous miscarriage ≥ 2	153 (15.3)
Recurrent ART failure ≥ 2	348 (34.7)
Celiac disease	7 (0.7)
Hashimoto's thyroiditis	48 (4.8)
Personal history of atherothrombotic disease	37 (3.7)
Family history of CV disease, n (%)	277 (27.6)

*Median (Range) Values are reported as median (range) or n (%).

BMI: Body Mass Index; WHR: Waist to hip ratio; MetS: Metabolic Syndrome; POI: Premature ovary insufficiency; ART: Assisted Reproductive Technology; CV: Cardiovascular

The evaluation of traditional cardiovascular risk factors evidenced a high prevalence of dyslipidemia (57.4%), smoking habit (26.6%), and overweight/obesity (29.1%). The evaluation of anthropometric measures, such as waist circumference and WHR, showed that values of waist circumference ≥ 80 cm, a measure of visceral adiposity, were present in 62.9% and WHR value >0.80 was also present in 52.8% of women investigated. In framing women risk profile we also considered personal and family history of cardiovascular disease, and we observed that 27.6% of ART women had a family history of cardiovascular disease, and 3.7% had a personal history of premature atherothrombotic disease (i.e. acute coronary syndrome or transient ischemic attack and venous thrombosis). As concerns migraine with aura, hypertension, and diabetes, which are known as stronger and more prevalent risks factor in women, we observed a prevalence of 5.1%, 4.1%, and 2.3% respectively. The metabolic syndrome, a cluster of cardiovascular risk factors, was present in 3.7%.

By analyzing personal negative obstetric history, a sex-specific cardiovascular risk factor, we found that 15.3% women had a recurrent spontaneous miscarriage (≥ 2), and 34.7% two or more ART failures (Table 1).

Table 2 reported humoral parameters of women planning ART. Based on the high prevalence of dyslipidemia in our study population, we analyzed each parameter of lipid metabolism to better frame the vascular risk profile in women planning Assisted Reproduction. We found a high percentage of women with both LDL cholesterol >115 mg/dL (43.2%), and low HDL cholesterol (<48 mg/dL) (13.5%); moreover, elevated concentration of Lipoprotein (a) was present in 25.6% of women investigated, thus confirming an unfavourable lipid profile after extending sample size.

Table 2: Biohumoral parameters of study population

Variables	n = 1003
Total cholesterol > 200 mg/dL	368 (36.7)
HDL-c < 48 mg/dL	135 (13.5)
LDL-c > 115 mg/dL	433 (43.2)
Tryglicerides > 150 mg/dL	71 (7.1)
Lipoprotein (a) > 300 mg/L	257 (25.6)
Homocysteine > 13 μ mol/L	105 (10.5)
Vitamin B6 μ g/L	10.7 (2.7-44.6)*
Vitamin B6 <3.6 μ g/L	21 (2.1)
Vitamin B12 pg/mL	346 (34-1684)*
Vitamin B12 <254 pg/mL	219 (21.8)
Folic Acid ng/mL	7.5 (1.5-62.1)*
Folic Acid <3.1 ng/mL	38 (3.8)
Creatinine mg/dL	0.7 (0.3-2)*
Fasting glucose mg/dL	87 (61-156)*
Fasting glucose ≥ 100 mg/dL	87 (8.7)
HbA1C mmol/mol	34 (22-52)*
HbA1C ≥ 38 mmol/mol	120 (12)
HOMA index	1.4 (0.2-27.1)*
hs-CRP mg/L	1.6 (0.1-33.2)*
TSH mIU/L	1.8 (0.1-6.6)*
Factor V Leiden heterozigotes	56 (5.6)
Prothrombin G20210A mutation heterozigotes	58 (5.8)
PC, PS, AT deficiency	36 (3.6)
Positivity for at least one of antiphospholipid antibodies, n (%)	89 (8.9)

*Median (Range)

HbA1c: Glycated hemoglobin; HOMA: Homeostatic model assessment; hs-CRP: High sensitive C Reactive Protein; TSH: Thyroid stimulating hormone; PC: Protein C; PS: Protein S; AT: Antitrombin

Data from thrombophilia, demonstrated a similar percentage of inherited parameters, as observed in our previous study (13), whereas an increased

positivity of at least one antiphospholipid antibodies was observed (Table 2).

Physical activity and Nutrition: To estimate habitual food intake, we used PREDIMED score. In Fig.1 (a,b) data concerning the adherence to the Mediterranean diet are reported. Only 9.5% of women showed a closer adherence to the Mediterranean diet corresponding to levels of adherence of ≥ 10 points in the 14-item score.

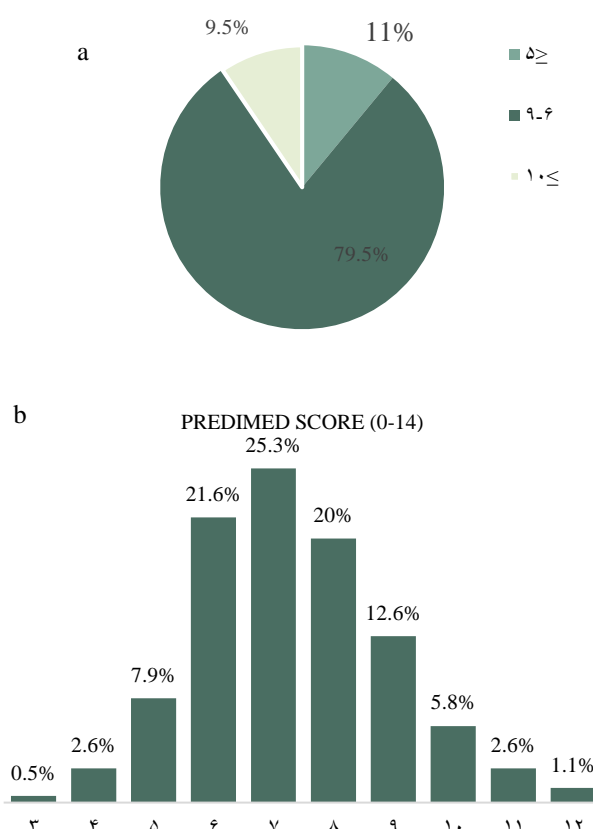


Figure 1: PREDIMED score consists of 14-items which evaluated Mediterranean typically dietary pattern. Three categories of adherence to Mediterranean diet ≤ 5 , 6-9, ≥ 10 points were considered. Values are expressed as percentage (a), Distribution of percentage of adherence to Mediterranean diet, according to achieved score (b).

A significant correlation between the Mediterranean diet score and both anthropometric and metabolic parameters was found (Table 3). By evaluating the relationship between metabolic syndrome and diabetes to categories of adherence to the Mediterranean diet (≤ 5 low, 6-9 moderate, ≥ 10 high adherence points), we observed that a lower score adherence was associated with both metabolic syndrome and diabetes (for both $p=0.02$), but not

with hypertension and smoking habit.

Table 3: Correlation between anthropometric, biohumoral parameters and 14-item Mediterranean diet assessment tool

	14-item Mediterranean diet assessment tool	
	r	p
BMI	-0.53	< 0.0001
WAIST circumference WHR	-0.47	< 0.0001
WHR	-0.37	0.01
Total cholesterol	-0.13	0.07
HDL-c	0.39	< 0.0001
LDL-c	-0.24	0.01
Triglycerides	-0.29	< 0.0001
Fasting glucose	-0.22	0.004
HbA1C	-0.18	0.04
HOMA index	-0.30	0.001

BMI: Body Mass Index; WHR: Waist to hip ratio; HbA1C: Glycated hemoglobin; HOMA: Homeostatic model assessment

Moreover, we investigated physical activity grade, and sedentary behaviour was observed in 73% of women.

Discussion

Findings from the present study confirm, in a larger sample, that women undergoing ART show an unfavorable vascular burden.

In the preconception period, it should be strongly advised to modify lifestyle habit, and to mitigate the effect of cardiometabolic disorders, which may impact women's cardiovascular health and reproductive outcomes. ART care represents a unique opportunity for preconception counseling, since the moment of conception is easily recognizable (1).

Nevertheless, the significance of preconception care in infertile couples is still an undervalued area of clinical practice.

Notably, additional data from the present study provided evidence of an unhealthy lifestyle, in particular, a closer adherence to a the Mediterranean diet was present only in about 9.5%, and sedentary behavior in more than 70% of women.

Cardiovascular disease is a global health concern amenable to behavior modifications. Diet is a vital lifestyle component that affects cardiovascular risk through body weight and many other pathways (21). It is well known that greater adherence to the Mediterranean diet is linked to a reduced risk of overall mortality, cardiovascular diseases, overall cancer incidence, neurodegenerative diseases, and diabetes (22). Our findings evidenced an inverse association between adherence to Mediterranean Diet

and cardiovascular risk markers related to glucose metabolism, adiposity, and lipids. These results, referring to preconception period, support previously reported benefits of the Mediterranean diet for cardiovascular risk reduction (23).

Moreover, a greater degree of protection may occur in particular when lifestyle factors are adopted before and throughout pregnancy. Recent data are suggesting that the Mediterranean Diet, rich in fruit and vegetables, whole grains, legumes, extra virgin olive oil, fish and low intake of red and processed meat, seems to be associated with increased chances of a successful pregnancy in women undergoing ART (4). Nevertheless, the benefits of a healthy diet in improving ART pregnancy outcomes, remain unclear (24).

Despite in several Italian Center dietary counseling is not routine before ART, our approach was different, aiming at identifying women at risk of less adherence to this dietary pattern as essential in implementing effective strategies to promote the health benefits of this dietary model. The other side of the matter is the adoption of physical activity in women planning a pregnancy, a promising intervention in the prevention of Gestational Diabetes Mellitus and pre-eclampsia (7, 8). This evidence underlines the opportunity to perform further interventions, in particular during the preconception period to ensure the best outcomes throughout pregnancy (7). There is however, a need for prospective studies to better understand the mechanisms by which physical activity and diet affect obstetric outcomes and maternal health.

In the present study, a poor pre-pregnancy cardiovascular health was found; in particular, about 60% of women had dyslipidemia, and about 30% were overweight/obese. This altered metabolic profile may further worsen if we considered anthropometric parameter values, such as waist circumference and WHR. In more than 50% of women, we observed both waist circumference value ≥ 80 cm and altered WHR. These findings suggest that medical advice prevention and treatment for preconception cardiovascular risk factors are needed and might contribute to control the added risk of ART; namely, we need to plan strategies and interventions aimed to change modifiable cardiovascular risk factors, thus improving health behaviors.

Data from literature evidenced that history of pregnancy complications determines an increased future cardiovascular risk (25, 26); because of its unique cardiovascular and metabolic stress,

pregnancy permits to estimate a woman's lifetime risk. Women who failed this stress test by experiencing placental disorders have an increased future cardiovascular risk, possibly unmasking early or pre-existing endothelial dysfunction and vascular disease (27); to date, a history of pregnancy complications as a major risk factor for cardiovascular disease in the AHA/ASA guidelines (28, 29). It is noteworthy that pregnancy transiently catapults a "healthy" woman into an altered metabolic status that predisposes to vascular endothelial dysfunction (30). Women already prone to this phenotype, and in particular, women undergoing ART, often develop gestational hypertension or diabetes mellitus, which re-emerge in later life as the metabolic syndrome returns (30).

Furthermore, women undergoing ART had a higher incidence of hypertension, and a trend toward a higher incidence of stroke, thus in turn a higher propensity to develop cardiovascular disease later in life (31). Therefore, there is a need to investigate the impact of ART on cardiovascular health, as reported by Becerra-Gonzales 2020 (32). This topic is timely in an era where more women are undergoing ART at a later age and recommendations for cardiovascular health and future consequences are not well known (33). This study has several strengths. It was based on a large sample, permitting to confirm previous findings (13), which evidenced a high prevalence of cardiometabolic risk factors in ART women, in particular dyslipidemia and overweight/obesity. The amount of collected data from participants was considered appropriate to make assumptions on future possible therapeutical approaches. Moreover, a full set of laboratory tests, along with a validated questionnaire, had been administered to all participants.

The current research represents a comprehensive analysis of multiple domains of preconception health, thus adding, with special regards, accurate and detail information on cardiovascular profile in women planning ART.

Many earlier published reports provide recommendations to improve preconception health care. It is well known that the implementation of the interventions preceding natural pregnancy to detect, treat, and help women modifying behaviors and risk factors, may contribute to improving maternal outcomes (9).

Nevertheless, the evidence about the role of preconception care in women undergoing ART are few (11) A low number of studies report all the

domains of preconception health in women undergoing ART, in particular in older women, who are at higher risk of adverse obstetric outcomes and cardiovascular diseases later in life (31). A recent review underlines that special attention must be paid to the workup of certain patient populations, such as those with age older than 35 years, comorbidities (especially hypertension, diabetes, and thrombophilias), and obesity (33). In keeping with our findings, the authors promote the need of patient-centered counseling before the initiation of ART.

On the other hand, our study has some potential limitations. One is represented by the cross-sectional nature of the research itself; besides that, the study does not include information regarding vascular and obstetric clinical outcomes after ART. Moreover, all participants were Caucasians, and thus findings may not be generalizable to other racial and ethnic groups.

Conclusion

Findings from the present study strengthen our previous results in a larger sample of ART women. Beyond reproductive health, clinicians should increase their awareness, envisioning a broader preconception approach in women undergoing ART. Our data highlight the complex clinical picture of ART women and underline the need for a multidisciplinary team consisting of gynecologists, who have a key role, and clinicians expert in women's healthcare.

Despite the widespread application of ART, the body of knowledge to preconception care in pregnancy after ART is limited.

During the preconception period, all women should be screened to determine their cardiovascular risk profile and to treat comorbidities before and during infertility treatment.

Further studies to improve the knowledge and behaviors of preconception health in women planning ART will be required.

Finally, before infertility treatment, the correction and/or the management of modifiable and non-modifiable cardiovascular risk factors are mandatory and represent the main clinical goal for both a safe pregnancy and lifetime women's health.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

Authors have no conflict of interests in this paper.

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