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The Prevalence of Metabolic Dysfunction in Fertile and Subfertile Women in a European Population: A Cross-Sectional Study

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Abstract

Metabolic dysfunction is known to impair female fecundity as it is linked to a longer time-to-pregnancy and infertility. Obesity is well-known for its association with ovulatory dysfunction, infertility and a reduced success rate with assisted reproductive technologies. We hypothesize that metabolic dysfunction may be more prevalent among the entire female subfertile population and not restricted to anovulatory patients. It is known that the prevalence of metabolic dysfunction is strongly susceptible to sociodemographic factors. We therefore aim to compare the prevalence of metabolic dysfunction among subfertile women and healthy controls in a predominantly European population. This cross-sectional study was conducted in a Dutch fertility clinic. All patients were referred with primary or secondary subfertility. Controls were healthy, parous women ≥ 6 months postpartum. 119 patients and 68 controls aged between 18 and 41 years were included over a time span of 3 years. Anthropometric measures (a.o. waist, blood pressure) and metabolic parameters (a.o. glucose and lipid metabolism) were collected on cycle day 2-4. Metabolic syndrome (MetS) was diagnosed using the ATP-III criteria. All measurements were corrected for age and body mass index (BMI). MetS was diagnosed in 4% of the patients and none in controls. No differences were found in the measurements comparing patients, including those with ovulatory dysfunction, to controls. As expected, a strong correlation was observed between BMI and metabolic dysfunction. Subfertility per se can therefore not be regarded as a risk factor for current metabolic health disturbances. Our findings apply to a largely homogeneous Dutch population.

Keywords: Metabolic dysfunction; metabolic syndrome; infertility; unexplained subfertility

List of abbreviations

AMH: Anti-Mullarian Hormone; ATP: adult treatment panel; BMI: body mass index; BP: blood pressure; CI: confidence interval; CKD-EP: chronic kidney disease epidemiology collaboration; FSH: follicle stimulating hormone; GFR: glomerular filtration rate; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; ISO: international standardization organization; IQR: interquartile range; MAP: mean arterial pressure; MDRD: modification of diet in renal disease; MetS: metabolic syndrome; NA: not applicable; PCOS: polycystic ovary syndrome; PCR: protein creatinine ratio

Introduction

There are numerous indications that imply that human female fecundity is strongly affected by metabolic distress. Subfertility is defined as failure to conceive after one year of unprotected regular intercourse. On a global scale, about one in six couples are diagnosed with primary or secondary subfertility [1]. Causes of subfertility including male and female causes are diverse. Still almost one third of cases remain unexplained. A better understanding of the influence of metabolic processes might provide new therapeutic targets and possible opportunities for

preventative strategies that are better tailored to the individual patient. It can be postulated that metabolic dysfunction *per se* may be a driving factor in anovulatory and unexplained subfertility. This hypothesis is substantiated by the observation that metabolic dysfunction has a negative influence on female fecundity as a whole [2]. Metabolic dysfunction has been linked to a longer time-to-pregnancy, and an association with subfertility seems to exist that is independent of obesity [3]. Several metabolic disorders have been linked to the impairment of ovarian functions or pituitary-hypothalamic axes – i.e. hypogonadotropic hypogonadism in diabetes. In addition, metabolic dysfunction causes higher risk on gynaecological cancers, which can influence fertility [4].

Surprisingly, data on the prevalence of metabolic dysfunction in sub fertile patient populations are scarce. Indeed, a high prevalence of metabolic syndrome (MetS) has been reported among sub fertile women in Mosul, Iraq, with a prevalence of 23% in women with a mean body mass index (BMI) of 27.6 kg/m^2 [5]. The lack of data in different ethnic and demographic populations makes it difficult to predict the influence of metabolic distress on fecundity. Following various definitions, MetS can be characterized by hypertension, central obesity, dyslipidaemia and insulin resistance [6]. As the presence of these characteristics varies greatly between different populations, so does the prevalence of MetS [7,8]. Estimates vary from 5% among normal-weight adults, 22% among adults with a BMI between 25-30 kg/m^2 and 60% in adults with a BMI >30 kg/m^2 [8]. However, the prevalence of the MetS has risen in the last decades among all age groups [9].

Obesity, a major driving factor behind metabolic dysfunction, is correlated with menstrual irregularities, ovulation disorders and subfertility. In addition, it is associated with an increased risk of miscarriage and a reduced chance of success with assisted reproductive technologies [10]. At present, it is uncertain how, and to what extent, obesity and metabolic dysfunction interrelate with subfertility. We know that women with polycystic ovary syndrome (PCOS), the most prevalent cause of anovulatory subfertility, specifically show a higher prevalence of MetS. At present, it is not clear whether this is due to the presence of obesity or the presence of PCOS itself [11]. PCOS patients had a three times higher prevalence of MetS when compared to randomly selected, age matched controls with lower BMI [12]. Hyperandrogenic PCOS patients also show a much higher risk of MetS than non-hyperandrogenic patients [13]. Taking all into account, we hypothesize that the prevalence of metabolic dysfunction and MetS may be higher in both ovulatory and anovulatory subfertile women, as compared to healthy controls.

Materials and methods

Aim, design, setting

This study aims to assess the prevalence of metabolic dysfunction in the entire subfertile population and compare this with fertile controls. This is performed in our urban, predominantly white, European population. Subfertile patients are included irrespective of the cause of subfertility (i.e. anovulation, unexplained subfertility or male factor – so presumably healthy). This cross-sectional study was performed at the secondary and tertiary referral fertility clinic of the Maastricht University Medical Centre+ in Maastricht, The Netherlands.

Participants

Women in the patient group were referred to the fertility clinic with primary or secondary subfertility that lasted for more than one year. Age at time of inclusion was between 18 and 41 years. Basic fertility workup was performed, after which a diagnosis was determined. Controls included healthy parous women, who were recruited through local advertisements. Controls were healthy, had had a spontaneous uncomplicated pregnancy, they were at least six months postpartum at time of inclusion and were of similar age. Exclusion criteria for both groups included current pregnancy, hormonal medication or lactation.

Measurements

All women were asked to fill out a questionnaire as part of the regular basic fertility work-up, including questions about their menstrual cycle, previous and/or current use of medication, medical and family history and intoxications. Body weight and height were determined at time of inclusion. BMI (in kg/m^2) was calculated as usual. Waist circumference (in centimetres) was measured by tape in standing position, at the midpoint between the top of the right iliac crest and the lowest palpable rib. Hip circumference (in centimetres) was measured by tape in standing position at a level parallel to the floor at the largest circumference of the buttocks [14]. Both measurements are performed at the end of a normal expiration. An extended 30-minute blood pressure measurement (in mmHg) was performed in sitting position, after 10 minutes rest, every 3 minutes in the first week of the menstrual cycle. The median of eleven consecutive measurements was taken as representative.

Venepuncture was performed after an overnight fast between cycle day 2 and 4. Laboratory analyses were performed by the Central Diagnostic Laboratory at the Maastricht University Medical Centre+ (The Netherlands). All reference intervals were locally established by the Central Diagnostic Laboratory. Laboratory measurements included insulin, glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, total cholesterol, glomular filtrating rate (GFR), urea, uric acid and creatinine were measured on top of the standard follicle stimulating hormone (FSH), estradiol and anti-Mullarian hormone (AMH) measurements. Insulin sensitivity was assessed by calculation of the homeostasis model assessment of insulin resistance (HOMA-IR) score; [fasting insulin (pmol/l) x fasting glucose (mmol/l)]/135 [15]. Insulin, FSH and estradiol were determined using chemiluminescent immunometric assay (Immulite XPi instrument, Siemens Healthcare Diagnostics, New Orleans, LA, USA). Glucose was

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determined using enzymatic spectrophotometric assay and triglycerides, HDL cholesterol, total cholesterol, urea, uric acid and creatinine using enzymatic colorimetric assay (both Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). GFR was calculated using the MDRD formula until October 2016, afterwards using the CKD-EPI formula [16]. AMH were analysed at the Clinical Chemical Laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands. All samples were stored at - 20˚C until assayed. AMH levels were determined by enzyme-linked immunosorbent assay (Gen II, Beckman Coulter, Brea, CA, USA).

A urine sample was collected between cycle day 8 and 10, measuring protein and creatinine. Protein-creatinine ratio was calculated dividing these measurements. Protein was analysed using Turbimetric method (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). Creatinine was analysed using enzymatic colorimetric assay (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). For a diagnosis of MetS we adhered to the Adult Treatment Panel (ATP) III criteria [6] including ≥3 of the following: waist circumference ≥88 cm; fasting glucose ≥5.6 mmol/l or drug treatment for reducing glucose; triglycerides ≥1.7 nmol/l or drug treatment for elevated triglycerides; HDL cholesterol <1.3 mmol/l or drug treatment for reduced HDL cholesterol; blood pressure ≥135/85 mmHg or drug treatment for hypertension.

Statistical analysis

Statistical analysis was performed with the statistical software SPSS version 25 (IBM-SPSS, Chicago, IL, USA). Data were checked for a normal distribution with the Shapiro-Wilk test. For baseline characteristics and metabolic and vascular parameters, data were summarized as median and interquartile range. Mann-Whitney U tests were used for comparison of baseline characteristics and metabolic parameters in patients and controls. Metabolic parameters were corrected for age and BMI using regression analysis including 95% confidence intervals. The prevalence of the MetS was expressed in numbers and percentages per subcategory. Next, patients were subdivided in BMI categories (normal vs overweight or obese) and metabolic parameters were compared using Mann-Whitney U tests.

Metabolic parameters were corrected for age and compared between these categories using regression analysis including 95% confidence intervals. The prevalence of the MetS was again expressed in numbers and percentages per subcategory. Missing data were excluded from that specific analysis. A two-tailed p-value ≤0.05 was considered as significant. Based on a normal prevalence of metabolic syndrome of 8% [17] and an expected 23% in subfertile women, 90 patients and controls should be sufficient to find differences with a power of 80%.

Results

Study population, baseline characteristics

A total of 119 patients and 68 controls were included. There was a small but significant difference in age (resp. 31 vs. 35 years, p<0.001) and height (resp. 1.67 vs. 1.69 meters, p<0.023) between patients and controls. Weight and BMI were similar in patients and controls. As expected, gravidity and parity were significantly lower among patients than controls (0 vs. 2, p<0.001). 45% of the subfertile patient population suffered from primary subfertility, 33% of secondary subfertility and 23% was unknown. Main causes of subfertility were male factor (12%), anovulation (20%), unexplained (47%) and less frequently endometriosis (2%), tubal factor (4%), ovarian failure (4%) or combined factors (4%). 5% of the causes was unknown (missing data). Baseline characteristics are summarized in Table 1.

Metabolic parameters in patients compared to controls

Among patients with unexplained subfertility, we observed higher HDL cholesterol levels compared to the control group, although the mean levels are equal (1.6 vs. 1.6 mmol/l, p=0.46). Patients with anovulatory subfertility showed higher glucose (4.9 vs. 4.8 mmol/l, p=0.003) and AMH levels (5.6 vs. 2.4 µg/l, p<0.001). MetS was diagnosed in 3 patients (6%) with unexplained subfertility, in 1 patient (4%) with male factor subfertility and in 1 patient (5%) with anovulatory subfertility. No controls were diagnosed with MetS. Metabolic parameters in patients and controls are described in Table 2.

Metabolic parameters in patients subdivided by BMI category

Comparing overweight subfertile patients (BMI 25-30 kg/m^2) to normal weight patients (BMI <25 kg/m^2), we observed higher waist circumference (85 vs. 73 cm, p<0.001), waist-to-hip ratio (0.81 vs. 0.76, p=0.001), insulin (37.7 vs. 27.6 pmol/l, p=0.002), HOMA-IR (1.14 vs. 0.88, p=0.012) and uric acid (0.27 vs. 0.25 mmol/l, p=0.023) levels.

In a comparison of obese patients (BM >30 kg/m^2) to normal weight patients we observed higher waist circumference (100 vs. 73 cm, p<0.001), waist-to-hip ratio (0.84 vs. 0.76, p<0.001), insulin (81.9 vs. 27.6 pmol/l, p<0.001), HOMA-IR (2.62 vs. 0.88, p<0.001), triglycerides (1.31 vs. 0.66 mmol/l, p<0.001), AMH (5.9 vs. 2.1 µg/l, p=0.009) and uric acid (0.31 vs. 0.25 mmol/l, p<0.001) and a lower HDL cholesterol (1.3 vs. 1.7 mmol/l, p=0.007). MetS was diagnosed in 1 normal weight patient (1%), in 1 overweight patient (4%) and in 3 patients (25%) with obesity. Metabolic parameters in patients with normal weight, overweight and obesity are summarized in Table 3.

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Table 1: Baseline characteristics

	Patients (n=119)	Controls (n=68)	p-value
Age (years)	31 [28-34]	35 [30-38]	<0.001
Height (m)	1.67 [1.62-1.71]	1.69 [1.64-1.74]	<0.023
Weight (kg)	64 [56-72]	65 [59-73]	0.321
BMI (kg/m2)	22.8 [20.8-25.6]	23.3 [21.0-25.4]	0.959
Gravidity	0 (0-6)	2 (1-4)	<0.001
Parity	0 (0-2)	2 (1-4)	<0.001
Subfertility			NA
Primary	53 (45)		
Secondary	39 (33)		
Unknown	27 (23)		
Cause of subfertility	113 (95)		NA
Male factor	23 (12)		
Anovulation	22 (20)		
Endometriosis	2 (2)		
Tubal factor	4 (4)		
Ovarian failure	5 (4)		
Combined	4 (4)		
Unexplained	53 (47)		
Unknown cause	6 (5)		

Data are presented as median [IQR], median (range) or number (%).

Abbreviations: BMI body mass index; IQR interquartile range; NA not applicable.

Table 2: Metabolic parameters in patients by cause of subfertility compared to controls, corrected for age and BMI

	Unexplained (n=53)	p-value	95% CI	Male factor (n=23)	p-value	95% CI	Anovulation (n=22)	p-value	95% CI	Controls
BMI (kg/m2)	23 [20.2-27.3]	0.77	-1.596 – 2.150	23.7 [21.9-25.3]	0.968	-2.340 – 2.247	22.8 [19.6-26.3]	0.896	-2.887 – 2.530	23.3 [21.0-25.4]
Waist (cm)	78 [72-87]	0.46	-1.783 – 3.914	76 [70-84]	0.759	-4.371 – 3.200	70 [67-87]	0.759	-4.647 – 3.400	77 [71-83]
Waist-to-hip ratio	0.8 [0.7-0.8]	0.116	-0.005 – 0.048	0.8 [0.8-0.8]	0.34	-0.016 – 0.046	0.8 [0.7-0.8]	0.529	-0.024 – 0.046	0.8 [0.7-0.8]
Systolic BP (mmHg)	109 [104-112]	0.647	-2.568 – 4.121	104 [100-112]	0.628	-5.312 – 3.223	106 [100-111]	0.136	-7.085 – 0.983	108 [102-114]
Diastolic BP (mmHg)	67 [64-72]	0.858	-2.503 – 3.002	68 [59-76]	0.865	-3.672 – 4.359	67 [64-71]	0.656	-4.488 – 2.840	68 [62-74]
MAP (mmHg)	83 [78-86]	0.949	-2.877 – 3.069	80 [76-91]	0.895	-4.284 – 3.747	81 [77-85]	0.254	-5.797 – 1.554	83 [78-89]
Glucose (mmol/l)	4.9 [4.6-5.1]	0.913	-0.128 – 0.143	4.9 [4.6-5.2]	0.115	-0.063 – 0.572	4.9 [4.7-5.3]	0.003*	0.265 – 1.266	4.8 [4.6-5.1]
Insulin (pmol/l)	33.3 [21.8-57.3]	0.168	-2.515 – 14.263	32.4 [22.2-52.0]	0.787	-8.468 – 11.148	26.0 [16.4-66.2]	0.184	-4.341 – 22.286	28.0 [17.2-47.5]
HOMA-IR	1.06 [0.69-1.85]	0.075	-0.027 – 0.562	1.06 [0.71-1.60]	0.455	-0.202 – 0.447	0.99 [0.52-2.07]	0.087	-0.056 – 0.815	0.90 [0.52-1.46]

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Total cholesterol (mmol/l)	4.5 [4.1-4.8]	0.763	-0.368 – 0.271	4.3 [3.9-4.9]	0.428	-0.592 – 0.253	4.3 [3.9-4.9]	0.785	-0.519 – 0.394	4.5 [4.0-4.9]
HDL cholesterol (mmol/l)	1.6 [1.4-1.9]	0.046	0.003 – 0.256	1.5 [1.2-1.9]	0.35	-0.240 – 0.086	1.6 [1.2-1.9]	0.512	-0.126 – 0.250	1.6 [1.3-1.9]
Triglycerides (mmol/l)	0.66 [0.51-0.88]	0.754	-0.176 – 0.128	0.75 [0.54-0.91]	0.586	-0.144 – 0.253	0.77 [0.60-1.07]	0.144	-0.063 – 0.425	0.71 [0.58-0.93]
FSH (U/l)	6.4 [5.4-8.0]	0.799	-1.595 – 1.231	6.1 [5.0-7.4]	0.702	-2.319 – 1.568	5.2 [4.8-6.7]	0.279	-3.290 – 0.962	6.40 [4.6-8.9]
Estradiol (nmol/l)	0.12 [0.09-0.17]	0.072	-0.158 – 0.007	0.11 [0.09-0.15]	0.078	-0.221 – 0.012	0.16 [0.10-0.28]	0.197	-0.082 – 0.394	0.14 [0.10-0.25]
AMH (µg/l)	2.5 [1.3-4.9]	0.325	-0.392 – 1.172	2.0 [1.1-4.8]	0.094	-0.202 – 2.510	5.6 [3.1-10.1]	<0.001	2.869 – 6.320	2.4 [0.9-3.6]
Urea (mmol/l)	4.4 [3.4-4.9]	0.67	-0.461 – 0.715	4.5[3.4-5.4]	0.988	-0.596 – 0.587	3.9 [3.3-4.6]	0.253	-1.006 – 0.268	4.2 [3.5-5.0]
Creatinine (µmol/l)	70 [60.0-79.3]	0.92	-7.680 – 6.938	69.0 [62.0-77.0]	0.768	-4.544 – 3.366	73.0 [64.0-77.5]	0.768	-3.944 – 5.320	69.5 [65.0-75.8]
Uric acid (mmol/l)	0.25 [0.21-0.29]	0.77	-0.019 – 0.025	0.25 [0.20-0.28]	0.618	-0.031 – 0.018	0.27 [0.23-0.30]	0.763	-0.033 – 0.024	0.24 [0.22-0.27]
PCR (g/molCre)	6.4 [4.8-8.1]	0.821	-1.482 – 1.178	7.1 [5.4-9.0]	0.679	-1.393 – 2.129	6.3 [5.4-8.3]	0.728	-1.575 – 2.246	6.3 [5.2-9.1]

Data are presented as median [IQR].

Abbreviations: AMH anti-Mullarian hormone; BMI body mass index; BP blood pressure; CI confidence interval; FSH follicle stimulating hormone; HOMA-IR homeostasis model assessment of insulin resistance; HDL high-density lipoprotein; IQR interquartile range; MAP mean arterial pressure; PCR protein creatinine ratio.

Table 3: Metabolic parameters in patients with overweight and obesity compared to patients with normal weight, corrected for age and BMI

	BMI <25 kg/m2 (n=82)	BMI 25-30 kg/m2 (n=25)	p-value vs BMI <25	95% CI	BMI >30 kg/m2 (n=12)	p-value vs BMI <25	95% CI
Waist (cm)	73 [69-76]	85 [80-91]	<0.001	9.937 – 16.129	100 [96-105]	<0.001	24.188 – 32.867
Waist-to-hip ratio	0.76 [0.73-0.80]	0.81 [0.78-0.85]	<0.001	0.023 – 0.078	0.84 [0.81-0.91]	<0.001	0.055 – 0.136
Systolic BP (mmHg)	107 [100-112]	109 [105-116]	0.056	-0.097 – 7.739	112 [107-114]	0.099	-0.997 – 11.437
Diastolic BP (mmHg)	67 [63-72]	66 [64-73]	0.674	-2.612 – 4.024	69 [65-73]	0.313	-2.477 – 7.646
MAP (mmHg)	81 [76-87]	83 [78-89]	0.269	-1.550 – 5.497	86 [80-89]	0.178	-1.713 – 9.100
Glucose (mmol/l)	4.9 [4.5-5.1]	4.9 [4.6-5.2]	0.624	-0.569 – 0.343	4.5 [4.9-5.4]	0.558	-0.507 – 0.932
Insulin (pmol/l)	27.6 [16.5-44.3]	37.7 [24.7-65]	0.002	5.502 – 24.295	81.9 [49.6-109.3]	<0.001	33.718 – 64.014
HOMA-IR	0.88 [0.52-1.51]	1.14 [0.77-2.22]	0.012	0.100 – 0.770	2.62 [1.69-3.81]	<0.001	1.150 – 2.227

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Total cholesterol (mmol/l)	4.4 [4.0-4.8]	4.5 [4.1-4.9]	0.885	-0.309 – 0.358	4.1 [3.7-5.3]	0.355	-0.252 – 0.693
HDL cholesterol (mmol/l)	1.7 [1.4-2.0]	1.5 [1.2-1.6]	0.087	-0.423 – 0.029	1.3 [1.2-1.5]	0.007	-0.696 – -0.112
Triglycerides (mmol/l)	0.66 [0.51-0.81]	0.78 [0.58-1.18]	0.093	-0.026 – 0.336	1.31 [0.82-1.89]	<0.001	0.345 – 0.912
FSH (U/l)	6.2 [5.3-8.8]	6.5 [5.3-7.7]	0.48	-4.336 – 2.053	5.2 [4.4-6.4]	0.619	-6.076 – 3.637
Estradiol (nmol/l)	0.13 [0.09-0.20]	0.12 [0.10-0.15]	0.291	-0.245 – 0.074	0.10 [0.08-0.13]	0.281	-0.376 – 0.110
AMH (µg/l)	2.1[0.9-5.3]	3 [1.9-4.3]	0.932	-1.676 – 1.826	5.9 [4.8-10.3]	0.009	0.868 – 5.954
Urea (mmol/l)	4.2 [3.4-5.0]	4.5 [3.5-5.4]	0.983	-0.715 – 0.731	4.0 [3.6-4.5]	0.58	-1.366 – 0.770
Creatinine (µmol/l)	71 [62.3-77.0]	73 [58.5-80.0]	0.892	-9.764 – 8.509	73.5 [63.8-85.3]	0.937	-14.699 – 13.570
Uric acid (mmol/l)	0.25 [0.20-0.27]	0.27 [0.21-0.30]	0.023	0.004 – 0.055	0.31 [0.26-0.40]	<0.001	0.042 – 0.115
PCR (g/molCre)	6.4 [5.4-8.2]	6.2 [5.0-8.7]	0.859	-1.630 – 1.361	5.6 [3.6-6.9]	0.128	-3.412 – 0.436

Data are presented as median [IQR].

Abbreviations: AMH anti-Mullarian hormone; BMI body mass index; BP blood pressure; CI confidence interval; FSH follicle stimulating hormone; HOMA-IR homeostasis model assessment of insulin resistance; HDL high-density lipoprotein; IQR interquartile range; MAP mean arterial pressure; PCR protein creatinine ratio.

Discussion

The present study addresses the prevalence of metabolic dysfunction and MetS among sub fertile women and healthy controls. Our findings are striking because MetS, according to ATP III criteria, was rarely diagnosed in the study group (n = 5, 4%) and controls (n = 0). Signs of metabolic dysfunction in association with subfertility (corrected for age and BMI) were not observed. Within patients with anovulatory subfertility, 64% were diagnosed with PCOS. This is substantiated by the presence of higher AMH levels in this particular subgroup. Unexplained subfertile patients showed significantly higher HDL cholesterol, with equal median levels and an effect size of only 0.1 mmol/L. Anovulatory subfertile patients showed significantly higher glucose, with a normal median level of 4.9 mmol/L which was only 0.1 mmol/L higher than controls. Both of these findings were regarded as clinically irrelevant. In a subgroup analysis among patients subdivided on BMI category, we observed clear evidence for metabolic dysfunction among overweight and obese subfertile patients, compared to subfertile patients with normal weight. As expected, we observed higher waist circumference, waist-to-hip ratio, insulin, HOMA-IR, triglycerides and uric acid and lower HDL cholesterol. In addition, MetS was diagnosed more frequently. Therefore, we conclude that BMI has a much greater effect on metabolic dysfunction than subfertility per se.

As expected, we observed significantly higher AMH levels among obese patients, owing to the fact that 33% of the patients with a BMI ≥ 25kg/m^2 were diagnosed with PCOS, which is associated with both obesity and higher AMH levels [18,19]. Comparing the prevalence of MetS in our study with that generally described in medical literature, it is apparent that the prevalence of MetS is very low among our study population. The mean reported BMI in both patients and controls is normal, and not significantly different between the groups. As such, the results of our study are not influenced by unequal distribution of overweight or obesity.

As stated before, it is important to realize that the presence of obesity is strongly dependent on socioeconomic and geographic determinants. The mean reported BMI in both patients and controls is healthy and lower than expected on the basis of reported means in Europe [20]. This may be typical for the Dutch population, who are reported to be among the lowest reported percentages of obesity [21]. Also, living in an urban layout has been described to lower the risk of obesity than living in rural areas [22]. It is important to note that our findings apply to a

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largely ethnically homogeneous white female population in urban surroundings in Europe.

Possible limitations of this study are the chance of selection bias, since a study concerning metabolic health might attract more healthy patients than those struggling to get a healthy weight. However, the fact that both groups have a healthy and comparable BMI makes our comparison in metabolic function parameters highly reliable. Data on the prevalence of metabolic distress among both general and subfertile populations is mainly based on research in North American and Middle Eastern populations. Our findings stress that conclusions from that data might not be applicable to other populations – including ours. With 68 controls among whom 0 meet the diagnosis of MetS, we feel we have solid grounds to conclude that the prevalence of metabolic dysfunction is lower in our population than described in literature and not different than in patients, although we included less than the expected ninety controls. The results of the present study may be influenced by the presence of PCOS patients, since it is known that they have a higher prevalence of MetS. Since these patients are included in the anovulatory patient group, it is assumed that the results of the other groups are not influenced. Strengths of our study are that it is performed by trained staff and with the use of standardized protocols, providing high precision data. The groups were very well comparable based on their similar baseline characteristics. Laboratory measurements were all analysed in the same ISO accredited laboratory. At first glance, these results seem positive and comforting, although there are concerns related to the overweight or obese patients. Obese women are at risk for diabetes, cardiovascular disease, asthma and other breathing problems, musculoskeletal disorders, mental illness and some cancers – such as postmenopausal breast cancer and endometrial cancer). Mortality is higher in this population and rises with BMI [23-26]. It is plausible that our subfertile patients are too young to already meet MetS criteria, although they can have the risks stated above later in life. Therefore, it might be more adequate to use other metabolic predictors in this stage of life, such as HOMA-IR, dyslipidaemia or sex hormone-binding globulin. Also, a tailored program to help patients struggling to lose weight and improve metabolic health, might have great benefits in the future. Our hypothesis was that metabolic dysfunction and MetS are more prevalent in subfertile female patients (including anovulatory patients) compared to healthy controls. Based on our results, this hypothesis should be rejected. We observe no signs that suggest a higher frequency of metabolic dysfunction among subfertile women, including anovulatory subfertility. However, a clear and strong association exists for the presence of metabolic dysfunction and dyslipidaemia among subfertile women with higher BMI-where lifestyle intervention should be considered.

Conclusion

In conclusion, the present study shows that there is no higher prevalence of metabolic dysfunction among subfertile women in our population. As expected, a strong correlation was observed between BMI and metabolic dysfunction. Subfertility per se cannot be regarded as a risk factor for current metabolic health disturbances.

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