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Cardiometabolic risk is unraveled by color Doppler ultrasound of the clitoral and uterine arteries in women consulting for sexual symptoms: a gender perspective

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Abstract

Introduction: Female sexual dysfunction (FSD) may be a mirror of a poor cardiometabolic state. In a small pilot study enrolling 71 women with FSD, we previously demonstrated that clitoral Pulsatility Index (PI) evaluated by using color Doppler ultrasound (CDU), reflecting vascular resistance, was associated with cardiometabolic risk factors. Data on uterine CDU in this context are lacking.

Aim: First, to confirm previously reported data on the direct association between clitoral PI and cardiometabolic risk factors on a larger study population of women consulting for sexual symptoms; second, to investigate eventual similar correlations between cardiometabolic risk factors and CDU parameters of the uterine artery. We also ascertained whether uterine artery PI, similarly to what had previously been observed for clitoral artery PI, was directly related to body image uneasiness and psychopathological symptoms, assessed by validated questionnaires.

Methods: N=230 women consulting our clinic for sexual symptoms were examined with clitoral CDU and blood sampling and were asked to fill out the Female Sexual Function Index (FSFI), the Middlesex Hospital Questionnaire (MHQ) and the Body Uneasiness Test (BUT). In a subgroup of women (n=164), we also performed transvaginal CDU with measurement of uterine artery parameters.

Results: At multivariate analysis, we found a direct association between clitoral PI and body mass index (BMI) (p=0.004), waist circumference (WC) (p=0.004), triglycerides (p=0.006), insulin (p=0.029) and HOMA-IR (p=0.009). Furthermore, a correlation between obesity and Metabolic Syndrome (MetS) and a higher clitoral PI was observed (p=0.003 and p=0.012, respectively). Clitoral PI was also correlated with MHQ-S (p=0.010), a scale exploring somatized anxiety symptoms,

and BUT-B Positive Symptom Distress Index (p=0.010), a measure of body image concerns. Similarly, when investigating the uterine artery, we were able to demonstrate an association between its PI and BMI (p<0.0001), WC (p=0.001), insulin (p=0.006), glycated haemoglobin (p=<0.0001), and HOMA-IR (p=0.009). Women diagnosed with obesity and MetS showed significantly higher uterine PI values vs. those without obesity or MetS (p=0.001 and p=0.004, respectively). Finally, uterine PI was associated with BUT-A Global Severity Index (p<0.0001) and with several other BUT-A subdomains.

Conclusion: Vascular resistance of clitoral and uterine arteries is associated with cardiometabolic risk factors and body image concerns in women consulting for sexual symptoms. If further confirmed in different populations, our data could suggest CDU, a common examination method, as a useful tool for an identification - and possible correction - of cardiometabolic risk factors.

Introduction

Sexuality is the result of a complex interaction of biological (age, hormones, health status) and psychological (mood, body image, self-esteem) factors modulated by education and personal experiences[1]. The most recent revision of The World Association for Sexual Health Declaration of Sexual Rights shows the impartiality of sexual rights between men and women, victims of a delayed interest by the scientific community in regards to their sexuality[2]. The psycho-relational component represents a prominent aspect in female sexual behavior, making it more complex to understand its pathophysiological mechanisms and making a multidimensional approach necessary.

Over the decades, several models have been developed to facilitate the understanding of the female sexual response, which also aimed at clarifying pathological and dysfunctional aspects. One of the first and best known, and applicable to both sexes, is the one theorized by Masters & Johnson (Master and Johnson, 1966). In this model, which dates back to the sixties, four stages are identified: excitement, plateau, orgasm, resolution. In the following decade, Helen Kaplan modified this model introducing the concept of sexual desire, and highlighting how the different phases are interrelated but controlled by different neuropathophysiological processes. This view suggests that the different areas of the sexual response can be altered even in a completely isolated and independent way (Kaplan 1979).

In 2000, a new model of sexual response was proposed by Rosemary Basson. This model was innovative in that it was circular, compared to previous linear models,

thus contemplating the idea that the sexual response may be initiated in the absence of spontaneous desire; therefore, desire and arousal may follow, thanks to an adequate sexual stimulation (responsive desire vs. spontaneous desire). This model highlights another key element of the physiology of female sexual response. In women, the motivation for sexual involvement may not be strictly related to sex, but also concern other personal aspects, such as intimacy, general relationship satisfaction, desire to feel close to the partner, need to feel loved, etc. In this view, sexual satisfaction in women can be reached independently from orgasm (Basson 2000)

More recent studies have drawn further attention to the significant heterogeneity of the female sexual response, leading to the conclusion that not only it is difficult to describe a model suitable for every woman, but also that every woman can describe

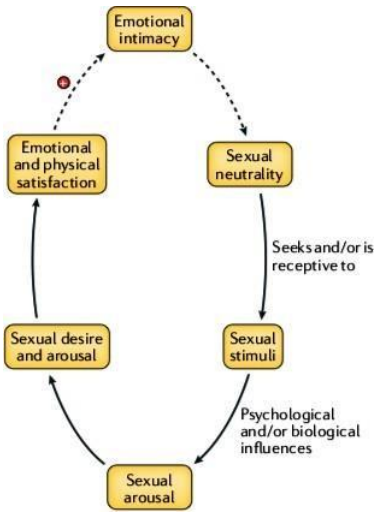

Fig. A: Basson's Model

herself in a different pattern depending on different circumstances, relationships or life stage (Giraldi et al 2015).

1.1 Desire

"What does a woman want?" (Freud, 1925) is the question that weaves through the history of the study of female sexuality; literature has been widely spent over the decades to identify a sufficiently broad and complex definition to frame the multifactorial nature of female desire. Recent approaches to the subject have highlighted how "pure" desire cannot be defined. It's impossible not to take into account the socio-cultural context, life experiences, and personal sexual history. The definition is therefore complex and multifactorial (van Anders, S. M. 2012). One of the definitions most often found in both recent and past literature describes desire as "the presence of sexual thoughts, fantasies, urges, and motivations to engage in sexual behavior in response to relevant internal and external cues". (American Psychiatric Association, 2000; Bancroft, 2009; Kafka, 2010; Singer & Toates, 1987). In this broad definition it is necessary to take into account biological, psychological, and relationship factors, fundamental both for the understanding of physiology and the pathology of desire. A recent publication introduced the concept of attachment and sexual body self-representations as a further determinant of the phenomenology of sexual desire in women. (E. Cherkasskaya, M. Rosario, 2017)

Desire is composed of 3 fundamental components: the instinctual biological stimulus, regulated by endocrine and neurochemical factors; the motivational-

affective stimulus, related to affection and sexual identity and orientation; the cognitive assessment, based on what is expected from sexual behavior and the risks associated with it. With regard to the neurobiological component, desire seems positively regulated by dopamine and melanocortine, whereas serotonin, opioids and endogenous cannabinoids have been reported to exert an inhibitory effect (Kingsberg et al,. 2015). Regarding the role of sexual steroids, recent evidence suggests that androgens play a major role in promoting libido in synergy with estrogen, while progesterone has an inhibitory role.

1.2 Arousal

Female sexual arousal is a multiform and dynamic process that includes emotional, behavioural and physiological factors related to each other but partly independent (Levin et al., 2008). The dual control model, proposed by Bancroft and Janssen in 2000, states that "sexual response and associated behavior depend on dual control mechanisms, involving excitatory and inhibitory neurophysiological mechanisms" (E. Janssen, H. Vorst, P. Finn & J. Bancroft. (2002a). In the dual control model, two distinct but interconnected mechanisms are identified, both involved in regulating the sexual response. This model therefore defines how sexual behavior can be interpreted as a balance between the two components, excitatory and inhibitory, and how the sexual response is characterized by different levels of arousal and inhibition, determined by these two components.

It has been widely reported that female sexual arousal involves two components: the genital or peripheral arousal and the subjective or central arousal. (McCabe et

al. 2015; Basson 2001). The first refers to neurovascular changes occurring at in the genital tissues in response to sexual stimuli; the second could be described as positive or stimulatory mental excitation occurring in response to sexual stimulation. (Althof, et al.. 2017).

As far as the physiology of the peripheral arousal response is concerned, much information can be derived from the well-known male model. Penile erection is a central psychoneuroendocrine as well as a peripheral neuro-vascular event caused by sexual/erotic stimulation with subsequent blood filling the sinusoidal spaces of the paired corpora cavernosa and the corpus spongiosum (O.G.F, Rampin, J. J.Bernabe, A. Jardin, G. Benoit.1996; P. Bondil, JD Doremieux. 1992) In basal conditions (i.e., in the absence of sexual stimuli), under the control of norepinephrine, the vascular and non-vascular smooth muscles in the genital organs are contracted, and blood flow is at minimum levels (Traish et al. 2010). The relaxation of the corpora cavernosa occurs through the cholinergic stimulation of acetylcholine and the subsequent release of nitrogen monoxide (NO) by the endothelium, with activation of guanylate cyclase within the smooth muscle cell and production of cyclic GMP (cGMP). The cGMP activates the protein kinase G (PKG), which induces a depletion of cytoplasmic calcium resulting in muscle release. Conversely, the contraction of corpora cavernosa is mediated by the stimulation of adrenergic fibers, via the RhoA-Rho kinase pathway. (Cellek S. et al. 2003).

A recent study by the University of Florence has shown that these well-known molecular mechanisms underlying the regulation of erection are similar and in both

sexes. In a rodent model, the female clitoris was found to express the same pattern of genes related to NO/cGMP signaling than that found in the male rat, even if at significantly lower levels. This study also demonstrates the high expression of the androgenic receptor in the clitoral tissue and shows that androgens can induce an up-regulation of the genes related to the NO-cGMP patheay, while estrogens up-regulate those related to the RhoA-Rho kinase pathway (Comeglio et al. 2016). These findings suggest that both androgens and estrogens are involved in the process that controls clitoral tumescence.

In this context, it has been widely reported in animal studies that ovariectomy leads to reduced blood flow in the pelvic district, resulting in reduced vaginal lubrication, fibrosis of clitoral tissue and thinning of the vaginal wall (Goldstein et al. 1998). Furthermore, human studies report that vaginal administration of estrogen restores the integrity of the vaginal wall in menopausal women. (Stuenkel et al. 2015).

1.3 Orgasm

Orgasm is the peak of sexual arousal, and has been seen as the primary motivation for individuals to engage in sexual intercourse. In women orgasm can be triggered by a large variety of stimuli, different among subjects and in the same subjects according to personal and environmental conditions. Essentially, women can reach orgasm through direct or indirect stimulation of the clitoris, and through more superficial or deeper vaginal stimulation. Some women experience orgasm only with penile penetration, whereas other women require concurrent stimulation of the external parts of the clitoris during coitus, and some other women never experience

orgasm during intercourse under any condition. Despite a debate lasting more than 100 years, the existence of different orgasms (mental, from nipple/breast stimulation, clitoral, vaginal, cervical, anal, etc.) in the human female is still contentious.

There are substantial differences between women and men in the onset of orgasm. In the post-pubertal male the mechanism of orgasm appears simple and spontaneous, as identified by the ejaculatory reflex. In women, orgasm occurs in a slower and less predictable way. Another "gender gap" in orgasm concerns the fact that, while in men the triggering process tends to be similar, in women a much higher variability of stimuli has been reported. There are women who reach orgasm very easily and regularly, as well as there are women who experience multiple orgasms within the same sexual intercourse. Another difference between the two genders is represented by the pattern of orgasm, which is extremely variable among women, and may lack the refractory period, unlike what happens in men (Pirozzi Farina et al 2007).

Orgasm pathology is a large chapter of female sexual dysfunction, since primitive or secondary anorgasmia is common. (Wallen K et al, 2011 May)

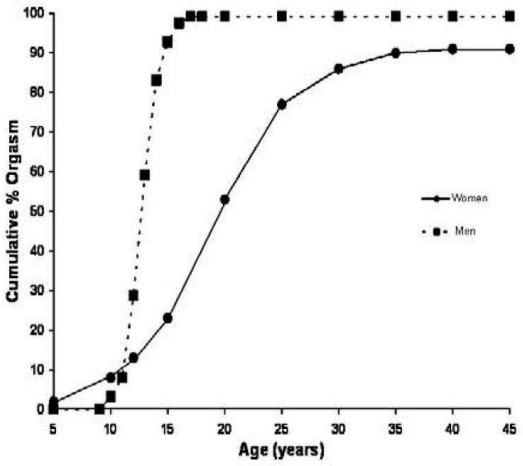

Fig B Illustrates the sex difference in the occurrence of orgasm in males and females in relation to age. Males show a rapid transition from few boys experiencing orgasm prior to puberty to all men experiencing orgasm soon after puberty. Women, by contrast show a much more gradual developmental curve. Male data are adapted from Kinsey, Pomeroy, and Martin, 1948 and the female data are adapted from Kinsey, et al., 1953.

In women, orgasm is associated with rhythmic contractions of the pelvic floor, uterine and anal muscles, followed by the resolution of vasocongestion, along with the perception of a deep and intense sense of well-being (Meston et al. 2004). Several studies have been carried out with the purpose of locating the erogenous zone involved in the generation of orgasm associated with vaginal penetration that some Authors identify with the Gräfenberg point or "G point". In 2009, a study by Foldes and Buisson suggested that the movements of the clitoral raphe against the anterior vaginal wall during coitus may underlie the increased erotic sensitivity of the so-called "G spot".

Modern literature has also focused in trying to locate the real "anatomy of female orgasm". Recent studies propose an anatomical relationship and a functional interaction between the distinct anatomical parts apparently involved in originating female orgasm, namely the clitoris, urethra, and anterior vaginal wall. According to this view,a new anatomical-functional entity, the clitourethrovaginal (CUV)

complex, has been introduced, defined as a multi-faceted morphofunctional area that undergoes stimulation during penetration and that consequently could be identified as the origin of the orgasmic sensation itself. (Emmanuele A. Jannini, Odile Buisson and Alberto Rubio-Casillas. Beyond the G-spot: clitourethrovaginal complex anatomy in female orgasm,).

A very interesting and groundbreaking paper published in 2013 added essential information regarding the use of the ECD technique in sexual medicine. In this work, a comparison was made between the ultrasound parameters of the clitorourethrovaginal complex during direct clitoral stimulation and during vaginal penetration, showing that the clitorourethrovaginal complex is equally involved in both cases. (Odile O and Jannini EA, 2013. Pilot Echographic Study of the Differences in Clitoral Involvement following Clitoral or Vaginal Sexual Stimulation).

Therefore in women, the mechanism underlying orgasm is not well known and defined, in view of the many factors that may be the basis of orgasmic sensation and consequently of its dysfunction.

An interesting 2018 paper by Prof Jannini's group validated a visual analog scale to measure subjective perception of orgasmic intensity in women, called "Orgasmometer-F".

This represents "a new psychometrically robust tool to measure orgasmic intensity in the female population, has shown that SD impairs orgasmic intensity." (Mollaioli D et al, 2018. Validation of a Visual Analogue Scale to measure the subjective perception of orgasmic intensity in females: The Orgasmometer-F).

1.4.1 Echo-color-doppler ultrasound: physical basis

Doppler ultrasound is an instrumental method that exploits the physical phenomenon whereby the frequency of the sound of a source (f0) seems to increase as it approaches a listener (fd+) or, on the contrary, seems to shrink when it moves away (fd-), the apparent change in frequency is said *Doppler shift.* This phenomenon is called "Doppler effect".

The Methodology of Doppler-Derived Blood Flow Measurements

The methodology of Doppler is named by the mathematician and physicist Christian Johann Doppler who first described this effect in 1842 by studying light from stars. He demonstrated that the colored appearance of moving stars was caused by their motion relative to the earth. This relative motion resulted in either a red shift or blue shift in the light's frequency. This shift in observed frequencies of waves from moving sources is known as the Doppler effect and applies to sound waves as well as light waves.

The Doppler effect applied to diagnostic ultrasound

As widely explained in the work by K Nicolaides, G Rizzo, K Hecher,"Doppler in Obstetrics. Chapter on Doppler ultrasound: principles and practice" the "Ultrasound images of flow, whether color flow or spectral Doppler, are essentially obtained from measurements of movement. In ultrasound scanners, a series of pulses is transmitted to detect movement of blood. Echoes from stationary tissue are the same from pulse to pulse. Echoes from moving scatterers exhibit slight differences in the time for the signal to be returned to the receiver. These differences can be measured as a direct time difference or, more usually, in terms of a phase shift from which the `Doppler frequency' is obtained. They are then processed to produce either a color flow display or a Doppler sonogram".

In ultrasound, this principle is therefore used to visualize blood flows: the red blood cells represent the interfaces on which the echoes are generated, the frequency of which will seem to increase, in the case of inflows at the probe (Doppler positive - fd+), or will appear to shrink in the opposite case (Doppler negative - fd-) relative to the frequency of ultrasound emitted by the probe ($\mathbf{f_0}$).

There are different Doppler acquisition modes: the continuous Doppler (CW), in which the transducer consists of 2 piezoelectric crystals mounted on the same support, one continuously emitting and the other continuously receiving. This mode allows a morphodynamic study (ie morphology and movement) of flows. Its main advantage is to be able to measure even very high flow rates. Instead in the pulsed Doppler the transducer is constituted by a single piezoelectric crystal that isplaced

alternately in phase of emission and in phase of reception, the emission istherefore phasic rather than continuous. The Color Doppler (CD) is an evolution of the Pulsed Doppler in which the flow, represented with the average speed, is displayed as a color map superimposed on the image in B-mode. The color is usually encoded in such a way that the red is assigned to the flow directed towards the probe, while the blue is assigned to the one that moves away from it. A variant of the Color Doppler is the Power Doppler suitable for detecting slow fluxes, displayed with a color scale, usually from yellow to magenta, based on intensity and not flow direction.

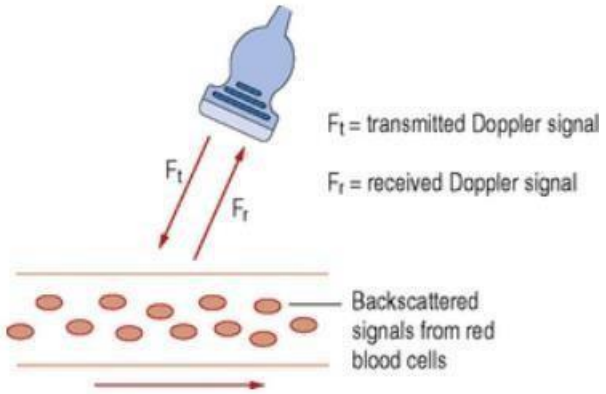

Fig C. By: Physical principles of Doppler ultrasound

The Doppler effect in diagnostic imaging can be used to study blood flow, for example, and provides the operator with three pieces of information to determine:

- ✓ Presence or absence of flow
- ✓ Direction of blood flow
- ✓ Velocity of blood flow.

The size of the Doppler signal is dependent on:

- Blood velocity: as velocity increases, so does the Doppler frequency;
- Ultrasound frequency: higher ultrasound frequencies give increased Doppler frequency. As in B-mode, lower ultrasound frequencies have better penetration.
- The choice of frequency is a compromise between better sensitivity to flow or better penetration;
- The angle of insonation: the Doppler frequency increases as the Doppler ultrasound beam becomes more aligned to the flow direction (the angle between the beam and the direction of flow becomes smaller). (Nicolaides K et al, 2002)

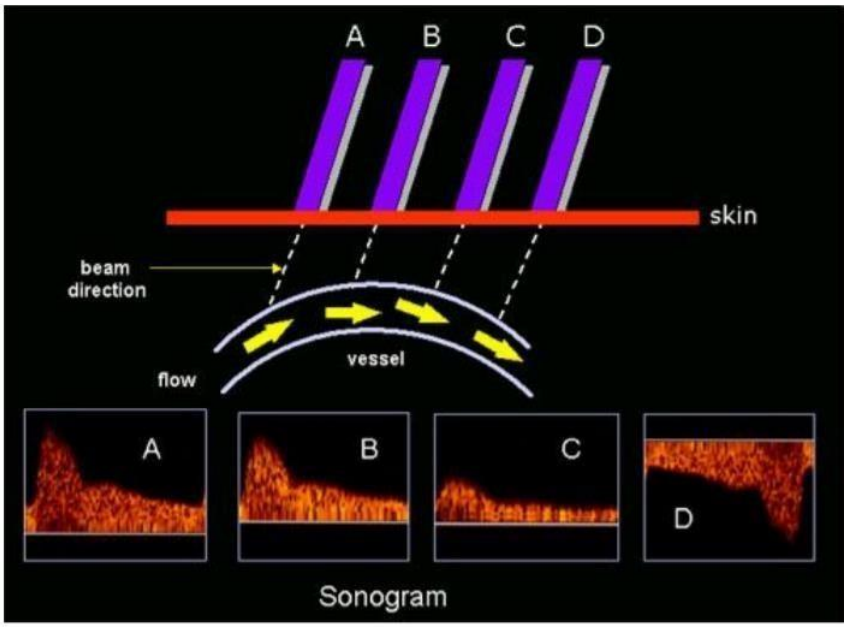

Fig D: Effect of the Doppler angle in the sonogram. By "Doppler in Obstetrics. Chapter on Doppler ultrasound: principles and practice"

Flow waveform shape: indices of measurement

Different evaluation indices can be used to describe the shape of wavefores in a quantitative and therefore usable way to verify possible pathology of vascularization.

Commonly used indices are:

• Systolic / diastolic ratio: (S/D);

• Resistance index: (S-D) / D, also called Pourcelot's index;

• Pulsatility index: (S-D) / Vm. The PI is the only useful index when there is no end-diastolic flow.

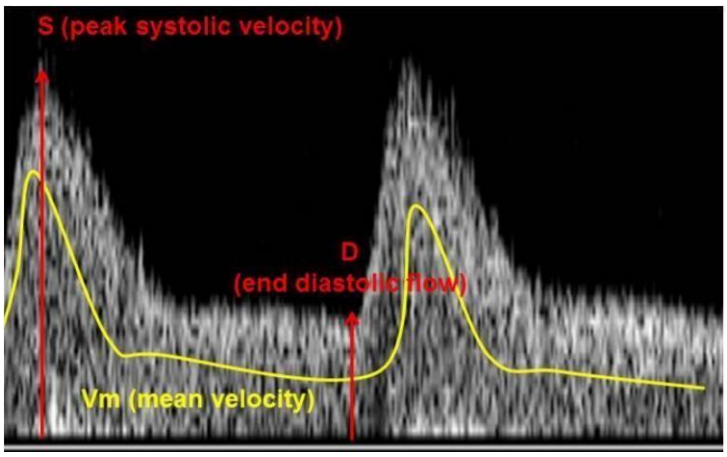

Fig E: Flow velocity indices: By: Physical principles of Doppler ultrasound.

The latter has been described as a good marker for assessing vascular resistance and atherosclerosis (Lim HS, Gustafsson F, 2020).

2. Our approach

It is now known that male erectile dysfunction is a sign of subclinical cardiovascular pathology and a predictive marker of major cardiovascular events (Rowen TS et al, 2020), since it has been shown that an endothelial damage underlies such conditions (McCall-Hosenfeld JS et al 2008; Yeoh SH et al 2012). In women, despite the long therapeutical use for female sexual dysfunction (FSD) aimed at improving clitoral blood flow, the clinical consequences of altered blood flow in the genital districts have not yet been clarified.

Cardio-metabolic risk factors, such as arterial hypertension, dyslipidaemia, metabolic syndrome (MetS), obesity and diabetes mellitus (DM), are important determinants of erectile dysfunction (ED) in men and may contribute to the development of cardiovascular diseases in a similar mechanism in women (Maseroli E et al, 2018).

In the past, several studies have shown an increased prevalence of FSD in women with MetS, ranging between 19.4% and 36.6% in pre-menopausal age and between 37.9% and 54.7% in post-menopausal age (Ponholzer A et al, 2008. Martelli V et al, 2012. Alvisi S et al, 2014); however, this evidence is not strong enough to establish a clear correlation between MetS and FSD, differently from what is known for erectile dysfunction (DE). Recently, it has also emerged that an important pathogenetic link between MetS and FSD could be insulin resistance (Zsoldos M et al, 2019). A recent review showed that women with MetS had a greater prevalence of sexual inactivity, low libido, anorgasmia and personal dissatisfaction. In

particular, a correlation emerged between diabetes mellitus (DM), dyslipidaemia and arterial hypertension with reduction of libido and the Female Sexual Function Index score (FSFI) (Di Francesco S et al 2019).

Clitoral Doppler Ultrasound is a non-invasive method that can be used to obtain information about the vascularization of the female genital tracts, a parameter that was very closely linked to female sexual function (Vignozzi L et al, 2014). Pulsatility index (PI) is a very important parameter for assessing vascular resistance. PI represents the difference between the peak systolic and diastolic flowsdivided by the average maximum flow rate (Mazloomdoost D, et al, 2015).

It has been demonstrated that the different components of MetS, including central obesity, dyslipidaemia and insulin resistance, could be associated independently with the increase of the clitoral PI, which in turn correlates to a reduction in sexual arousal and to an increase in body discomfort, especially in areas strictly related to sexuality (eg uterus, genitals and breast) (Vignozzi L et al, 2014).

The first study that demonstrated an association between cardio-metabolic risk factors and clitoral PI, conducted by Maseroli et al, hypothesized that these factors may have a role in determining FSD (Vignozzi L et al, 2014). In particular, the results of this study showed an increase of clitoral PI depending on the different cardiometabolic risk factors, including MetS.

The physiopathology of MetS is mainly focused on insulin resistance, hypertriglyceridemia and increased visceral adiposity. In the aforementioned study, a close association was found between clitoral PI and parameters related to insulin

resistance, such as insulin and triglyceride levels and waist circumference, as well as a positive association between clitoral PI, HOMA index and total and LDL cholesterol levels (Vignozzi L et al, 2014)

Furthermore, an increased clitoral PI seemed to be strongly associated with a lower FSFI score, especially in the arousal domain (Vignozzi L et al, 2014). Therefore, it can be hypothesized that an increase in vascular resistance leads to a reduction in the blood flow to the clitoris, especially during the phases of female sexual function, which require an appropriate arterial perfusion (Scaruffi E et al, 2019). Instead, clitoral PI is not significantly associated with other FSFI domains including desire, orgasm and pain (Castellini G et al, 2019).

These data are in line with the results of the Women's Health Initiative, which show a correlation between the increase in the prevalence of peripheral arterial disease and dissatisfaction with sexual activity (Dalle Grave R et al. 2007).

Maseroli et al. also showed that the clitoral PI was associated with a higher score of MHQ somatization domain, which mainly reflected the somatization of the anxiety state (Vignozzi L et al, 2014). This increase in clitoral resistance can be considered an expression of the genital district dysfunction, leading to the development of concerns and hypervigilance regarding bodily sensations (Balercia G et al 2007; Hoehn-Saric R et al, 1988).

The color Doppler assessment of the uterine artery was used in the obstetrical-gynecological field in the evaluation of fetal umbilical vessel flow and

of fetal circulation (Corona G et al, 2016; Goswamy RK et al, 1988) and in uterus-placental studies to predict fetal growth-related delays (Adibi A et al, 2015)

The determination of the uterine artery *PI* and *resistance index* (*RI*) in the first trimester of pregnancy (from 11 to 13 + 6 weeks) was for several years part of prenatal screening for the risk determination of preeclampsia (PE) and intrauterine growth restriction (FGR) (Koo HS et al 2016; Brosens I, et al, 2011)

It was demonstrated that, during the normal menstrual cycle, the average values of uterine arteries PI and RI gradually decreased during the luteal phase, with a further reduction during pregnancy (Brosens I, et al, 2011). The normal process of placentation, which will end at the sixteenth week, leads to the transformation "from a system of high resistance and low flow to a system of low resistance and high flow" (Kim N et al, 2006). This substitution of resistance frequently does not occur during pregnancies, in which will developed PE and FGR, leading to a significant increase of systolic peak velocity (Vs), RI and PI. The exact pathogenesis is not completely clear, but it would seem connected to the inadequate invasion of the spiral arteries by the cytotrophoblast during the placentation phase (Kim N et al, 2006).

Furthermore, studies in assisted reproductive technology demonstrated that uterine artery resistance can be a good indicator of probability of pregnancy (Esposito K et al, 2005). The literature showed that uterine receptivity in the mid- PI range showed to be optimal (Hollis B et al, 2003); the reason why the highest rate of implants not occurred in the lower PI range did not known, it could be due to the low number of women in the group of this aforementioned study.

In literature there are data that demonstrate that uterine PI increased in women with PCOS, although not following a homogeneous pattern and the range of PI, in the various conditions, is wide (between 1.57 and 7.25) (Morelli A et al, 2019). The mechanism underlying the increased uterine PI is not known, maybe the elevated circulating androgens could be responsible for blocking the effect that oestrogen exerts on the endometrium (Miner M et al, 2012).

Although some studies have obtained conflicting results regarding the correlations between hormone levels and uterine PI in PCOS (Petersen LJ et al, 1997), the usefulness of the doppler in the diagnosis of this pathology is worthy of further scientific studies.

2.1 Aim of the study

The aim of this study was to consolidate and substantiate the data previously published on the correlation between clitoral PI, assessed by color Doppler ultrasound, and cardiovascular risk factors (Vignozzi L et al, 2014), using a larger sample of women with sexual dysfunction. Furthermore, in a subgroup of patients, we were also able to assess the uterine district (specifically through assessment ofthe PI of a uterine artery branch) in order to investigate whether, analogously to what has been demonstrated with the clitoral artery, there could be a correlation with cardiometabolic risk parameters, such as MetS, and uterine PI in women withsexual dysfunction. The possible correlation between the uterine artery PI, sexual function and body uneasiness was also evaluated.

3. Methods

We enrolled 230 female pre- and post-menopausal patients referring to our Sexual Medicine Unit (Andrology, Women's Endocrinology and Gender Incongruence Unit, Careggi Hospital, University of Florence, Italy, protocol 37.589/SPE. 13.034, for sexual symptoms. Women were admitted by self-referral or referred by their general practitioners or other specialists (i.e. urologist, oncologist, neurologist, diabetologist, etc.). Inclusion criteria were being sexually active in the previous 4 weeks and having a partner. In particular, the presence of a relationship was investigated by a specific question included in an interview administered during the visit: “Do you have a stable relationship with a partner? Do you live together?”, with scoring 0= Stable relationship, living together; 1= Stable relationship, not living together; 2= No stable relationship; 3 = No relationship [19]. Only women scoring 0 to 2 were included in the analysis.

Clinical data were collected during outpatient visits, after administration of an informed consent. The study protocol was designed according to the Helsinki Declaration and approved by the local ethics committee (protocol 37.589/SPE. 13.034, Comitato Etico Area Vasta Centro CEAVC, Careggi Hospital, Florence, Italy).

During the first visit, demographic, physiological and pathological data were collected, and body mass index (BMI), waist circumference (WC) and systolic (SBP) and diastolic blood pressure (DBP) were measured.

3.1 Psychometric assessment

Standardized questionnaires relative to sexual and psychological health were administered, including the Female Sexual Function Index (FSFI) (Rosen R, et al 2000), the Female Sexual Distress Scale-Revised (FSDS-R) (Derogatis L et al, 2008), the Body Uneasiness Test (BUT) (Cuzzolaro M et al, 2006) and the Middlesex Hospital Questionnaire (MHQ) (Crown S et al, 1966).The average time taken to fill the questionnaires was around 20 minutes. To avoid distractions, participants completed the questionnaires alone, in a quiet context.

The FSFI is the most common questionnaire used for the screening of FSD and consists of 6 domains investigating different phases of the female sexual response (desire, arousal, orgasm), sexual satisfaction and dyspareunia (Rosen R, et al 2000).

The score of each item ranges from a minimum of 0/1 to a maximum of 5 and is obtained by the addition of the single question score multiplied by a specific factor. The total score is the result of the 6 score items' addition. The patient with a total score ≤26.55 is suffering from FSD. The Desire domain is the only domain that can be used independently (Meston CM et al, 2020), and a cut-off score of 5 has been found to identify women with Hypoactive Sexual Desire Disorder with a good specificity and sensibility (Gerstenberger EP et al, 2010).

The FSDS-R is validated to assess sex-related distress (Derogatis L et al, 2008).

The BUT is used to assess body image concerns and eventual related pathological conditions. It includes two different parts: the first part (BUT-A) consists of questions regarding body-related attitudes, while the second part (BUT-B) explores the level of dissatisfaction towards 37 different body parts considered separately

(Derogatis L et al, 2008). BUT-A total score indicates global dissatisfaction with body image and is expressed as Global severity index (GSI), which is considered as pathological if > 1.2; BUT-A subscales define weigh-related phobia (Weight Phobia, BUT-WP), avoiding attitudes (Avoiding, BUT-AV), compulsive control of self-image (Compulsive self-monitoring, BUT-CSM), tendency towards separation from one's own body (Depersonalization, BUT-D), and concern about body image (BUT-BIC, Body image concerns) (Derogatis L et al, 2008). A 6-point score on a Likert scale (with answers ranging from "never" to "always") is attributed to every question, with the higher scores corresponding to a more severe discomfort (Derogatis L et al, 2008). BUT-B score indicates dissatisfaction with a single body part and is expressed in two global measures: a global dissatisfaction index (Positive Symptom Total, PST) and a discomfort index (Positive Symptom DistressIndex, PSDI) (Derogatis L et al, 2008)

The MHQ-modified is generally used in non-specialistic settings to evaluate psychopathological traits and it includes a total score and 6 different subscales: free anxiety symptoms (MHQ-A), phobic anxiety symptoms (MHQ-P), obsessive-compulsive traits and symptoms (MHQ-O), somatized anxiety symptoms (MHQ-S), depressive symptoms (MHQ-D) and hysteric/histrionic symptoms (MHQ-H) (Crown S et al, 1966).

3.2 Biochemical evaluation

Blood samples were drawn in the morning, after an overnight fast, for determination of the biochemical parameters considered necessary for the evaluation of FSD. In particular, the assessed parameters were: blood glucose (esokinase method; Dimension Vista 1500 Medical Solutions by Siemens Healthcare, Newark, USA);

total and high-density lipoprotein (HDL) cholesterol (high density lipoprotein) and triglycerides (automatic enzymatic colorimetric method; Dimension Vista 1500 Medical Solutions by Siemens Healthcare, Newark, USA); insulin (electrochemiluminescence immunoassay, "ECLIA"; Roche Diagnostics, Mannheim, Germania) and glycated haemoglobin (HbA1c) (high prestations liquid chromatography, HPLC, Variant II method, Biorad Laboratories, Hercules, CA, USA). LDL (low-density lipoprotein) cholesterol was calculated through Friedewald equation: LDL cholesterol = total cholesterol - (HDL cholesterol + triglycerides/ 5) and all parameters were expressed in mg/dl. HOMA-index (Homeostatic Model Assessment), a method used to estimate insulin-resistance (IR) and beta-cell function, was calculated according to the following formula: HOMA-IR = (glycaemia x insulin)/22.5 (see http://www.phc.ox.ac.uk/research/technology-outputs/ihoma2).

3.3 Metabolic Syndrome (MetS) diagnosis

MetS diagnosis was defined according to the National Cholesterol Education Program - Third Adult Treatment Panel (NCEP-ATPIII; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), in the presence of ≥3 of the following factors: central obesity (waist circumference ≥ 88 cm), high triglyceride serum levels (≥150 mg/dL or specific therapy), arterial hypertension (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or specific therapy), impaired fasting glycaemia (≥110 mg/dL or

specific therapy) and low HDL cholesterol serum levels (< 50 mg/dL or specific therapy).

3.4 Instrumental investigations

All patients (n = 230) underwent color Doppler ultrasound (CDU) with examination of the clitoral cavernous artery, in order to measure its Pulsatility Index (PI). In fertile women, CDU was performed in the follicular phase of the menstrual cycle (days 3-5). The phase of the menstrual cycle was registered during the visit as reported by the patient and later confirmed by the ultrasound measurement of endometrial thickness. The evaluation was performed by an experienced operator, blinded to other clinical data, with a linear probe (LA523, 6-13 MHz) using a MyLabClass-C ultrasound system (Esaote S.p.A., Genoa, Italy). In order to reduce the impact of external factors on blood flow, the patients were examined in a quiet environment, with constant temperature and lighting. To minimize the risk of situational anxiety altering the data due to vasoconstriction, only one operator stayed in the room, and the exam was carried out following a clear and complete explanation. The procedure follows that the one previously published by Battaglia and collaborators (Battaglia C et al, 2006; Battaglia C et al 2011)

To standardize operating conditions, all patients were instructed to refrain from sexual intercourse and masturbation for at least 12 hours. CDU was performed in a gynecological position and with an empty bladder. An adequate amount of ultrasound gel was used in order to avoid air interference, and to prevent artifacts, a slight pressure on the genitals was exerted. The transverse scan of the clitoris was obtained by positioning the probe transversely, on the upper part of the vulva; this

projection allows operators to easily locate the cavernous arteries, which appear well defined in the centre of the two cavernous bodies. When an adequate signal was detected, the pulsed-wave Doppler mode, which records the velocity of blood flow, was activated. Clitoral PI is automatically calculated and represents the difference between the systolic peak velocity and the end-diastolic velocity divided by the average velocity (Gosling RG et al, 1974); since it characterizes the shape of the wave, the PI is independent of the angle between the probe and the vessel (Lumb P et al, 2014). For each cavernous artery, at least 3 waves of similar shape were sampled, and the mean PI was calculated. No significant difference was observed between the left and the right clitoral artery PI.

In addition, in a subgroup of patients (n = 164), transvaginal CDU was performed to evaluate the uterine artery PI. Since several factors, common in pre-menopausal women, can influence uterine vascularization (i.e. the phase of the menstrual cycle, endometriosis, organic disorders including fibroids, puerperium or recent abortion), we analysed the sample according to patients' pre- (n = 99) or post-menopausal (n = 65) status. All patients were evaluated at the same time of the day, to avoid flow changes due to the circadian rhythm. The examination was performed in a dorsal lithotomy position. The measurement was performed on the right side, lateral to the cervix at the internal orifice, before the branching of the artery. Three surveys were carried out in a time window of 1-3 minutes to define a mean value.

3.5 FSD work-up

After recruitment, all participants underwent a complete diagnostic work-up performed by a multidisciplinary team, involving an endocrinologist, a gynaecologist and a mental health professional (psychiatrist and/or psychologist) all trained in sexual medicine. As per clinical practice, after FSD diagnosis, and following a complete evaluation of their personal, relational and social background, needs, preferences, and contraindications, women could be offered medical (i.e. local treatment for vulvo-vaginal atrophy, off-label systemic testosterone treatment) and/or psychological treatment (i.e. cognitive behavioral therapy, sexual therapy). The partner was not directly involved in the initial assessment, but the possibility of his involvement was offered to the patient during the following visits.

3.6 Statistical analyses

Data were expressed as mean ± standard deviation when normally distributed, as median (interquartile range) when non-normally distributed, and as percentage when categorical. When significant differences among groups were found, the unpaired 2-sided Student t test was used for comparisons between 2 groups. For non-normally distributed parameters, comparison between groups of variables was also performed with non-parametric tests (Mann Whitney U test for comparisons between 2 groups). Correlations between variables were evaluated through Spearman method and ANCOVA with post-hoc Bonferroni test was used for differences between groups. Finally, linear or ordinal regression was used for multivariate analysis, considering confounding factors as specified. All statistical analyses were performed using SPSS for Windows 25.0 (IBM, Armonk, NY, USA).

In order to consider the multiple comparisons problem, we performed a False Discovery Rate Correction. After 10% FDR calculation, we adjusted the cut-offs for significant p-value at <0.038.

4. Results

4.1 Characteristics of the sample

Table 1 shows the main baseline characteristics of the study population (n=230), including hormonal, cardio-metabolic, psycho-sexual scores and the mean clitoral pulsatility index (PI). FSFI, FSDS-R, MHQ and BUT questionnaires were used to assess psycho-sexual parameters were assessed by using. These baseline characteristcs are also reported when stratifying the study population according to menopausal status (Supplementary Table 1a and b; post-menopausal n=114; pre-menopausal n=116). In an adjusted model , post-menopausal women demonstrated an older age, a higher number of parities, a more frequent history of breast or pelvic surgery and a worse cardio-metabolic profile compared to pre-menopausal subjects (Supplementary Table 1a). Concerning the psychosexual assessment, in an age-adjusted model, post-menopausal women only showed lower FSFI total and desire domain scores (Supplementary Table 1b). In contrast, post-menopausal and premenopausal women did not show any statistical significant difference concerning the clitoral PI (Supplementary Table 1b).

4.2 Correlation between clitoral PI and cardiometabolic/psychosexual parameters

At univariate analysis, clitoral PI demonstrated to be positively correlated to BMI, WC, triglyceride levels, insulin levels and HOMA index (Table 2); interestingly these associations retained statistical significance after adjusting for confounders (age, smoking habit, and years since menopause),

At analysis of covariance, women with obesity (BMI≥30 kg/m^2) or MetS (owing ≥ 3 MetS factors) showed significantly increased clitoral PI values when compared to non-obese subjects or to women without MetS (F=8.962, p=0.003; F=6.281, p=0.013, respectively). These differences retained statistical significance after adjusting for confounders (age, years since menopause and smoking habit) (F=8.814, p=0.003 for obesity, Figure 1A; F=6.361, p=0.012 for Mets, Figure 1B). No significant associations were observed between clitoral PI and FSFI or FSDS-R scores (not shown). In contrast, clitoral PI showed significant and positive associations with the somatized anxiety symptoms (assessed by MHQ questonnaire) and with BUT-B Global measure PSDI, a score related to global distress for body parts, either in a univariate or multivariate model (Table 2). Interestingly, among the 37 body parts explored by BUT-B, increased clitoral PI only showed a significant positive association with all the items exploring dissatisfaction for the genitals, which retained statistical significance even in the fully adjusted model (β=0.169; p=0.05).

4.3 Correlation between uterine PI and cardiometabolic/psychosexual parameters

In the subset of patients (n=164) who were also studied by using the CDU of the uterine artery during the transvaginal ultrasound analysis, PI. The baseline characteristics of this subgroup, even when stratified according to the menopausal status, are reported in Supplementary Table 2.

Similarly to what observed for clitoral PI, but only in the subset of post-menopausal women (n=65), uterine PI showed a significant positive association withseveral metabolic parameters (BMI, WC, insulin, HbA1c, and HOMA-IR index), in either the unadjusted or fully adjusted model (Table 3). In the same post-menopausal population, obese women (BMI≥ 30 kg/m2) showed a significantlyincreaseduterine artery PI value when compared to non-obese ones (Figure 2A). Asimilar trend of an increased uterine artery PI value was also found in post- menopausal women with MetS as compared to those without (Figure 2B). In particular, among MetS factors, having triglyceride levels ≥ 150 mg/dL (or taking lipid lowering drugs) (Figure 2C), or having HDL levels < 50 mg/dL (or taking lipidlowering drugs) (Figure 2D), as well as having a WC > 88 cm (Figure 2E) was associated with a significantly higher PI value. Noteworthy, uterine artery PI was found to increase as a function of the number of MetS components, even after adjusting for confounders (age, smoking habit, and years since menopause;$\beta = 0.439$, $p = 0.001$; Figure 3).

Among the sexual parameters, as assessed by FSFI, post-menopausal women, only ,showed a significant but negative association between the Desire domain PI, which was not confirmed at multivariate analysis (not shown). Increased uterine PI also correlated with several items of the Body Uneasiness Test, such as BUT-A global measure (GSI) and BUT-B global distress measure (PSDI) in both univariate and multivariate analysis (Table 3). Uterine PI was also positively associated with several subdomains of BUT-A which explored weight phobia (WP), body image concerns (BIC), avoidance (AV), and depersonalization (DEP), even after adjusting

for age, smoking habit, and years since menopause (Table 3); all these associations retained statistical significance also when introducing WC as a further covariate (β=0.546, p=0.002; β=0.427, p=0.013; β=0.636, p=0.002; β=0.451, p=0.009; β=0.508, p=0.005 for BUT-A GSI, WP, BIC, AV and DEP respectively).

4. **Discussion**

In the present study we substantiate our previous results showing that , in women consulting for sexual symptoms, clitoral artery pulsatility index (PI), a color Doppler ultrasound (CDU) hallmark of vascular resistance, closely associated with increased BMI and the presence of several MetS factors. This study support clitoral PI as a potential marker for ascertainthe cardiometabolic risk profiles in the sexological setting. Notably, also uterine PI showed a similar correlation with the abovementioned parameters, but only in the subset of post-menopausal women. An increased PI of either clitoral or uterine arteries also showed a significant association with body image, as assessed by the Body Uneasiness Test. We previously originally demonstrated a tight relationship between clitoral PI and BMI or MetS factors but in a small pilot study (n= 71) (Maseroli E et al, 2016); hereby, we consolidate these previous findings in a larger study involving 230 women consulting for sexual symptoms. Essentiallyt herein we showed that clitoral PI increased as a function of WC, as well as of triglyceride, fasting insulin, and HOMA-IR levels, which are considered accurate biomarkers mirroring insulin resistance (Lotti 2019 et al; Corona G et al 2016). In the second part of the study, a subgroup of patients was evaluated with transvaginal CDU to investigate the uterine artery's vascular parameters. Only in the subset of post-menopausal women, we found similar results while showing that uterine PI independently associated to several cardiometabolic risk factors, including increased BMI and WC, but . In addition significantly higher uterine PI values were also observedin post-menopausal women affected by

obesity and MetS, when compared to non-obese or non-MetS women, respectively. A stepwise increase of uterine PI was also observed as a function of the increasing number of MetS parameters. These data suggest that uterine vascularization, which is easily explored by transvaginal CDU, is prone to specific changes caused by cardiometabolic disorders, as already observed in the clitoral district (Maseroli E et al, 2016). Therefore, uterine PI, as already proposed for clitoral PI, might be a mirror of CV health in women seeking medical care for sexual concerns, at least in the post-menopausal period. This is in line with previous studies conducted in women affected by PCOS, reporting that uterine PI was not only higher in overweight than in normal weight PCOS subjects, but it was also strongly correlated with the LDL- C/HDL-C ratio, a reliable predictor of CV risk (Battaglia C et al, 1996; Hollis B et al, 2003). Concerning lipid parameters, a close association between clitoral PI and triglyceride level, and between uterine PI and and HDL cholesterol werefound. Differences between the two study populations (PCOS vs. post- menopausal women) in terms of CV risk could account for the milder association that we observed in our study. However, similarly to what has beenobserved for clitoral PI, uterine PI appeared to be positively correlated to severalparameters linked to glucose homeostasis and insulin resistance, specifically fasting insulin, HbA1c and HOMA-IR. Similar results were reported in a retrospective study of 155 women with pre-gestational diabetes, in which a significant association emerged between uterine PI and HbA1c (Hollis B et al, 2003). Uterine CDU is already a widespread and workable diagnostic technique

in the obstetric and gynecological field (i.e.in pregnancy as an index of placental vascularization, in order to predict the risk of fetal growth restriction and pre-eclampsia (Gill RW et al, 2016; Campbell S et al, 1983). ore recently it has been highlighted as a tool to evaluate fertility outcomes in the field of assisted reproductive technology (ART) (Goswamy RK et al, 1988; Brosens I et al 2011). Indeed, an increased vascular resistance of the uterine artery has been correlated to a reduced endometrial flow and reduced success rate in ART outcomes (Koo HS et al 2016). Our work suggests a novel application of uterine CDU as an indirect, non-invasive evaluation of cardiometabolic profile, especially in the post-menopausal phase in the sexological setting.

In other districts, an increased PI was found to be directly related to micro-arteriosclerosis processes in the cerebral (Kidwell CS et al, 2001) and the renal (Petersen LJ et al, 1997) districts, as well as in the aforementioned uterus-placental one (Goswamy RK et al, 1988). Finally our study partially contributes to filling a gender gap in sexual medicine. It is well-established that CDU of penile arteries has a relevant role in identifying atherogenic ED and adverse CV and metabolic profiles in men (Rastrelli G et al, 2011, Rastrelli G et al, 2019). However, while preclinical evidence suggests that the same mechanisms underpin male and female genital arousal disorders in metabolic diseases. the impact of MetS-related endothelial dysfunction on male sexuality, in particular in the development of ED, is well established (Corona et al, 2014; Morelli A et al, 2019), while its role in women is likely milder, but also still under-investigated (Miner M et al, 2012). In a male rabbit model, high fat diet-induced

Mets was related to modifications of molecular markers underlying nitric-oxide-cGMP-mediated relaxant pathways in penile tissue, thus inducing ED (Corona et al, 2014 Morelli A et al, 2019).

Accordingly, relevant histomorphological alterations of the clitoris have been observed in diabetic women, as compared to non-diabetic ones (Tarcan T et al, 1999) with degeneration of smooth muscle cells being significantly correlated with CV risk (Miner M et al, 2012). In women, an increased content of collagen and a degeneration of smooth muscle cells was also found in the clitoral tissue of diabetic compared to non-diabetic subjects (Mazloomdoost D. et al., 2015). Interestingly, the degeneration of smooth muscle demonstrated by the histomorphometric analysis of 14 human autopsy clitories (Tarcan T. et al., 2015) was significantly correlated with cardiovascular risk. Our study further indicates a direct negative impact of MetS factors in the development of genito-pelvic arteriopathy in FSD women. Accordingly, an increased PI has been directly related to micro-arteriosclerosis processes in districts such as the cerebral (Kidwell CS. et al., 2001) and the renal (Petersen LJ et al., 1995) as well in the aforementioned uterus- placental one. However, preclinical studies aimed at exploring the molecular mechanisms underlying these vascular alterations are urgently needed.

When analyzing hormonal parameters, we did not find any correlation with the hemodynamic indices of clitoral or uterine arteries. Very few data are available on this topic. In PCOS patients, a positive association of uterine PI with DHEAS (Adali E et al., 2009) and testosterone (Chekir C. et al., 2005) have been

reported, whereas in patients with unexplained infertility and low endometrial perfusion of the implanted area not significant correlations were reported between flow indices and hormonal parameters, including FSH and progesterone levels (Uysal S et al., 2012). This finding already suggested that the altered uterine vascularization represent an hormonal-independent contributing factor for infertility (Uysal S et al., 2012).

In the present study, we found an inverse association between not only clitoral (Maseroli E et al, 2016), but also uterine PI, and several psychologic parameters, especially those related to dissatisfaction towards one's general body image and genital area. Clitoral and uterine PI correlated with body uneasiness explored by the global BUT-B and the PSDI (Positive Symptom Distress Index) score. A correlation between uterine PI and BUT-A Global Severity Index and subdomains Weight Phobia, Body Image Concerns, Avoidance, and Depersonalization was also observed. These data suggest that, in women with sexual symptoms, a worse metabolic profile may negatively influence one's body image, acting through a poor physical condition, as already observed in women with metabolic disorders. (Scaruffi E et al, 2019. Dalle Grave R et al, 2007). Moreover, subjects affected by metabolic disorders, are likely to reflect their idea of chronic illness on their body and on its self- perception, therefore suffering from body uneasiness symptoms (Scaruffi E et al., 2019; Castellini et al., 2019). Consistently, a study on PCOS women reported that body image played a central role in social and affective relationships, revealing a deep discomfort with respect to their body and an

attitude of anger, hostility and mistrust (Scaruffi E et al., 2019). This effect seems to depend on psychological factors related to body image, and not on weight loss itself (Dalle Grave R et al., 2007). In addition, a worse genito-pelvic haemodynamic function could result in an excessive focus on one's body, especially on those parts directly involved in the sexual response (Woertman L et al, 2012), such as the genitals.

Furthermore, clitoral PI increased as a function of the MHQ score related to somatized anxiety symptoms (MHQ-S). This observation is consistent with our previous work (Maseroli E et al, 2016), further suggesting that an increased vascular resistance (due to a dysfunctional vascular bed in subjects with an unfavorable metabolic profile) could lead to performance anxiety and body hypervigilance (Bradford A et al, 2006; Balercia G et al, 2007). Vice versa, the opposite may occur, with anxiety-mediated hyperactivation of the sympathetic nervous system (Hoehn-Saric R et al, 1988).

In contrast with our previous study (Maseroli E et al, 2016), no significant associations were observed between the clitoral PI and sexual function as assessed by the FSFI total and subdomain scores. Since the present data are representative of a much larger sample, they support the idea that the FSFI may not be an accurate tool to detect and ascertain the organic component(s) of FSD. Indeed, the use of psycho-sexual questionnaires instead of color Doppler ultrasound directly targeting the genital vascular district was hypothesized to be one of the main reasons accounting for the lack of conclusive clinical evidence on the association between CV and sexual health in women (Miner M et al,

2012). Interestingly, we might also speculate that vascular alterations may occur earlier than the sexual symptoms, or in any case before the disorder is perceived (McCall-Hosenfeld JS et al., 2008). In this perspective, in our population of women seeking medical care for sexual concerns, hemodynamic parameters, such as PI, might lead to the screening for vascular alterations, as compared with indirect, subjective measures such as the FSFI.

A recent review has put FSFI under the magnifying glass, outlining its fundamental usefulness but also highlighting some substantial limitations. As outlined in this paper, it would be critical to tailor the FSFI to sexually inactive patients, as well as important to modulate it based on different ethnicities, cultural groups, and sexual orientation. In addition, it would be essential to include a measure of distress to clinically diagnose sexual dysfunction, as defined by current standards (Meston CM et al, 2019. Scoring and Interpretation of the FSFI: What can be Learned From 20 Years of use?).

Our study presents several limitations. First of all, the sample is heterogeneous, composed of patients with different clinical, pharmacological and gynecological histories. Second, the study was conducted in women consulting for sexual symptoms, limiting the generalization of the results. In addition, CDU is a dynamic and operator-dependent method, and uterine CDU evaluation can be influenced by gynecological conditions such as fibrosis or adenomyosis. However, we set our CDU protocol by avoiding the vessels close to the uterine abnormalities. Furthermore, parameters related to the partner and the dyadic relationship were not included (Maseroli E et al, 2016b, Roslan NS et al, 2019).

Clinicians should assess sexual function concerning both partners and encompassing several dimensions like sexual satisfaction and perceived sexual interest in a patient's partner. This may involve an interdisciplinary approach. A meta-analysis and systematic review found an association between sexual dysfunction in men partnered with women with sexual problems, especially in the domains of erectile and ejaculatory function (Chew PY et al, 2021). Finally, we have to recognize the lack of a longitudinal analysis investigating changes in cardiometabolic risk factors and the lack of a healthy control group as important limitation.

6. Conclusions

In conclusion, increased vascular resistance, not only in clitoral but also in uterine arteries, is associated with cardiometabolic risk factors and body image concerns in women suffering from sexual symptoms. CDU of these genital districts may be thus proposed as an accessible method for the evaluation of cardiometabolic health in women counselling for sexual dysfunctions. If further confirmed in different populations of women, other than FSD ones, our data could suggest CDU, a common examination method widely used in gynecological practice, as a useful tool for an identification - and possible correction – of cardiometabolic risk factors. We could therefore suggest transvaginal CDU as a non-invasive method for the evaluation of women's cardiometabolic and sexual health. Since transvaginal ultrasound is a common examination method, widely used in gynecological practice as a diagnostic and screening tool in patients of all ages, many women may benefit of an early identification - and possible correction – of cardiometabolic risk factors. However, longitudinal studies are required to clarify whether increased clitoral and/or uterine artery PI may predict CV event.

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Table and Figure

Figure legends.

Figure 1. Differences in clitoral artery pulsatility index (PI) in women with FSD according to obesity (BMI≥ 30 kg/m2, panel A) and metabolic syndrome (MetS, panel B). Data were adjusted for age, years of menopause and smoking habit. BMI = body mass index.

Figure 2. Differences in uterine artery pulsatility index (PI) in women with FSD according to obesity (BMI≥ 30 kg/m^2, panel A), metabolic syndrome (panel B), high triglyceride levels (≥ 150 mg/dL or taking lipid lowering drugs, panel C), low HDL-C levels (< 50 mg/dL, or taking lipid lowering drugs, panel D), and abdominal obesity (waist circumference > 88 cm, panel E). Data were adjusted for age age, years of and smoking habit. FSD = Female Sexual Dysfunction. BMI = body mass index. MetS = metabolic syndrome. TG = triglycerides. HDL-C = high density lipoprotein cholesterol. WC = waist circumference.

Figure 3. Association between uterine artery pulsatility index (PI) and the number of individual components of the metabolic syndrome (MetS), based on NCEP- ATP III criteria. Data were adjusted for age, years since menopause and smoking habit.

	N=230 women
Clinical history	
Age (years)	43.1±12.9
Menopause, % (n)	49.9% (114)
Menopause, Surgical, % (n)	5.0% (6)
Stable relationship, % (n)	89.9% (207)
Current smoking habit, % (n)	19.0% (44)
Physical activity, % (n)	33.8% (78)
Parity, % (n)	14.3% (33)
Waist circumference (cm)	93.1±16.6
BMI (kg/m^2)	24.9±6.1
Cardiovascular diseases, % (n)	3.0% (7)
Diabetes mellitus, % (n)	4.3% (10)
Dyslipidemia, % (n)	15.8% (36)
Hypertension, % (n)	18.5% (43)
Specific medications	
Hypoglycemic drugs, % (n)	6.7% (15)
Lipid-lowering drugs, % (n)	5.8% (13)
Antihypertensive drugs, % (n)	15.4% (35)
Psychiatric drugs, % (n)	23.3% (53)
Urinary or gynecologic infections (actual or in the past 3 months), % (n)	56.5% (130)
Urinary or gynecologic diseases and infections (in the past), % (n)	52.2% (120)
Endometriosis, % (n)	6.1% (14)
PCOS, % (n)	5.5% (13)
Oral Contraception, % (n)	16.9% (39)
Hormonal Replacement Therapy, % (n)	9.2% (21)
Pelvic Surgery, % (n)	26.9% (62)
Breast Surgery, % (n)	8.6% (20)
Other Surgery , % (n)	30.0% (69)
Oncologic diseases, % (n)	11.7% (30)
Breast Cancer, % (n)	1.6% (4)
Psychiatric diseases, % (n)	33.3% (77)
Neurological diseases, % (n)	1.8% (4)
Metabolic parameters	
Systolic blood pressure (mm Hg)	120.00 [110.00-130.00]
Diastolic blood pressure (mm Hg)	75.00 [70.00-80.00]
Fasting glucose (g/L)	0.90±0.14
Fasting insulin (mU/L)	9.20±8.91
HbA1c (mmol/mol)	36.01±5.48
Total Cholesterol (mg/dl)	201.90±38.08
HDL Cholesterol (mg/dl)	63.65±15.59
LDL Cholesterol (mg/dl)	119.38±32.37
Triglycerides (mg/dl)	80.00 [60.25-112.00]
Psycho-sexual parameters	
FSFI Total score	20.6 [11.9 – 26.3]
FSFI Desire	2.4 [1.8 – 3.6]

FSFI Arousal	2.7 [1.5 – 4.5]
FSFI Lubrication	3.6 [1.5 – 5.4]
FSFI Orgasm	3.6 [1.2 – 5.2]
FSFI Satisfaction	3.6 [2.0 – 5.2]
FSFI Pain	3.6 [1.2 – 6.0]
FSFI pathological total score % (n)	92.2% (212)
MHQ Total score	35.5 [26.0 – 46.0]
FSDS-R score	19.0 [7.0 - 33.0]
FSDS-R pathological score % (n)	64.8% (149)
FSFI and FSDS-R pathological scores % (n)	58.3% (134)
BUT-A global severity index (GSI)	0.7 [0.4 – 1.5]
BUT-A weight phobia (WP)	1.1 [0.5 – 2.4]
BUT-A body image concern (BIC)	1.0 [0.5 – 1.9]
BUT-A avoidance (AV)	0.2 [0.0 – 0.8]
BUT-A compulsive self-monitoring (CSM)	0.6 [0.2 – 1.2]
BUT-A depersonalization (DEP)	0.3 [0.0 – 0.8]
BUT-B positive symptom Total (PST)	9.0 [5.0 – 17.0]
BUT-B positive symptom distress index (PSDI)	2.0 [1.6 – 1.8]
CDU parameters	
Clitoral PI	1.6±07

Table 1. Baseline characteristics of the sample (N=230): clinical history, metabolic parameters, psycho-sexual parameters and CDU parameters. Data are expressed as mean ± SD when normally distributed, median (quartile) when not normally distributed, and percentage when categorical.

BMI= body mass index. Hba1c= glycated hemoglobin. HDL= high-density lipoprotein. LDL= low-density lipoprotein. PCOS= polycystic ovary syndrome. CDU = color Doppler ultrasound. PI = pulsatility index.

	Total sample N=230	Post-menopausal N=114	Pre-menopausal N=116	P
Clinical history				
Age (years)	43.1±12.9	55.9±7.1	35.4±9.0	**<0.0001**
Menopause, % (n)	49.9% (114)	-	-	-
Menopause, Surgical, % (n)	5.0% (6)	-	-	-
Stable relationship, % (n)	89.9% (207)	87.5% (96)	89.3% (107)	0.674
Current smoking habit, % (n)	19.0% (44)	20.0% (22)	15.0% (18)	0.378
Physical activity, % (n)	33.8% (78)	43.8% (48)	43.0% (52)	1.000
Parity, % (n)	14.3% (33)	72.0% (79)	45.0% (54)	**0.026**
Waist circumference (cm)	93.1±16.6	96.1±14.57	91.55±17.91	0.059
BMI (kg/m^2)	24.9±6.1	25.8±5.55	24.42±6.60	0.084
Cardiovascular diseases, % (n)	3.0% (7)	2.9% (3)	3.0% (4)	1.000
Diabetes mellitus, % (n)	4.3% (10)	5.8% (6)	4.1% (5)	1.000
Dyslipidemia, % (n)	15.8% (36)	19% (17)	7% (8)	**0.004**
Hypertension, % (n)	18.5% (43)	24.3% (27)	6% (7)	**<0.0001**
Specific medications				
Hypoglycemic drugs, % (n)	6.7% (15)	8.3% (9)	5.4%(6)	1.000
Lipid-lowering drugs, % (n)	5.8% (13)	10.2% (11)	1.5%(2)	**0.006**
Antihypertensive drugs, % (n)	15.4% (35)	27.8% (30)	5.4%(5)	**<0.0001**
Psychiatric drugs, % (n)	23.3% (53)	25% (27)	24.2%(26)	0.757
Urinary or gynecologic infections (actual or in the past 3 months), % (n)	56.5% (130)	25% (27)	32.8%(103)	0.308
Urinary or gynecologic diseases and infections (in the past), % (n)	52.2% (120)	51.9% (59)	50.8% (61)	0.785
Endometriosis, % (n)	6.1% (14)	2.9% (3)	6.6% (9)	0.234
PCOS, % (n)	5.5% (13)	1.0% (1)	7.4% (12)	**0.023**
Oral Contraception, % (n)	16.9% (39)	0%	32.5% (39)	**<0.0001**
Hormonal Replacement Therapy, % (n)	9.2% (21)	19.1% (21)	0%	**0.003**
Pelvic Surgery, % (n)	26.9% (62)	41.3% (45)	21% (17)	**0.001**
Breast Surgery, % (n)	8.6% (20)	15.7% (17)	5% (3)	**0.012**
Other Surgery, % (n)	30.0% (69)	49.1% (54)	35.4% (15)	0.059
Oncologic diseases, % (n)	11.7% (30)	24.8% (27)	2.5% (3)	**<0.0001**
Breast Cancer, % (n)	1.6% (4)	3.7% (3)	1.0% (1)	**<0.0001**
Psychiatric diseases, % (n)	33.3% (77)	34.3% (37)	33.3% (40)	0.390
Neurological diseases, % (n)	1.8% (4)	5.6% (3)	0.9% (1)	0.065
Metabolic parameters				
Systolic blood pressure (mm Hg)	120.00 [110.00-130.00]	125.00 [95.00-170.00]	117.50 [89.00-160.00]	**0.001**
Diastolic blood pressure (mm Hg)	75.00 [70.00-80.00]	79.50 [55.00-105.00]	50.00 [70.00-100.00]	0.067
Fasting glucose (g/L)	0.90±0.14	0.95±0.24	0.90±0.23	0.096
Fasting insulin (mU/L)	9.20±8.91	9.75±7.67	10.47±10.60	0.671
HbA1c (mmol/mol)	36.01±5.48	37.97±7.47	35.06±6.25	**0.013**
Total Cholesterol (mg/dl)	201.90±38.08	218.19±36.72	192.81±34.75	**<0.0001**
HDL Cholesterol (mg/dl)	63.65±15.59	66.42±18.21	62.79±16.17	0.135
LDL Cholesterol (mg/dl)	119.38±32.37	130.61±32.15	112.96±29.12	**<0.0001**
Triglycerides (mg/dl)	80.00 [60.25-112.00]	90.00 [66.00-126.50]	70.50 [55.00-107.50]	**0.002**

Supplementary Table 1a. Baseline characteristics of the sample (N=230), considered as a whole or after stratification according to the menopausal status: clinical history and metabolic parameters. Data are expressed as mean ± SD when normally distributed, median (quartile) when not normally distributed, and percentage when categorical. P values are derived from multivariate analysis, after adjusting for age. Bold indicates statistically significant difference ($p < 0.038$) between the 2 group.

BMI= body mass index. Hba1c= glycated hemoglobin. HDL= high-density lipoprotein. LDL= low-density lipoprotein. PCOS= polycystic ovary syndrome.

	Total sample N=230	Post-menopausal N=114	Pre-menopausal N=116	P
Psycho-sexual parameters				
FSFI Total score	20.6 [11.9 – 26.3]	18.5 [11.2 – 24.7]	22.4 [12.5 – 28.3]	**0.034**
FSFI Desire	2.4 [1.8 – 3.6]	2.4 [1.2– 3.0]	2.4 [1.8 – 4.2]	**0.001**
FSFI Arousal	2.7 [1.5 – 4.5]	2.7 [1.5–4.2]	3.3 [1.8 – 4.8]	0.113
FSFI Lubrication	3.6 [1.5 – 5.4]	3.3 [1.3 – 4.7]	4.2 [1.9– 5.6]	0.017
FSFI Orgasm	3.6 [1.2 – 5.2]	3.2 [1.6 – 4.7]	3.2 [1.2 – 5.2]	0.859
FSFI Satisfaction	3.6 [2.0 – 5.2]	3.6 [1.2 – 5.1]	3.8 [2.0 – 5.2]	0.161
FSFI Pain	3.6 [1.2 – 6.0]	3.6 [1.8 – 0.6]	3.6 [1.6 – 6.0]	0.071
FSFI pathological total score % (n)	92.2% (212)	91.2% (104)	93.1% (108)	**0.014**
MHQ Total score	35.5 [26.0 – 46.0]	38.0 [29.0 – 49.0]	37.0 [27.0 – 46.0]	0.223
FSDS-R score	19.0 [7.0 - 33.0]	25.5 [12.0 – 36.2]	21.0 [7.0 – 33.0]	0.146
FSDS-R pathological score % (n)	64.8% (149)	61.4% (70)	68.1% (79)	0.232
FSFI and FSDS-R pathological scores % (n)	58.3% (134)	56.1% (64)	60.3% (70)	0.866
BUT-A global severity index (GSI)	0.7 [0.4 – 1.5]	0.8 [0.4 – 1.6]	0.8 [0.3 – 1.8]	0.882
BUT-A weight phobia (WP)	1.1 [0.5 – 2.4]	1.1 [0.8 – 2.3]	1.1 [0.6 – 2.4]	0.779
BUT-A body image concern (BIC)	1.0 [0.5 – 1.9]	1.0 [0.5 – 2.0]	1.0 [0.4 – 2.2]	0.583
BUT-A avoidance (AV)	0.2 [0.0 – 0.8]	0.3 [0.0 – 1.1]	0.2 [0.0 – 0.8]	0.183
BUT-A compulsive self-monitoring (CSM)	0.6 [0.2 – 1.2]	0.6 [0.4 – 1.1]	0.8 [0.2 – 1.4]	0.436
BUT-A depersonalization (DEP)	0.3 [0.0 – 0.8]	0.3 [0.0 – 0.8]	0.3 [0.0 – 0.9]	0.573
BUT-B positive symptom Total (PST)	9.0 [5.0 – 17.0]	8.0 [5.0 – 17.0]	9.5 [7.0 – 16.0]	0.469
BUT-B positive symptom distress index (PSDI)	2.0 [1.6 – 1.8]	2.0 [1.4 – 3.1]	2.0 [1.6 – 1.8]	0.906
CDU parameters				
Clitoral PI	1.6±0.7	1.7±0.8	1.5±0.6	0.767

Supplementary Table 1b. Baseline characteristics of the sample according to post- vs. pre-menopausal status: psycho-sexual parameters. Data are expressed as median (quartile). P values are derived from multivariate analysis, after adjusting for age. Bold indicates statistically significant difference (P < 0.038) between the 2 groups.

BUT= Body Uneasiness Test. FSDS-R= Female Sexual Distress Scale-Revised. FSFI= Female Sexual Function Index. MHQ= Middlesex Hospital Questionnaire. CDU= color Doppler ultrasound. PI= pulsatility index.

	Clitoral PI			
	Univariate analysis		Multivariate analysis*	
	Pearson's r	P	β	P
Clinical and metabolic parameters				
BMI (kg/m2)	0.200	**0.002**	0.215	**0.004**
Waist circumference (cm)	0.214	**0.003**	0.240	**0.004**
SBP (mm Hg)	0.142	0.043	1.055	0.293
DBP (mm Hg)	0.011	0.876	-0.052	0.533
Fasting glycemia (g/L)	0.062	0.380	0.056	0.490
Total cholesterol (mg/dL)	0.121	0.085	0.163	0.069
HDL cholesterol (mg/dL)	-0.045	0.519	-0.088	0.285
Triglycerides (mg/dL)	0.191	**0.006**	0.220	**0.006**
LDL cholesterol (mg/dL)	0.109	0.129	0.157	0.068
Fasting insulin (mU/L)	0.193	**0.027**	0.233	**0.029**
HOMA-IR (units)	0.199	**0.033**	0.293	**0.009**
HbA1c (mmol/mol)	0.009	0.909	-0.031	0.753
Psychological parameters				
MHQ Total Score	0.082	0.282	0.129	0.123
MHQ Free-floating anxiety symptoms	0.040	0.597	0.084	0.312
MHQ Phobic anxiety symptoms	0.058	0.443	0.071	0.394
MHQ Obsessive-compulsive	0.027	0.722	0.070	0.401
MHQ Somatized anxiety symptoms	0.176	**0.021**	0.217	**0.010**
MHQ Depressive symptoms	0.096	0.206	0.142	0.090
MHQ Hysterical symptoms	-0.019	0.802	-0.004	0.961
BUT-A global severity index (GSI)	-0.048	0.536	0.008	0.923
BUT-A weight phobia (WP)	-0.067	0.392	0.004	0.967
BUT-A body image concern (BIC)	0.006	0.941	0.065	0.458
BUT-A avoidance (AV)	-0.044	0.573	-0.038	0.666
BUT-A compulsive self-monitoring (CSM)	-0.102	0.189	-0.050	0.564
BUT-A depersonalization (DEP)	-0.053	0.500	-0.016	0.859
BUT-B positive symptom distress index (PSDI)	0.155	0.050	0.225	**0.010**
BUT-B positive symptom Total (PST)	-0.068	0.396	-0.066	0.461

Table 2. Associations between clitoral pulsatility index (PI) and metabolic and psychological parameters (n=230). *Data adjusted for age, smoking habit, and years since menopause. After 10% False Discovery Rate calculation, the cut-off for significant p-value was adjusted at <0.038.

BMI= body mass index. SBP= systolic blood pressure. DBP= diastolic blood pressure; HDL= high-density lipoprotein. LDL= low-density lipoprotein. HOMA-IR= homeostasis model assessment - insulin resistance. HbA1c= glycated hemoglobin. MHQ= Middlesex Hospital Questionnaire. BUT= Body Uneasiness Test

	Total sample (subgroup) N= 164	Post-menopausal N=65	Pre-menopausal N=99	P
Clinical history				
Age (years)	46.1±12.9	55.5±7.4	35.1±8.7	**<0.0001**
Menopause, % (n)	39.1% (65)	-	-	-
Menopause, Surgical, % (n)	2.9% (5)	-	-	-
Stable relationship, % (n)	89.9% (147)	90.5% (59)	86.6% (86)	1.000
Current smoking habit, % (n)	19% (31)	27.3% (18)	13.7% (14)	0.043
Physical activity, % (n)	32.4% (53)	27.1% (17)	36.2% (36)	0.860
Parity, % (n)	51% (83)	73.8% (48)	36% (36)	**<0.0001**
Waist circumference (cm)	93.15±16.65	96.4±14.74	90.8±17.62	0.053
BMI (kg/m²)	24.97±6.15	25.8±5.65	24.4±6.42	0.157
Cardiovascular diseases, % (n)	3.0% (5)	3.1% (2)	3.0% (3)	1.000
Diabetes mellitus, % (n)	4.3% (7)	5.1%(4)	3.1% (3)	0.705
Dyslipidemia, % (n)	10.4% (17)	17.2% (11)	6.0% (6)	**0.034**
Hypertension, % (n)	12.8% (21)	25.0% (16)	5.0% (5)	**<0.0001**
Specific medications				
Hypoglycemic drugs % (n)	8.3% (14)	11.4% (8)	6.3% (6)	0.250
Lipid-lowering drugs % (n)	11.1% (18)	22.2% (14)	3.2% (4)	**0.004**
Antihypertensive drugs % (n)	17.8% (29)	28.3% (19)	9.3% (10)	**<0.0001**
Psychiatric drugs % (n)	25.0% (41)	27.4% (18)	24.5% (24)	0.173
Urinary or gynecologic infections (actual or in the past 3 months), % (n)	32.7% (53)	27.7% (17)	36% (36)	0.310
Urinary or gynecologic diseases and infections (in the past), % (n)	56.5% (93)	59.0% (38)	55.0% (54)	0.628
Endometriosis, % (n)	6.1% (10)	3.2% (2)	8.0% (8)	0.319
PCOS, % (n)	5.5% (9)	1.6% (1)	7.9% (8)	0.156
Oral Contraception, % (n)	16.2% (27)	-	-	-
Hormonal Replacement Therapy, % (n)	5.8% (9)	-	-	-
Pelvic Surgery, % (n)	25.3% (41)	31.3% (20)	21.4% (21)	0.196
Breast Surgery, % (n)	11.9% (19)	24.2% (15)	4.1% (4)	**<0.0001**
Other Surgery, % (n)	44.4% (73)	50.8% (50)	39.4% (23)	0.200
Psychiatric diseases, % (n)	27.4% (45)	34.0% (22)	23.0% (23)	0.177
Neurological diseases, % (n)	1.5% (3)	1.6% (1)	2.0% (2)	1.000
Metabolic parameters				
Systolic blood pressure (mm Hg)	120.00 [110.00-130.00]	125.00 [110.00-135.00]	110.00 [110.00-125.00]	**0.002**
Diastolic blood pressure (mm Hg)	75.00 [70.00-80.00]	80.00 [70.00-80.00]	65.00 [70.00-80.00]	**0.034**
Fasting glucose (g/L)	0.93±0.16	0.93±0.11	0.87±0.16	**0.014**
Fasting insulin (mU/L)	9.20±8.91	8.92±6.95	9.29±10.05	0.842
HbA1c (mmol/mol)	35.03±5.26	37.18±4.40	34.93±6.09	**0.033**
Total Cholesterol (mg/dl)	204.90±38.11	217.72±35.68	190.72±35.75	**<0.0001**
HDL Cholesterol (mg/dl)	64.63±15.61	65.66±17.35	62.42±14.20	0.215
LDL Cholesterol (mg/dl)	121.22±25.47	131.21±31.96	111.60±30.20	**<0.0001**
Tryglicerides (mg/dl)	81.00 [60.00-112.00]	94.00 [68.00-121.00]	70.50 [55.00-99.75]	**0.007**
Psycho-sexual parameters				
FSFI Total score	18.8 [10.8 - 25.1]	18.5 [11.2 - 24.7]	22.6 [13.4 - 28.5]	0.053
FSFI Desire	2.4 [1.2 – 3.6]	2.4 [1.20-3.00]	2.4 [1.95-4.20]	**0.005**
FSFI Arousal	2.7 [1.2 – 4.2]	2.7[1.5 -4.45]	3.3 [1.8– 4.8]	0.081

Supplementary Table 2. Baseline characteristics of the subgroup of patients (N=164) on

which transvaginal color Doppler ultrasound (CDU) with evaluation of uterine artery pulsatility index (PI) was performed, considered as a whole or after stratification according to the menopausal status: clinical history, metabolic parameters, and psycho-sexual parameters. Data are expressed as mean ± SD when normally distributed, median (quartile) when not normally distributed, and percentage when categorical. P values are derived from multivariate analysis, after adjusting for age. Bold indicates statistically significant difference ($P < 0.038$)between the 2 groups.

BMI= body mass index. BUT= Body Uneasiness Test. FSDS-R= Female Sexual Distress Scale-Revised. FSFI= Female Sexual Function Index. Hba1c= glycated hemoglobin.HDL= high-density lipoprotein. LDL= low-density lipoprotein. MHQ= Middlesex Hospital Questionnaire. PCOS= polycystic ovary syndrome. CDU= color Doppler ultrasound. PI= pulsatility index.

	Uterine PI (in menopausal women)			
	Univariate analysis		Multivariate analysis*	
	Pearson's r	**P**	β	**P**
Clinical and metabolic parameters				
BMI (kg/m^2)	0.526	**<0.0001**	0.511	**<0.0001**
Waist circumference (cm)	0.491	**<0.0001**	0.474	**0.001**
SBP (mm Hg)	0.091	0.485	0.083	0.578
DBP (mm Hg)	-0.107	0.413	-0.016	0.918
Fasting glycemia (g/L)	0.197	0.165	0.189	0.211
Total Cholesterol (mg/dL)	0.120	0.390	0.055	0.721
HDL Cholesterol (mg/dL)	-0.250	0.074	-0.260	0.088
Triglycerides (mg/dL)	0.181	0.203	0.202	0.192
LDL Cholesterol (mg/dL)	0.181	0.213	0.098	0.538
Fasting insulin (mUI/L)	0.416	0.018	0.481	**0.006**
HOMA-IR index	0.425	0.019	0.494	0.009
HbA1c (mmol/mol)	0.448	**0.003**	0.564	**<0.0001**
Psychological parameters				
MHQ Total score	-0.031	0.841	0.089	0.618
BUT-A global severity index (GSI)	0.436	**0.003**	0.652	**<0.0001**
BUT-A weight phobia (WP)	0.314	0.038	0.543	**0.001**
BUT-A body image concern (BIC)	0.531	**<0.0001**	0.669	**<0.0001**
BUT-A avoidance (AV)	0.361	0.016	0.569	**0.001**
BUT-A compulsive self-monitoring (CSM)	0.070	0.653	0.185	0.270
BUT-A depersonalization (DEP)	0.430	**0.004**	0.684	**<0.0001**
BUT-B positive symptom distress index (PSDI)	0.414	**0.006**	0.518	**0.001**
BUT-B positive symptom Total (PST)	0.095	0.548	0.271	0.131

Table 3. Associations between uterine pulsatility index (PI) and metabolic and psychological parameters in menopausal patients (N=65). *Data adjusted for age, smoking habit, and years since menopause. After 10% False Discovery Rate calculation, the cut-off for significant p-value was adjusted at <0.038.

BMI = body mass index; BUT = Body Uneasiness Test; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment - insulin resistance; LDL = low-density lipoprotein; MHQ = Middlesex Hospital Questionnaire; PI
= pulsatility index.

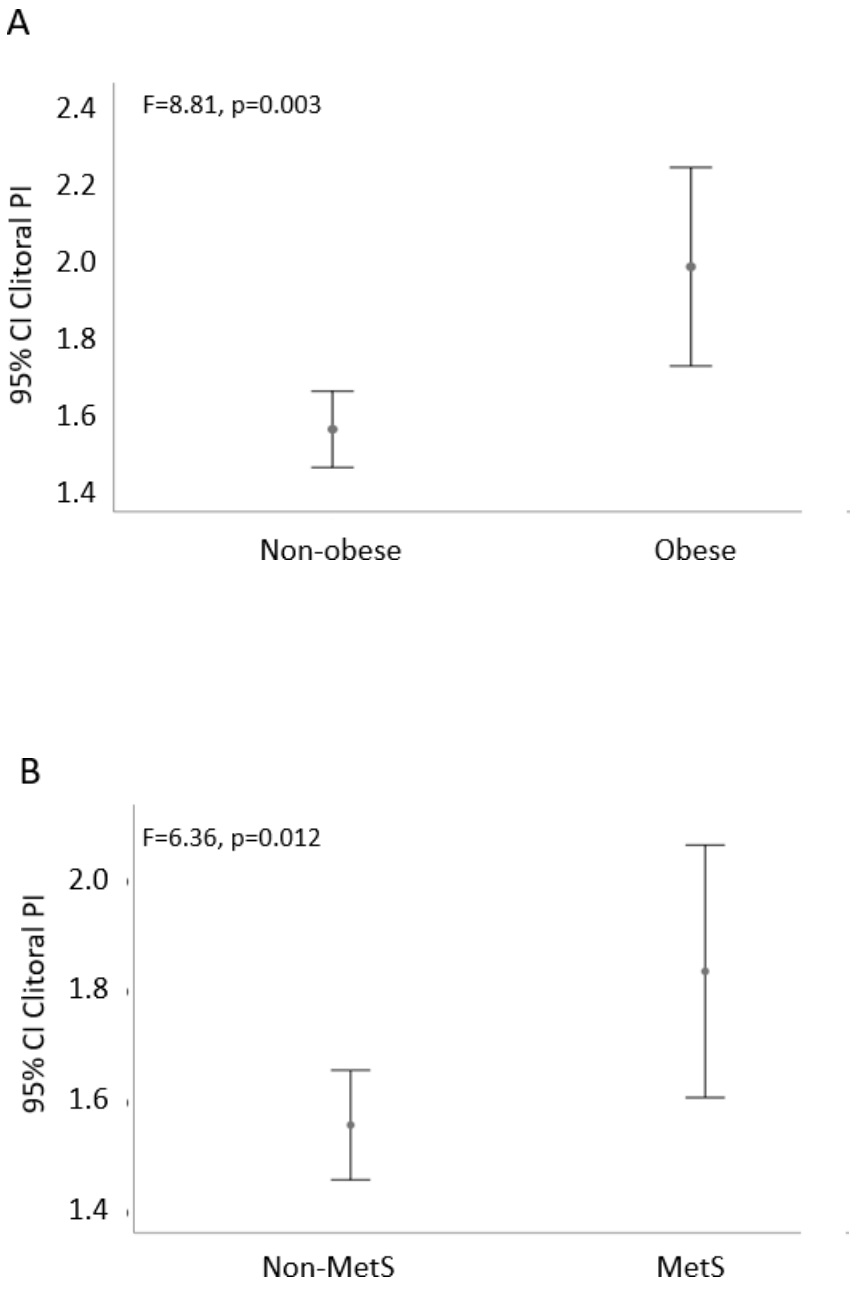
A
F=8.81, p=0.003
95% CI Clitoral PI
2.4
2.2
2.0
1.8
1.6
1.4
Non-obese
Obese
B
F=6.36, p=0.012
95% CI Clitoral PI
2.0
1.8
1.6
1.4
Non-MetS
MetS

Fig 1

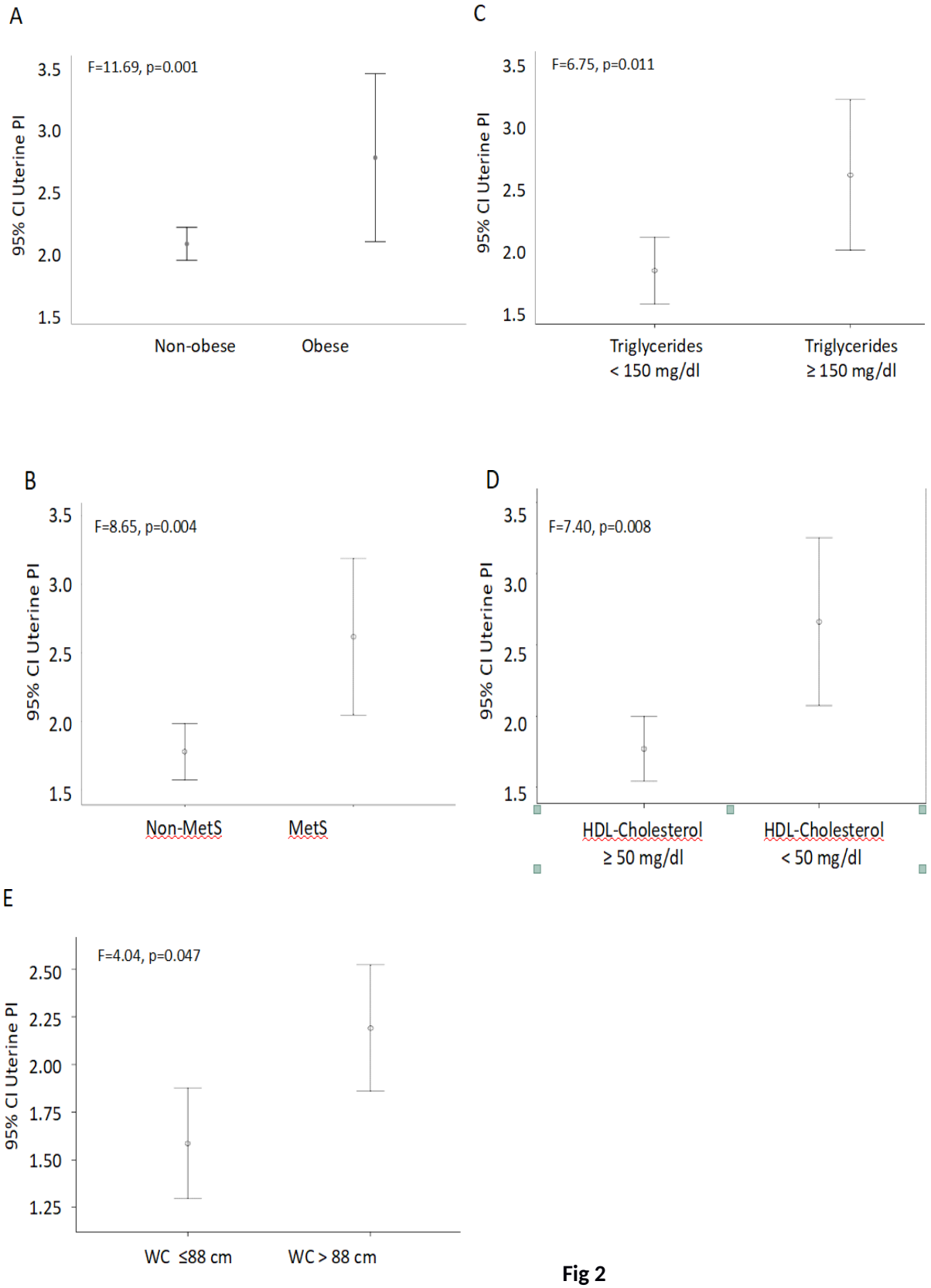
A
F=11.69, p=0.001
95% CI Uterine PI
3.5
3.0
2.5
2.0
1.5
Non-obese
Obese
C
F=6.75, p=0.011
95% CI Uterine PI
3.5
3.0
2.5
2.0
1.5
Triglycerides
< 150 mg/dl
Triglycerides
≥ 150 mg/dl
B
F=8.65, p=0.004
95% CI Uterine PI
3.5
3.0
2.5
2.0
1.5
Non-MetS
MetS
D
F=7.40, p=0.008
95% CI Uterine PI
3.5
3.0
2.5
2.0
1.5
HDL-Cholesterol
≥ 50 mg/dl
HDL-Cholesterol
< 50 mg/dl
E
F=4.04, p=0.047
95% CI Uterine PI
2.50
2.25
2.00
1.75
1.50
1.25
WC ≤88 cm
WC > 88 cm

Fig 2

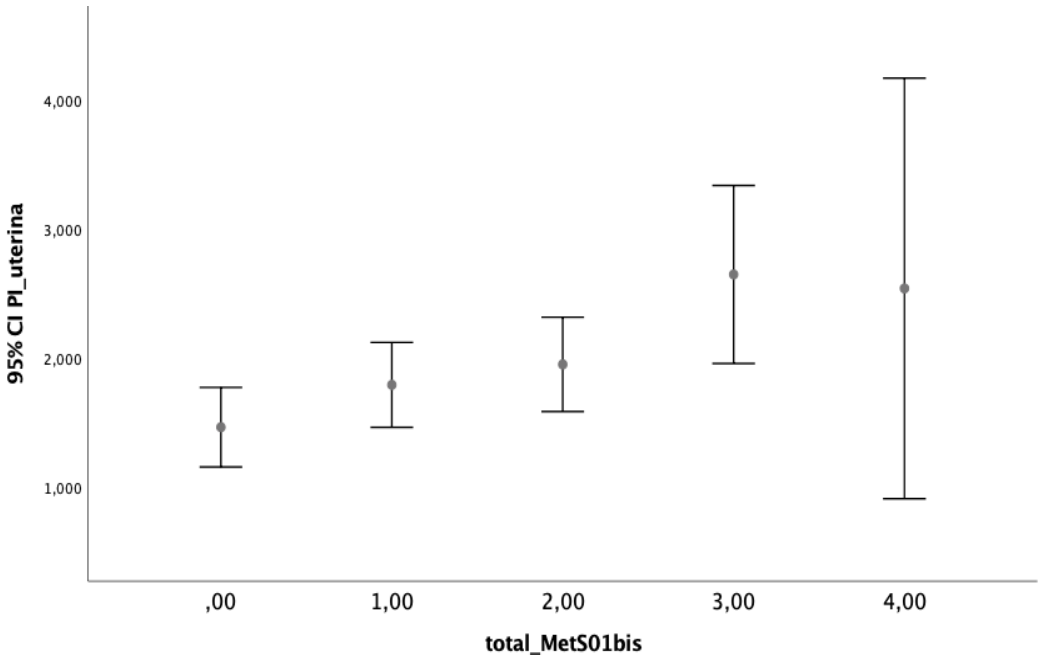
95% CI PI_uterina
4,000
3,000
2,000
1,000
,00
1,00
2,00
3,00
4,00
total_MetS01bis

Fig 3

Ringraziamenti

Per mia fortuna ho l'onore nella vita di poter dire tanti "grazie", di vivere dell'amore e del sostegno di tante persone, tasselli di questo disegno.

La mia famiglia, sempre e per sempre dalla mia parte, in ogni modo possibile, ma sempre nei modi di cui ho bisogno. Senza di loro nulla esisterebbe.

La mia "famiglia lavorativa" che mi ha "adottata", arricchita, spronata, cresciuta.

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Ringrazio mia figlia, la mia tenace, dolce, sensibile, splendida bambina.
Perché il sacrificio di questi anni è stato per primo il suo: cedere il tempo a lei dedicato ad un progetto che spero la renda sempre fiera di questa mamma…che si sveglia ogni mattina sperando di poter fare del proprio meglio, e si addormenta ogni sera con la certezza di non esserci completamente riuscita.

Ad Aurora

«Quando mio figlio mi tiene per mano, ogni strada del mondo è la strada giusta»