Novel approach for management of clitorial vascular insufficiency and sexual dysfunction

Objective

To objectively diagnose patients with sexual dysfunction by using clitorial vascular Doppler measures and investigate the effect of platelet rich plasma injection (PRP) on clitoral artery blood flow and sexual response in women with sexual disorders (FSD).

**Introduction**

 Female sexual dysfunction (FSD) is defined as disorders of libido, arousal, orgasm, and sexual pain that lead to personal distress or interpersonal difficulties. It is a common problem, affecting 30–78% of women. Sexual dysfunction can have a major impact on quality of life in women. Impaired sexual function can have damaging effects on the self‑esteem, sense of wholeness and interpersonal relationships of women. If female sexuality is disturbed, this may lead to familial discord and divorce . Treatment of FSD is complicated by the lack of a single causative factor, limited proven treatment options, overlap of different types of dysfunction, and limited availability of treatment. Therefore, there was a need for further research in this area [1].

Since the first anatomical description of the clitoris, there has been an active search for objective tools to assess its function and role in female sexual response. The clitoral artery Doppler is now used as an objective tool in evaluation orgasmic dysfunction among sexually active women. Although there have been few reports on the use of this approach, some studies have used clitoral artery Doppler to measure changes due to drug treatment. (2-9) or differences under certain circumstances: stage of the menstrual cycle, weight gain and obesity, alcohol consumption, sclerosis, high-performance sport, or pregnancy. (10- 15) However, a range of different terms have been used to describe the clitoral Doppler methods, and the actual location of measurement and procedure used is unclear in many reports. (2,3,5,7,13,14,16)

Battaglia et al (14) assessed various parameters during the menstrual cycle, including clitoral blood flow, also were the first to find that PI in clitoral arteries, as assessed by CDU, was significantly higher in heavy smokers as compared with nonsmoking women. This finding suggests that unhealthy lifestyle factors may contribute to alterations in the stiffness of female clitoral blood vessels. They described a different procedure to that reported by Khalifé et al (17) in which echography is performed in a sagittal section that measures the body of the clitoris, just before the bend (or clitoral raphe).

A study conducted on 90 healthy volunteers assesed clitoral artery Doppler by using the sagittal section approach described by Battaglia et al in 2008 calculated peak systolic velocity (PSV), time-averaged maximum velocity, time-averaged mean velocity, end-diastolic velocity, pulsatility index, resistance index, and volume flow (v-flow) in all groups. After calculating intraobserver, interobserver, and intraobserver intersession variability and reliability for all Doppler parameters they found that clitorial artery volume flow (v-flow) is a new validated, reliable, and promising parameter which could be useful for assessing clitoral blood flow. (18)

Platelet-rich plasma (PRP) treatment aims to increase the self-healing ability of the human body by increasing neovascularization and collagen formation through the effect of high concentration autologous growth factors administered to the tissue. The most important advantages are in being autologous and reliable. Studies have demonstrated that PRP induces regrowth of new tissue by activation of pluripotent stem cells that are indigenous to most parts of the body. These cells are capable of differentiating into several tissue types, when stimulated by growth factors produced by activated platelets. (19) When PRP is activated by adding calcium chloride, and injected in to the anatomic areas such as clitoris; pubo-cervical fascia; G spot; Skene’s glands, then growth factors may cause differentiation of pluripotent stem cells resulting in neo-angiogenesis, fibroblast growth, and neuronal growth, improving physiologic responsiveness. PRP is non-antigenic and contains no synthetic agents that could cause unwanted local or systemic reaction. (20) Improved vascularity and neuronal regrowth in the vagina and clitoral area could restore or possibly enhance sexual responsiveness and sensitivity by increasing blood flow to the area. In addition to increased blood flow, collagen and sensory nerve regrowth might relieve coital discomfort as well as enhance vaginal sensitivity.  Also, increased blood flow in the clitoris, if induced by PRP injections, could also lead to improved arousal and orgasm. (19)

We firstly use a questionnaire among women attending our clinic to evaluate sexual satisfaction abnormalities and confirm diagnosis by using clitorial artery doppler measures. Then we recruit these women with sexual disorders diagnosed by abnormal clitorial vascularity to assess the effect of PRP injection on both clitoral artery blood flow and sexual cycle response.

Patient and Method

 This cross-sectional study evaluates the function of the dorsal clitoral artery through the spectral wave analysis of color Doppler ultrasonography (US) in 20 women diagnosed with FSD according to Female sexual function index questionnaire (FSFI) and 20 healthy controls. By comparing blood flow of the dorsal clitoral artery in women diagnosed with female sexual dysfunction (FSD) and in healthy controls using color Doppler ultrasonography, we hypothesize that women with FSD will have a restricted blood flow compared to controls. Therefore, these patients will undergo clitorial platelet rich plasma (prp) and will be evaluated again by clitorial artery Doppler measures and female sexual function index questionnaire 4-12 weeks after receiving treatment.

Female sexual function index questionnaire (FSFI), and the Female Sexual Distress Scale Revised (FSDS-R) (24,25) which include questions on six topics, that is, sexual desire, arousal, lubrication, orgasm, satisfaction, and pain, are applied on all women fulfilling the study inclusion criteria and attending gynecological clinic at the Egyptian National Research Center during the period spanning from April 2024 to September 2024 ; The study is approved by the ethical committee of the center. All patients with FSD are initially assessed for local and general gynecological and psychological problems at the gynecology and psychiatric clinic, respectively, and any suspected case is excluded from our clinical trial. An informed consent is required from all participants.

Assessment is performed by an assessor blinded to participant diagnosis, in the morning after a 10-min rest period in a supine lying position in a room with temperature set at 22 °C. Measurements of clitorial artery peak systolic velocity (PSV), the end diastolic velocity (EDV), the resistance index (RI = PSV − EDV/PSV), and the pulsatility index (PI = PSV − EDV/mean flow velocity of clitoral artery peak systolic velocity (PSV), and volume flow (v-flow) at baseline, after one and three months of PRP by using the sagittal section approach described by Battaglia et al in 2008.(14,16) Ultrasound was performed using a vulson p8 with a convex 2d /4d transducer by the same investigator. Each woman was scanned in the gynecological position. The Doppler convex probe was placed sagittally on the clitoris at an angle of <20 degrees, without exerting any significant pressure on the tissues. After identifying the clitoral artery using color flow mapping, the Doppler probe was positioned over the vessel and at least three sequential Doppler waveforms were obtained.

The women included in our study have a stable, satisfying heterosexual relationship for at least 6 months, they are not paid either to receive the procedure or to complete the survey.  All patients will be fully informed of the innovative therapeutic and experimental nature of the localized PRP injection and consented to the procedure.

Blood samples were obtained from all study participants to measure hormonal levels of total T, FT, TSH, FSH and PRL.

Two standardized tests to monitor the effects of these procedures on sexual function are employed. The FSFI questionnaire measures arousal, desire, pain, orgasm, satisfaction, and lubrication. (21) The FSDS-R questionnaire measures sexually related distress in Females With Sexual Dysfunction (FSD). (22) The FSFI and the FSDS-R are administered before and after the procedure by the patient. Data is obtained at the time of application of this procedure and at 4-12 weeks after receiving treatment. The outcomes measured are the improvement in clitorial vascular measures and the patients’ responses to the FSDS-R and FSFI surveys prior to and after receiving the intervention.

**Inclusion criteria:**

The inclusion criteria will be as follows: -

* Female in reproductive age group between 18- 45 years old.
* Normal haemoglobin level.
* Normal prolactin, thyroid hormones level.
* Normal testosterone level.

**Exclusion criteria:**

The exclusion criteria will be: -

* History of hypertension, coronary artery disease, or thromboembolic disorder.
* History of impaired hepatic and renal function.
* History of pituitary adenoma and diabetes.
* History of smoking and alcohol abuse.
* Patients who did not have a sexual partner, or had a partner with sexual dysfunction
* Patients who had sexual dysfunction like vaginismus and dyspareunia
* Current use of oral contraception or had received any hormonal medications for at least 3 months before the start of the study.
* Patients who were pregnant during study duration
* Patients who suffer from any mental or psychological disorders

There is no consensus in the literature about how many times and how often PRP administrations should be performed, Runels et al. made one single application for sexual dysfunction and they expressed positive results. (19) In a previous study by sukjen et al (23), performed four administrations, and found a significant change in total and all subdomains of FSDI after the first application. As the repetitions of the application increased, the acceleration of the positive effect decreased, but the increase continued. Therefore, the frequency of PRP and the number of repetitions can be planned according to the patient’s condition.

Firstly, the clitoral hood will be retracted and anesthetic cream (lidocaine 5%) will be applied to the clitoris and anterior vaginal wall. Delaying the PRP injection for 20 minutes after anesthetic application achieved complete or near complete analgesia for the procedure. 15 cm blood was obtained from the arm by a 20 cm wide pore syringe and transferred into a sterile specific PRP tube (Ycellbio) containing 1,5 cm sodium citrate as anticoagulant; it was centrifuged for PRP preparation. PRP was prepared by the two-spin method; the first spin was at 2500 rpm for 3 min, and the second spin was at 4000 rpm for 15 min. PRP was obtained by gentle manipulation without shaking the tube. One of either of two FDA-approved, proprietary collection systems is used according to the standard recommendations for each system: (1) Regen® or (2) TruPRP® [150,160]. Both systems use centrifugation to separate and concentrate PRP. The TruPRP® system concentrates 5 ml of PRP from 60 ml of whole blood using a laser device that visualizes the buffy coat to separate the PRP from RBC’s. The Regen® system concentrates 5ml of PRP from 10 ml of whole blood using a gel separator. After centrifugation of 15cm peripheral blood by using specific PRP tube(Ycellbio), we obtain 5cm platelet poor plasma and 4cm platelet rich plasma.

 After isolation of the PRP, calcium chloride (0.5ml) will be added to the 5 ml of PRP isolate to activate the thrombin cascade, thereby causing degranulation of platelets, releasing growth factors and cytokines, and starting the transformation of the PRP to platelet rich fibrin matrix (PRFM). Before the PRFM become too gelatinous for passing through a needle (less than 10 minutes), Patients are placed in lithotomy position and Two injections are administered after using a disinfectant agent to the genital area, one in the clitoris to form pili of 6cm around the clitoris in the direction of clock positions of 3 and 9 each with 3 cm, and the other remaining 3cm of PRP is injected in the vaginal wall in a space between the vagina and the urethra away from the bladder a probable site for Grafenberg spot (G spot). The mean location of G-spot is 4.5 ± 2 cm below the urethral meatus. Safety is measured by monitoring and documenting side effects during and after the procedure.

These procedures will be done once and not to be repeated. The patients will be evaluated by repeating the questionnaires and clitorial artery Doppler after one and three months from receiving the treatment.

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