PDE -5 inhibitors' implications in women: Are they of help?

Review Article

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ABSTRACT

Introduction: Introduction of the oral phosphodiesterase isoenzyme-5 inhibitors (PDE5-Is) has revolutionized sexual medicine by affording effective treatment for erectile dysfunction. PDE5 hydrolyses cyclic GMP specifically to 5′-GMP. Since its launching, PDE5-Is have stimulated scientific interest for their impending benefits in various implications for the welfare of the human beings.

Aim: To highlight the possible potential implications of PDE5-Is in women.

Participants and methods: A systematic review was carried out till June 2017 based on a search of concerned articles in Medline, medical subject heading databases, Scopus, The Cochrane Library, Embase, and CINAHL databases without language restriction. Keywords used to assess that outcome and concerned associations were PDE5 inhibitors, sildenafil, tadalafil, vardenafil, avanafil, women, and females.

Main outcome measures: Different implications for PDE5-Is in women.

Results: Oral PDE5-Is have beneficial medical implications in women. Sexual implications include female sexual dysfunction, female sexual arousal disorder, antidepressant-associated sexual dysfunction, and affected relationship. Gynecological implications include endometrial thickness, abortion, preeclampsia, fetal growth restriction, clitoral engorgement, primary dysmenorrhea, uterine blood flow, oligohydramnios, poor ovarian response, ovarian ischemia/reperfusion, and uterine contractility. Urological implications include overactive bladder and interstitial cystitis, whereas dermatological implications include systemic sclerosis and cellulite. In addition, PDE5-Is proved to be beneficial in pulmonary arterial hypertension, coronary dysfunction, esophageal motility, and some metabolic effects.

Conclusion: Oral PDE5-Is are an eye-catching therapeutic class of agents with beneficial effects for women, which could be potentially applied after well-designed clinical trials.

Key Words: Females, female sexual dysfunction, phosphodiesterase isoenzyme-5 inhibitors, sildenafil, tadalafil, vardenafil, women

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INTRODUCTION

Nowadays, oral phosphodiesterase isoenzyme-5 inhibitors (PDE5-Is) are considered the first-line therapy for erectile dysfunction (ED)[1]. Specifically, PDE5 hydrolyses cyclic cGMP to 5′-GMP by blocking cGMP hydrolysis, and potentiates the effects of cGMP resulting in decreased intracellular calcium leading to penile smooth muscle relaxation and vasodilatation with increased penile blood flow[2–5]. As well, this family demonstrated significant antiapoptotic and antioxidant properties[6–8]. Four orally PDE5-Is were approved by the Food and Drug Administration (FDA), namely, sildenafil, vardenafil, tadalafil, and avanafil. Sildenafil citrate was the first to be released at 1998 with maximal plasma concentration (Tmax) at 60 min on empty stomach and acts for 4–6 h[9]. Vardenafil hydrochloride was approved at 2003 with Tmax of 60 min on empty stomach and acts for up to 7 h[10]. Tadalafil was approved at 2003 of Tmax of 120 min with duration of action up to 36 h and is not affected by food[11,12]. Avanafil was approved in 2012 with Tmax 30–45 min on empty stomach establishing coitus as early as 10 min[13]. PDE5-Is' high tolerability made them an attractive tool to investigate further physiological functions beyond ED with collateral benefits for multitude of nonsexual implications[14–18].

This review aimed to highlight the potential nonsexual implications of PDE5-Is in women.

Sexual implications

Female sexual dysfunction

Female sexual dysfunction (FSD) is defined as a disorder of sexual desire, arousal, or orgasm, and/or sexual pain, which results in personal distress and affects quality of life and interpersonal relationships[19]. The pathophysiology, diagnosis, and treatment of female sexual interest in pre- and post-menopausal women present a complex arena. Lately, flibanserin was approved by the US FDA in August 2015 as the first pharmacologic treatment for hypoactive

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sexual desire disorder (HSDD) in premenopausal women[20,21]. Testosterone, buspirone, sildenafil, bupropion, bremelanotide, and herbal medications have verified some clinical benefits in women with FSD but with significant design, dosing, or generalizability limitations. Discordance between genital and subjective measures of sexual response in women may be augmented by PDE5 effects on genital vasocongestion rendering successful treatment unlikely via pharmacological treatment alone[22].

In their study, Caruso *et al.*[23] suggested that sildenafil may improve sexual performance of women affected by sexual difficulties such as arousal disorder and may indirectly improve other aspects of sexual life. Caruso *et al.*[24] showed that sildenafil improved arousal, orgasm, and enjoyment with respect to placebo. Significant differences were noted during sildenafil use with respect to the baseline for arousal, orgasm, and sexual enjoyment. It is suggested that sildenafil acts on the different sexual pathways in healthy women, improving their sexual experience.

Dasgupta *et al.*[25] assessed the effects of sildenafil in women with multiple sclerosis and sexual dysfunction. Significant improvement following sildenafil was reported in the lubrication domain of sexual function during the double-blind phase with a significant correlation between the latency of tibial and pudendal evoked potentials. Ferrara *et al.*[26] presented a case report of neurogenic FSD owing to ruptured L5-S1 intervertebral disk treated with 50-mg sildenafil, and her symptoms were recorded using a FSFI score. The patient reported a good response with subjective increase in vaginal blood flow, achieved better vaginal lubrication, and noted more clitoral engorgement.

Snoeren *et al.*[27] supported the finding that combination treatment of testosterone and vardenafil could be used as a treatment for women with HSDD. van der Made *et al.*[28] demonstrated that the combination of testosterone and vardenafil could increase the sensitivity for sexual stimuli and improve the desire and arousal components of the sexual response. In an initially low-attention for sexual cues group, preconscious attentional bias for sexual cues increased under the testosterone condition. In these women, the combination of testosterone and vardenafil caused an improvement in genital response and subjective indices of sexual function. In the group that had initially a high attention for sexual cues, preconscious attentional bias for sexual cues decreased under the condition of testosterone. van der Made *et al.*[29] assessed if the combination of testosterone and vardenafil causes an increase in sensitivity for sexual cues and an increase in the physiological sexual responding in women with HSDD. In women without childhood sexual abuse, testosterone appears to activate central sexual mechanisms resulting in higher vaginal pulse amplitude under the combination of testosterone and vardenafil.

Zeinalzadeh *et al.*[30] assessed women with HSDD using the FSFI and Spielberger's questionnaire. They were divided into Elaeagnus angustifolia flower (4.5 g/day for 35 days), sildenafil tablet (50 mg for 4 weeks), and controls. In the sildenafil group, the mean score of state anxiety decreased from 22.15 to 20.1 and that of trait anxiety decreased from 23.07 to 21.55 after the intervention.

Poels *et al.*[31] showed that on-demand T+PDE5i is a potentially promising treatment for women with HSDD, particularly in women with low sensitivity for sexual cues. Poels *et al.*[32] suggested two new on-demand drug treatments for women with HSDD/Female Sexual Interest/Arousal Disorder (FSIAD) based on different causal mechanisms. Testosterone combined with a PDE5 inhibitor has been developed for women with HSDD/FSIAD owing to a relatively insensitive system for sexual cues, whereas testosterone combined with a serotonin 1A receptor agonist has been used for women with HSDD/FSIAD owing to dysfunctional activation of sexual inhibitory mechanisms.

Akbarzadeh *et al.*[33] compared the effect of Elaeagnus angustifolia flower extract and sildenafil on female orgasmic disorder. The first group had to consume 4.5 gr of E. angustifolia extract in two divided doses for 35 days and the second used 50-mg sildenafil tablets for 4 weeks 1 h before coitus. The frequency of orgasmic disorder before the intervention was 41.5, 40.5, and 57.1% compared with 29.3, 16.7, and 50% after the intervention in the Elaeagnus angustifolia, sildenafil, and control groups, respectively. The highest reduction of changes after the intervention (58.8%) was observed in the sildenafil group. Borghi *et al.*[34] showed that PDE5 inhibitors could be an effective option for many subtypes of FSD, with improvement in many aspects of sexual function, such as desire, arousal, orgasm, and sexual satisfaction.

Alp *et al.*[35] investigated the effects of PDE-5 inhibitors on osteoporosis by the NO/3′,5′-cGMP/protein kinase G signalling pathway on female rats. The first group was healthy controls with no ovariectomy, whereas other groups underwent a bilateral ovariectomy. Six months after ovariectomy, vardenafil, udenafil, and tadalafil were given to the third, fourth, and fifth groups but not to the positive control (10 mg/kg/day for 2 months). These inhibitors may have caused a positive effect on the increased bone mass density and reduction of bone resorption markers. There were positive effects of PDE5 inhibitors on oxidative stress, increased angiogenesis in bone tissue, and improved reformation rate of bone in rats with osteoporosis.

Female sexual arousal disorder

FSAD is a common disorder encountered in clinical practice, with self-reported arousal difficulties[36]. FSAD is a heterogeneous condition whose underlying causes are difficult to diagnose, and its appropriate treatment requires a thorough sexual, psychological, and medical history[37]. Several agents have been studied as possible treatments for FSAD, though none have received regulatory approval from the US FDA. These drugs include topical alprostadil, α-adrenergic receptor antagonists, melatonin receptor agonists, and PDE inhibitors. PDE5 has been found to be

expressed in vaginal, clitoral, and labial smooth muscle, indicating its involvement in female sexual functions, particularly genital arousal[38] PDE5, however, is expressed in smaller quantities in the female clitoris than in the male corpus cavernosum[39,40].

Berman *et al.*[41] determined the efficacy of sildenafil use in women with FSAD. Genital blood flow, vaginal lubrication, intravaginal pressure-volume changes, and genital sensation were recorded presexual and postsexual stimulation at baseline and following 100-mg sildenafil using a validated sexual function inventory at baseline and the following 6 weeks. Following sildenafil, poststimulation physiologic measurements improved significantly compared with baseline. Baseline subjective sexual function complaints such as low arousal, low desire, low sexual satisfaction, difficulty achieving orgasm, decreased vaginal lubrication, and dyspareunia also were improved significantly following 6-week home use of sildenafil.

Nevertheless, the presence of PDE5 in female genital tissue has supported the hypothesis that sildenafil may be useful in treating some forms of FSD, such as FSAD. In addition, the mechanism of action that sildenafil has on cellular tissue indicates that greater success would be achieved in the treatment of genital rather than subjective arousal disorder[42–44]. In their study, Claret *et al.*[45] developed a model to explore the dose response of sildenafil in patients with FSAD based on telephone sexual activity daily diary data. Sildenafil showed a dose-dependent effect in patients with FSAD. Alexander *et al.*[46] evaluated oral sildenafil in women with FSAD as a result of paraplegia/tetraplegia in a 4-week baseline period followed by 12 weeks of treatment (50–100 mg or decreased to 25 mg once during the treatment period). Sildenafil Sildenafil-treated women and placebo-treated women had an increase in their sexual activities. Omidi *et al.*[47] compared the effects of 50-mg oral sildenafil 1 h before intercourse and weekly sessions cognitive-behavioral therapy for 8 weeks on women with arousal and orgasm dysfunction. The mean scores for the FSFI, sexual satisfaction, and the Enrich marital satisfaction scale were increased in both groups during treatment.

Caruso *et al.*[48] determined whether daily tadalafil 5 mg is effective in type 1 premenopausal women affected by FSAD. Women reported quality-of-life improvement at the 12th week follow-up with improved experience of sexual genital arousal/orgasm, sexual enjoyment, satisfaction by frequency of sexual activity, and frequency of sexual thoughts or fantasies. Moreover, dyspareunia was decreased with respect to baseline. After tadalafil administration, the mean peak systolic velocity increased, and the mean diastolic velocity was decreased, whereas the mean resistance index and the mean pulsatility index (PI) were significantly higher compared with the baseline values.

Antidepressant-associated sexual dysfunction

Administration of selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors relieves depressive symptoms but may cause sexual dysfunction in women that frequently results in premature treatment discontinuation. Many strategies have been reported to assist the patients in minimizing such impairment, with variable degrees of success, one of them is PDE5-Is. Fava *et al.*[49] observed significant improvement in all domains of sexual functioning such as libido, arousal, orgasm, and sexual satisfaction, with 69% of patients reporting themselves as much/very much improved. In an open study[50], sildenafil 50 mg was prescribed for women reporting FSD induced by antidepressant medication, primarily SSRIs, 1 h before sexual activity. They were told to increase the dose to 100 mg on the next occasion if experienced either partial or a lack of response. These patients, all of whom had experienced either anorgasmia or delayed orgasm with/without associated disturbances, reported significant reversal of sexual dysfunction, usually with the first dose of 50 mg of sildenafil. Laan *et al.*[51] examined the effect of a single oral dose of sildenafil on vaginal vasocongestion and subjective sexual arousal in healthy premenopausal women or matching placebo in the first session and the alternate medication in the second session. Significant increase in vaginal vasocongestion was found with sildenafil treatment compared with the placebo with no differences on subjective sexual arousal. Significantly stronger sexual arousal and vaginal wetness were reported for sildenafil versus placebo, indicating that sildenafil was effective in enhancing vaginal engorgement during erotic conditions in healthy women without sexual dysfunction but was not associated with an effect on subjective sexual arousal.

Ashton and Weinstein[52] reported that three women had derived benefit from using 20 mg tadalafil before anticipated sexual activity to reverse medication-induced sexual dysfunction. Angulo *et al.*[52] evaluated the effects of vardenafil on inhibition of genital vascular responses induced by antidepressants in female rabbits. Potentiation of NO pathway by vardenafil improved vascular sexual responses in female rabbits and overcomes the inhibitory effects of acutely administered antidepressants on genital vascular responses, irrespective of the underlying pathophysiologic mechanism of disruption of the NO pathway or enhancement of α-adrenergic mechanisms.

Nurnberg *et al.*[53] evaluated the efficacy of sildenafil for FSD associated with selective and nonselective antidepressants in women who were randomly assigned to take sildenafil or placebo at a flexible dose starting at 50 mg adjustable to 100 mg before sexual activity with a mean Clinical Global Impression-sexual function score of 1.9 compared with those on placebo with a mean end point difference of 0.8. Assigning baseline values carried forward to the 22% of patients who prematurely discontinued resulted in a mean end point in the sexual function score of 1.5 among women on sildenafil compared with 0.9 on placebo with a mean end point difference of 0.6.

In addition, it was hypothesized that polymorphisms

in the androgen receptor gene, encoded by the nucleotides cysteine, adenine, and guanine, influence the effect of testosterone on sexual functioning. In their studies, van Rooij *et al.*[54,55] investigated the effects of sublingual testosterone combined with a serotonin1A receptor agonist buspirone, and of sublingual testosterone combined with sildenafil (50 mg) on sexual function in premenopausal and postmenopausal women with SSRIs-induced FSD. Women on low dose and having relatively long cysteine, adenine, and guanine repeats reported marked improvement in sexual function in response to both treatments compared with placebo.

Affected relationship

Women's quality of sexual life is strongly impaired by male ED. After treatment with sildenafil versus untreated patients, the quality of partnership reported by both men and their female partners is significantly better in appropriately treated ED patients than untreated controls[56]. After treating male ED, Cayan *et al.*[57] observed significant improvement in sexual arousal, lubrication, orgasm, satisfaction, and pain in the women suggesting that female sexual function is affected by male erection status and its improvement after treatment. Moreover, Goldstein *et al.*[58] showed that vardenafil significantly increased total female sexual function index and sexual desire, subjective arousal, lubrication, orgasm and satisfaction domains after treatment-related improvement in erectile function of their male partners.

Conaglen and Conaglen[59] investigated the treatment preference of women whose partners use oral ED medications. A total of 79.2% of the women preferred their partners' use of tadalafil, whereas 15.6% preferred sildenafil, which was not affected by age or treatment order randomization. Women preferring tadalafil reported feeling more relaxed, experiencing less pressure, and enjoying a more natural or spontaneous sexual experience, whereas those preferring sildenafil focused on satisfaction and drug effectiveness for their partner.

Chevret-Méasson *et al.*[60] assessed the effect of ED treatment on female partners using the Index of Sexual Life (ISL), specific of the quality of sexual life of women with ED partners. The ISL sexual life satisfaction score was low at baseline and increased after treatment. The final ISL sexual life satisfaction score was dependent on women's age and final international index of erectile function scores. It is concluded that women satisfaction with their sex life was improved by ED treatment. Martín-Morales *et al.*[61] showed that vardenafil treatment of men with ED improved both their erectile function and the sexual quality of life of their female partners.

Gynecological implications

Endometrial thickness

Vaginal sildenafil has been shown to be useful in increasing endometrial thickness and achieving pregnancy in women with varied uterine disorders. Sher *et al.*[62] assessed the effects of sildenafil vaginal suppositories (25 mg, four times/day) for 3–10 days on endometrial thickness and in-vitro fertilization (IVF) outcome in infertile women younger than 40 years with poor endometrial development. Vaginal sildenafil showed enhanced endometrial development in 70% of patients with high implantation and ongoing pregnancy rates. Zinger *et al.*[63] had successfully managed two women having inadequate endometrium after surgical resection of uterine synechiae with a history of a postpartum uterine curettage with subsequent secondary infertility. Postoperatively, both patients had thin endometrium and failed to conceive despite fertility treatment. These women achieved pregnancy in the first treatment cycle with vaginal sildenafil with improved endometrial thickness. Takasaki *et al.*[64] showed that sildenafil improves uterine radial artery-resistance index being useful for patients with thin endometrium. Dehghani Firouzabadi *et al.*[65] pointed out that oral sildenafil is a good way to improve the endometrial receptivity recommending its routine use in patients with previous failure of assisted reproduction technology cycles owing to poor endometrial thickness. Malinova *et al.*[66] showed the role of sildenafil and serophene on endometrial thickness and volume, endometrial flow index and vascularization flow index, resistivity index (RI) and PI to uterine artery on the day of human chorionic gonadotropin, in prediction of intrauterine insemination outcome in anovulatory women. In sildenafil plus serophene group, the patients got 25 mg sildenafil vaginally and serophene 100–150 mg orally, and in serophene group, 100–150 mg of serophene orally. The mean endometrial thickness and endometrial volume was 11.8 versus 10.2 and 5.2 versus 3.6 respectively with significant decrease in PI and RI to uterine artery in group I. In addition, Soliman *et al.*[67] assessed in-situ thermosensitive gels for the vaginal administration of sildenafil as a potential treatment of endometrial thinning as a result of using clomiphene citrate for ovulation induction in women with type II eugonadotrophic anovulation. In-situ sildenafil vaginal gel was shown to significantly increase endometrial thickness and uterine blood flow.

Abortion

Recurrent pregnancy losses are common women's health issue associated with inflammatory and thrombotic events including excessive production of cytokines, in particular tumor necrosis factor-α (TNF-α). Jerzak *et al.*[68] assessed the effect of sildenafil on peripheral natural killer cell activity in women with a history of recurrent miscarriage. The natural killer-cell activity was significantly decreased after vaginal sildenafil therapy and their endometrial thickness was significantly increased. El-Far *et al.*[69] presented vaginal sildenafil as a safe antiabortive option in treating threatened miscarriage that reduces vasoconstriction by increasing blood flow through relaxation of uterine arteries as indicated from measured PI in unexplained recurrent spontaneous miscarriage cases. Sildenafil was shown to improve the measured antioxidants and improved oxidative stress close to concentrations seen in women in their first trimester of pregnancy.

Ohams *et al.*[70] showed treating recurrent abortion with either PDE5 or TNF-α blocker before conception is a promising therapy of immune-dependent recurrent miscarriages, limiting the teratogenic influence of the drugs on the fetus. Luna *et al.*[71] showed that combined sildenafil plus heparin therapy was superior to either treatment alone for impending pregnancy loss or prophylactically in recurrent miscarriages. Bolnick *et al.*[72] showed that human first-trimester trophoblast cells proliferate at low O2, but its survival is compromised by oxidative stress, leading to uteroplacental insufficiency and recurrent pregnancy loss that was optimally inhibited by sildenafil. Bolnick *et al.*[73] added that sildenafil directly stimulated favorable trophoblast extravillous differentiation for implantation and reduces adverse pregnancy outcome. Luna *et al.*[74] evaluated the protective effect of sildenafil and dalteparin in a mouse model of Lipopolysaccharide-induced abortion showing that sildenafil either alone or combined with heparin showed the best response. Jerzak *et al.*[75] reported a patient with history of four recurrent pregnancy losses and IVF failures that used addition of intralipid to sildenafil and enoxaparin immunotherapy giving birth to a healthy male baby in the third IVF cycle.

Pre-eclampsia

Pre-eclampsia, the development of new-onset hypertension and proteinuria during pregnancy, affects 3–8% of all pregnancies and is characterized by systemic endothelial dysfunction. It is responsible for the majority of maternal and perinatal morbidity and mortality associated with complicated pregnancies owing to associated increased uterine artery resistance. Karasu *et al.*[76] assessed the effects of sildenafil and vardenafil in human umbilical artery preparations taken from pregnant women with pre-eclampsia and healthy pregnant women. Relaxation responses of sildenafil and vardenafil in the presence/absence of NOS and sGC inhibitors were compared. Sildenafil and vardenafil-induced relaxation responses were significantly attenuated in the presence of preeclampsia. In all experiments, a maximal relaxation response was achieved by vardenafil unlike sildenafil. Vardenafil seemed to affect vascular responsiveness of human umbilical artery through the involvement of NO/cGMP-dependent and independent pathways whereas sildenafil-induced responses seemed to be completely NO/cGMP-dependent. In their study, Karasu *et al.*[77] clarified that sildenafil-induced relaxation responses were significantly attenuated in the presence of preeclampsia but not totally abolished indicating that sildenafil might affect vascular responsiveness of human umbilical artery through the involvement of NO/cGMP-dependent and NO/cGMP-independent pathways.

Herraiz *et al.*[78] showed that sildenafil reverses the maternal effects of preeclampsia and improves uteroplacental/fetal perfusion. George *et al.*[79] showed that sildenafil provides an effective option for managing hypertension during preeclampsia by improving uteroplacental function. Trapani *et al.*[80] assessed whether oral sildenafil prolongs gestation in singleton pregnancies with pre-eclampsia between 24 and 33 weeks of gestation randomized to 50 mg sildenafil/8 h or placebo. Pregnancy duration was on average 4 days longer, and the reduction in PI of both uterine and umbilical arteries was higher for patients on sildenafil compared with placebo.

Gillis *et al.*[81] hypothesized that sildenafil would improve the maternal syndrome and fetal outcome in a rat model of superimposed preeclampsia on oral sildenafil (50 mg/kg/day) from day 10 through day 20 of pregnancy. Untreated rats had a significant rise in blood pressure and a 2-fold increase in urinary protein excretion from baseline to late pregnancy. However, sildenafil-treated rats exhibited ≈40 mmHg drop in the blood pressure with no rise in protein excretion. Sildenafil also increased creatinine clearance, reduced uterine artery RI during late pregnancy, and improved fetal outcome. In addition, 19% of all pups showed resorption in untreated rats, with no incidence of resorptions in the treated group. In addition, TNF-α, endothelin-1, and oxidative stress, which are increased in experimental models, were reduced in treated rats. Stanley *et al.*[82] showed that sildenafil rescues the dysfunction in uterine arteries of women with preeclampsia by increasing uterine artery vasodilation, thereby decreasing uterine artery resistance and, hence, ameliorated preeclampsia in a mouse model of preeclampsia.

Nevertheless, one of the key molecules implicated in severe preeclampsia pathogenesis is heme oxygenase-1 (HO-1), a rate-limiting enzyme that breaks down heme into carbon monoxide (CO), biliverdin, and free iron[4,83]. CO and bilirubin account for the angiogenic, vasodilatory, and antioxidant properties of HO-1[84,85]. These collective actions of the heme breakdown metabolites generated by HO-1 offer protection against cytotoxicity, inflammation, hypoxia, and other forms of cellular stress[86–89].

Fetal growth restriction

Fetal growth restriction (FGR) is the inability of a fetus to achieve its genetic growth potential. It affects up to 8% of all pregnancies and has both massive short-term (increased fetal morbidity and mortality) and long-term (increased incidence of cardiovascular disease in adulthood) health implications. Wareing *et al.*[90] showed that sildenafil improves endothelial function of myometrial vessels from women whose pregnancies are complicated by intrauterine FGR. von Dadelszen *et al.*[91] offered sildenafil (25 mg three times a day until delivery) for women if their pregnancy was complicated by early-onset FGR and either the gestational age younger than 25 weeks or an estimate of the fetal weight of less than 600 g. Sildenafil treatment was associated with increased fetal abdominal circumference growth compared with institutional sildenafil-naive early-onset FGR controls.

Dastjerdi *et al.*[92] assessed whether sildenafil affects uteroplacental perfusion in pregnant women with intrauterine FGR at 24–37 weeks of gestation by Doppler ultrasound of the umbilical and middle cerebral arteries. Sildenafil group fetuses showed a significant decrease in systolic/ diastolic ratios and PI of the umbilical artery and a significant increase in the middle cerebral artery PI. They concluded that sildenafil improves fetoplacental perfusion in pregnancies complicated by intrauterine FGR. Dilworth *et al.*[93] pointed out that sildenafil improves fetal growth even in the absence of abnormal placental blood flow.

Clitoral engorgement

Alatas *et al.*[94] determined the effect of sildenafil on the uterine circulation and clitoral artery blood flow in postmenopausal women. After sildenafil intake, the mean RI and PI of uterine artery were significantly lower compared with baseline values, and the mean peak systolic velocity of the clitoral artery was significantly higher. It is concluded that sildenafil improves the clitoral and uterine blood flow in healthy postmenopausal women without erotic stimuli. Cavalcanti *et al.*[95] assessed the effects of 50-mg dose of sildenafil or placebo daily for 15 days on clitoral blood flow and sexual response in postmenopausal women with orgasmic dysfunction. The Golombok Rust Inventory of Sexual Satisfaction (GRISS) was used for subjective evaluation of the sexual-response cycle, whereas the clitoral blood flow was measured at baseline, after 1 h of the first dose, and after 15 days of treatment. Blood flow was significantly improved in the sildenafil than the placebo group with a positive correlation between Doppler values and GRISS scores in the sildenafil group after 15 days of treatment.

Yang *et al.*[96] determined if MRI could quantify a difference in clitoral response following vasoactive medication, in women with FSAD. Sildenafil 50 mg versus placebo were administered 1 h before genital MRI performed while patients viewed alternating segments of nonerotic and erotic video. The mean change in clitoral volume for the entire group was higher in the sildenafil MRI session compared with the placebo. On the contrary, Leddy *et al.*[97] concluded that sildenafil did not augment the genital response in women with FSAD, and most women did not have impaired clitoral engorgement, suggesting that FSAD is not predominantly a disorder of genital engorgement.

Primary dysmenorrhea

Primary dysmenorrhea is a condition that most women have and seek a treatment for.

Dmitrovic *et al.*[98] compared vaginal preparation of sildenafil (100 mg single dose) with a placebo in patients with primary dysmenorrhea at the time of painful menstruation. At baseline and 1, 2, 3, and 4 h after treatment, the patients were asked to assess their degree of pain using two scales: pain on the five-level ordinal scale and pain level on the visual analog scale. Sildenafil group had significantly better pain relief compared with the placebo group and provided better pain relief than placebo at each time point. At the 2-h time point, the PI was significantly lower in the sildenafil-treated group compared with the placebo group.

Uterine blood flow

Hale *et al.*[99] assessed the effect of sildenafil on uterine volumetric blood flow (UVF) and vascular impedance in nonpregnant, nulliparous women who received placebo or sildenafil (25 or 100 mg) during the luteal phase of the cycle. Those who received sildenafil had significantly increased UVF and decreased RI over the 3-h monitoring period. When UVF responses to sildenafil were examined as a function of baseline, a significant increase in UVF was observed in those with higher baseline UVF. Overall, women in the luteal phase showed a significant increase in UVF in response to sildenafil. Moreover, Ramesar *et al.*[100] speculated that sildenafil improves uterine artery blood flow resulting in improved fetal outcome in pregnant rats.

Oligohydramnios

Maher *et al.*[101] compared sildenafil (25 mg/8 h) plus hydration with hydration alone in improving the amniotic fluid index and neonatal outcome in pregnancies at more than 30 weeks of gestation complicated by idiopathic oligohydramnios (amniotic fluid index <5 cm without maternal or fetal causes and with normal fetal growth). The amniotic fluid volume was higher in the sildenafil group (11.5 vs. 5.4 cm), was delivered later (38.3 vs. 36.0 weeks of gestation), had a lower rate of cesarean delivery (28 vs. 73%), and resulted in neonates less likely to be admitted to the neonatal ICU (11 vs. 41%). The authors concluded that sildenafil increases amniotic fluid volume in pregnancies complicated by oligohydramnios.

Poor ovarian response

The use of sildenafil as an adjunct to controlled ovarian hyperstimulation protocols may enhance ovarian response in women with poor ovarian response. Trakakis *et al.*[102] presented a case of a pregnancy achieved by administering sildenafil to a 37-year-old woman not responding to controlled ovarian hyperstimulation with the sole use of gonadotropins without follicular growth. Addition of oral sildenafil improved her ovarian response.

Ovarian ischemia/reperfusion

Arikan *et al.*[103] showed that tadalafil prevents tissue damage induced by ovarian ischemia/reperfusion (I/R) in rat ovaries. Celik *et al.*[104] pointed that sildenafil ameliorates antioxidant enzyme activities, lipid peroxidation, and histopathological changes in ovarian tissue after I/R injury in rats. Incebiyik *et al.*[102] reported the protective activity of sildenafil against I/R damage in rat ovaries by decreasing tissue damage and oxidative stress.

Uterine contractility

Winston *et al.*[105] showed that sildenafil inhibits the

contractility of isolated nonpregnant human myometrium by opening Ca-sensitive K channels.

Urological implications

Overactive bladder

Razdorskaia *et al.*[106] assessed the treatment outcome in women with overactive bladder (OAB) with imperative incontinence and obstructive urination disorders by a combination of alpha1-adrenoblockers (alfuzosin 5 mg at night) and PDE-5 inhibitors (tadalafil 5 mg daily in the morning) for a month. After treatment, the time of urination was reduced; urinary volume and maximum urinary flow rate, as well as cystometric capacity have increased; involuntary detrusor contractions in the bladder filling phase (spontaneous/provoked) became less, or absent; and the residual urine volume has decreased. Laser Doppler flowmetry showed an increase of neurogenic tone in precapillary, bypass coefficient and microcirculation effectiveness index, as well as increase in microcirculation index and the coefficient of variation, indicating improved microcirculation in the bladder mucosa.

Chen *et al.*[107] assessed the efficacy of daily low-dose 5-mg tadalafil or placebo for 3 months for OAB in women. The OAB symptom score significantly decreased, and the frequency, incontinence, and urgency episodes significantly improved in the tadalafil treatment group compared with the placebo group and baseline at weeks 4, 6, 8, 10, 12, as well as 3 months after treatment. In addition, voided volume and total bladder capacity were increased in the treatment group, whereas the Indevus Urgency Severity Scale was decreased from week 4 to 3 months after treatment in the treatment group.

Interstitial cystitis

Chen *et al.*[108] assessed the efficacy of daily low-dose sildenafil (25 mg) for nonulcer interstitial cystitis in women compared with placebo for 3 months. Interstitial cystitis symptom and problem indices scores and urodynamic index were significantly improved in sildenafil-treated group at week 4, 6, 8, 10, and 12, and 3 months after treatment. Urodynamic index including first desire to void, strong desire to void, and maximum cystometric capacity was significantly improved in sildenafil treated group at week 12 and at 3 months after treatment.

Dermatological implications

Systemic scleroderma

Alekperov *et al.*[109] analyzed the efficacy and safety of sildenafil in patients with systemic sclerosis in 14 women with mean duration of 8.8 years. The indications for treatment were significant Raynaud's phenomenon in three patients, digital ulcers (DU) and/or necroses in nine, pulmonary hypertension (PH) in five patients, and critical ischemia of the left fingers in one patient. There was a significant decrease in the frequency and intensity of Raynaud's attacks in 11/15 (73%) patients treated with sildenafil in the first days and remained stable throughout the treatment. All patients with DUs showed decreased sizes just within the first 2 weeks of treatment. Complete DU healing was observed within 4–12 weeks of treatment. During a month, the necrotic area reduced and the signs of reparation appeared in 4/6 patients. Pain ceased just within the first 5–7 days of treatment. The authors concluded that sildenafil is effective to treat the manifestations of scleroderma vasculopathy, such as Raynaud's phenomenon, DU/necroses, and PH.

Cellulite

Altabas *et al.*[110] provided a hypothesis considering the potential effect of PDE5a inhibitors on cellulite, a significant cosmetic problem for many postadolescent women. Its pathophysiology is complex and involves the presence of excess subcutaneous fat, the microcirculatory system, lymphatics, and the extracellular matrix. Many treatments were tested like iontophoresis, ultrasound, thermotherapy, pressotherapy, lymphatic drainage, and electrolipophoresis to enhance skin microcirculation. Human fat cell lipolysis is mediated by both cAMP-dependent and cGMP-dependent protein kinases. High-dose sildenafil pretreatment leads to increased lipolysis in adipocyte cultures. This effect could not be attributed exclusively to either PDE3b or PDE5a inhibition, as sildenafil inhibited ~50% of the PDE3b activity in pretreated adipocytes. Sildenafil was shown to have a potential beneficial effect on skin microcirculation and tissue hypoxia. The authors concluded that transdermal or local route of administration should be considered.

Other implications

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare condition characterized by sustained elevation in pulmonary arterial resistance leading to right heart failure. PAH afflicts predominantly women. Conventional treatment includes nonspecific drugs (warfarin, diuretics, and oxygen). The endothelin-1 receptor antagonists bosentan, sildenafil, and prostanoids have been shown to improve symptoms, exercise capacity, and hemodynamics. However, intravenous prostacyclin is the first-line treatment for the most severely affected patients[111]. Jiménez López-Guarch *et al.*[112] showed that the addition of oral sildenafil to chronic prostacyclin treatment in patients with severe PH improves functional capacity and reduces episodes of decompensated right heart failure, with nonsignificant adverse effects. Michelakis *et al.*[113] showed that sildenafil may be superior to iNO in that it increases cardiac output and does not increase wedge pressure. Gomberg-Maitland *et al.*[114] showed that subcutaneous treprostinil with sildenafil for PAH has additive beneficial effects. Milman *et al.*[115] showed that patients with severe pulmonary sarcoidosis have a high prevalence of PH, whereas sildenafil treatment was associated with significant improvements in hemodynamic parameters.

Olfert *et al.*[116] showed that sildenafil and bosentan equally improve arterial oxygenation in acute hypoxia,

which could account for improved physical performance at altitude. Watanabe *et al.*[117] concluded that sildenafil may improve dyspnea, exercise tolerance, and health-related quality of life in some patients with PH. Lopez-Meseguer *et al.*[118] suggested that therapy with inhaled iloprost-silenafil represents an acceptable alternative in patients with severe and unstable PAH.

Huang and DeSantis[119] described the successful treatment with sildenafil, a pregnancy category B drug, in pregnant patients with PAH. Sun *et al.*[120] explored the effect of sildenafil in treatment of pregnant women with PAH. Sildenafil can significantly improve the clinical symptoms, cardiac function, hemodynamics, pregnancy outcome, reduce premature delivery, the incidence of low-birth-weight children, and cesarean section rate. Cartago *et al.*[121] reported three cases of PAH in pregnancy treated with sildenafil combined with another drug. Treatment for PAH using sildenafil as monotherapy may allow stabilization of the maternal condition and improve clinical outcomes for both mother and baby.

Volkov *et al.*[122] assessed the effect of sildenafil 20 mg three times a day on the survival of patients with PAH associated with connective tissue diseases in women corresponded to functional class II. Three-year survival rates were 94% in the study group and 25% in controls. Rusiecki *et al.*[123] assessed treatment response by examining change in 6-min walk distance (6MWD) and time to clinical worsening with the effect of menopausal status on the same treatment measures before and after 16 weeks of treatment with tadalafil or placebo. For tadalafil-treated patients, a significant difference was shown in 6MWD with a mean 34.7 m for females. There was a trend toward a female age-dependent effect in change in 6MWD; the premenopausal group showed the greatest improvement. This trial suggested that premenopausal women may experience functional improvement when treated with tadalafil than older women.

Coronary dysfunction

Microvascular coronary dysfunction is associated with symptoms and signs of ischemia, and also adverse outcomes in women without macrovascular obstructive coronary artery disease (M-CAD). For women with symptoms and signs of ischemia and no M-CAD, PDE-5 inhibition is associated with acute improvement in coronary flow reserve, and the effect concentrates among those with coronary flow reserve of up to 2.5. If these acute effects are sustained, then PDE-5 inhibition would provide a rational strategy for management of microvascular coronary dysfunction in symptomatic women without M-CAD[124].

Esophageal motility

In 16 normal individuals (nine men and seven women), esophageal motility was recorded. After a basal period of 60 min, a tablet of sildenafil 50-mg ground and dissolved in water was infused in the stomach in eight individuals and a placebo tablet in the other eight individuals; the recording continued for 60 min. Sildenafil was shown to induce significant decrease of lower esophageal sphincter tone, residual pressure, wave amplitude, and propagation velocity and a significant increase of onset latency of pressure waves compared with the values of the basal period and placebo. The inhibitory effect reached its maximum 10–15 min after the infusion and lasted about 1 h[125].

Metabolic effects

It is suggested that reduced synthesis of NO in endothelial cells, that is endothelial dysfunction, contributes to the impaired action of insulin in the vasculature of patients with type 2 diabetes. Jansson *et al.*[126] assessed whether selective inhibition of PDE-5 by tadalafil has beneficial metabolic effects on peripheral microcirculation and glucose uptake. In women with type 2 diabetes, but not in the controls, tadalafil induced increases in the permeability surface area for glucose and forearm glucose uptake. However, fasting glucose and insulin concentrations were similar following treatment with placebo or tadalafil in the two groups. This study suggests that tadalafil evokes positive metabolic effects in insulin-resistant women with type 2 diabetes. Murdolo *et al.*[127] explored the acute in-vivo effects of tadalafil on local microcirculation and regional metabolism in skeletal muscle and adipose tissue. Tadalafil emerges as an acutely acting modulator of microvascular recruitment and glucose metabolism in skeletal muscle and adipose tissue.

CONCLUSION

PDE5 inhibitors as an effective and beneficial molecules have their potential implications in women, which could be considered as additional accomplishment. However, preclinical as well as pharmacological studies should be thoroughly searched for before establishing its uses.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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