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Effects of Oral Sildenafil versus Nifedipine on the Uterine Artery Blood Flow Indices and Endometrial Thickness in Women with Unexplained Recurrent Pregnancy Loss

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ABSTRACT

Introduction and aim: Unexplained recurrent pregnancy loss (RPL) is a challenging condition faced during daily obstetric practice. Increased uterine blood flow and endometrial thickness were suggested to ameliorate the condition and increased uterine receptivity. The current study was designed to compare oral nifedipine and sildenafil regarding their effectiveness and safety profile in improvement of uterine artery blood flow and endometrial thickness in cases with unexplained RPL.

Methodology: This study included 100 women with a history of unexplained RPL while they were not pregnant. They were divided into two equal groups. The **first** received oral Nifedipine (10 mg) twice daily, and the second received oral Sildenafil citrate (10 mg) three times a day from the 5th to 25th days of the menstrual cycle. All were submitted to a comprehensive clinical, laboratory and radiological assessment during the second phase of the menstrual cycle (day 15 to day 25). The transvaginal color doppler was used to estimate uterine artery pulsatility and resistive indices, and endometrial thickness before and after treatment.

Results: Both groups were comparable regarding patient demographics, clinical and laboratory data. The uterine artery PI, RI and endometrial thickness before treatment were comparable between both groups. The paired comparisons in each group showed significant reduction of PI and RI and significant increase of endometrial thickness after treatment than before. Furthermore, the difference (before – after) of PI, RI and endometrial thickness were significantly higher in sildenafil than nifedipine groups (0.577±0.029, 0.417±0.090 and 0.3605±0.817 vs 0.545±0.029, 0.300±.001 and 3.180±0.775 for PI, RI and endometrial thickness differences, respectively). The side effects were in the form of headache, palpitation and flushing. They were reported in 18.0%, 10.0% and 10.0%, respectively in the nifedipine group, compared to 24.0%, 16.0% and 16.0% respectively in sildenafil group, with no significant differences between groups.

Conclusion: Both oral nifedipine and Sildenafil demonstrated a good safety profile, with good effectiveness in improving uterine artery doppler indices and subsequently improved uterine blood flow and increased thickness in women with unexplained RPL. However, Sildenafil is associated with better results than nifedipine with nearly similar safety profiles.

Keywords: Nitric Oxide; Vasodilators; Endometrial thickness; Uterine blood flow; Recurrent miscarriage.

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INTRODUCTION

Recurrent pregnancy loss (RPL) (recurrent abortion) is a significant health issue of daily obstetric practice. It is usually defined as spontaneous loss of two or more consecutive pregnancies. The etiology, pathology and prognosis may be known or unknown. The causative etiology is unknown in about 50.0% of cases [1-3]. Each loss needs careful examination and assessment to determine potential causes and pathological issues. In addition to determine if there are specific evaluation methods of the women or her husband are indicated [4].

RPL may be categorized into primary or secondary types. The primary RPL is defined when there was no previous live births, while secondary RPL is defined when there was a previous live birth before the two or more consecutive abortions [5-7].

The possible etiologies of RPL include-but not limited to- genetic aberrations, uterine anatomical abnormalities (e.g., bicornuate uterus, unicornuate uterus, actuate uteri, didelphis uterus, etc..), endocrine diseases (e.g., thyroid diseases (hyper- or hypo-thyroidism) and diabetes mellitus), immune diseases (e.g., antiphospholipid syndrome), special bad habits (e.g., smoking), exposure to environmental pollutants and inherited thrombophilia [8-18].

The RPL prevalence rate ranged between 0.8 to 1.4 when occurred before 20th week of gestation. However, this prevalence rate increased to 2 to 3% when biochemical evidence (e.g., serum beta-hCG levels) of pregnancy is considered [19].

Implantation failure accounts for about two thirds of lost pregnancies and the chance of successful pregnancy in each cycle are modest (up to 30.0%). Optimal conditions of uterine blood flow and endometrial thickness are essential for successful implantation and continued pregnancy [20-23].

Improvement of uterine blood supply and increased endometrial thickness by relaxing the smooth muscles of uterine vessels could improve uterine success rate of implantation process and successful pregnancy. This represents the rational for using vasodilator drugs (e.g., nifedipine, sildenafil and others) in treatment of RPL. However, the safety and effectiveness of both drugs in such cases are not fully investigated. Thus, the current work was designed to compare nifedipine and sildenafil regarding their effectiveness in improvement of uterine artery blood flow and endometrial thickness in cases with RPL. In addition, the associated side effects were recorded to examine the safety of both drugs.

METHODS

This study included 100 women with a history of unexplained RPL (two or more consecutive abortions), while they were not pregnant. They were selected from Damietta Specilzed Hospital between January 2018 and August 2019. They were randomly assigned to one of two equal groups. Women in the **first** group received oral Nifedipine (10 mg) twice daily, and women in the second group received oral Sildenafil citrate (10 mg) three times a day from the fifth to twenty fifth days of the menstrual cycle.

The inclusion and exclusion criteria:

The inclusion criteria were women in their reproductive age, with normal or overweight (non-obese) body mass index, with history of first trimester RPR of unknown etiology and who have regular menstruation. The exclusion criteria were contra-indication to any of nifedipine or sildenafil, known etiology of RPL, obese women, or women with irregular menstruation. In addition, women refused to participate are excluded from the study (NB: the included women in analysis (100) were those who fulfilled inclusion criteria and continued the study till its end).

Patient assessment

Before starting the study, a comprehensive assessment was performed for each woman during the during the second phase of the menstrual cycle (day 15 to day 25). This involved medical and obstetric history taking, clinical examination and transvaginal color doppler to estimate uterine artery pulsatility and resistive indices, and measurement of endometrial thickness. Then each women received the assigned treatment according to the results of randomization from the fifth to twenty fifth days of the menstrual cycle of the next menstrual cycle. The next assessment of uterine artery doppler indices and endometrial thickness was recorded after the end of the treatment duration or one day before (days 24, 25 of menstrual cycle) using the same ultrasound device and the assessment was performed by the same physician who was blinded to the study groups. Obtained results and documented side effects were recorded and compared between both groups.

Data analysis: the statistical package for social sciences (SPSS) version 15 (SPSS Inc., Chicago, Illionis, USA) was used to complete all statistical tests. Data was coded to conceal the patient's identity, then fed to the program. Continuous data were summarized by their mean and standard deviation (SD), while qualitative data were summarized by their relative frequencies and percentages (calculated from each group). Comparison between both nifedipine and sildenafil groups were carried out by student "t" or Chi square (X^2) tests for quantitative and qualitative variables, respectively. Data before and after treatment in each group were compared by paired samples "t" test. In addition, the difference between values before and after treatment was calculated (before-after) and compared between groups by independent samples student's test. P value < 0.05 was considered significant.

RESULTS

In the current study, patient age ranged between 20-36; weight between 62-81 kg and height ranged between 1.60-1.76 m. Thus, BMI ranged between 23.11 to 29.74kg/m^2; and previous miscarriage ranged between 2 and 6. Both nifedipine and sildenafil groups were comparable regarding demographics data (Table 1).

The laboratory investigations in the current study revealed that RBCs ranged between 3.1- 5.6 million cell/cc, while WBCs ranged between 4.30-7.50 thousands/cc and platelets ranged between 198 to 405 thousands/cell; hemoglobin ranged between 10.40 and 13.50 g/dl, HbA1c ranged between 4.5 and 6.5. while TSH ranged between 1.20 and 5.20; prolactin ranged between 5.0 to 20; AST ranged between 10 and 22 IU/L; ALT ranged between 10 and 18 IU/L; creatinine between 0.2- 1.0 mg/dl; urea ranged between 12-23 mg/dl; Hct % ranged between 34 and 39. The nifedipine and sildenafil groups were comparable regarding laboratory data (i.e., no significant differences between groups) (Table 2).

The uterine artery doppler indices and endometrial thickness before and

after treatment was presented in table (3). Results indicated that uterine artery PI, RI and endometrial thickness before treatment were comparable between both groups. In addition, uterine artery PI after treatment was comparable between both groups. However, there was significant differences between nifedipine and sildenafil groups after treatment regarding uterine artery RI and endometrial thickness. In addition, the paired comparisons in each group showed significant reduction of PI and RI and significant increase of endometrial thickness after than before treatment. Furthermore, the difference (before – after) of PI, RI and endometrial thickness were significantly higher in sildenafil than nifedipine groups (0.577±0.029, 0.417±0.090 and 0.3605±0.817 vs 0.545±0.029, 0.300±.001 and 3.180±0.775 for PI, RI and endometrial thickness differences, respectively) (Table 3).

The side effects reported with treatment were in the form of headache, palpitation and flushing. They were reported in 18.0%, 10.0% and 10.0%, respectively in the nifedipine group, compared to 24.0%, 16.0% and 16.0% respectively in sildenafil group, with no significant differences between groups (Table 4).

Table (1): Demographic data of the study groups

Variables	Nifedipine	Sildenafil	Test	p
Age (years)	26.80±2.73	26.30±3.14	0.848	0.398
Wight (kg)	70.24±3.99	71.30±3.14	1.476	0.143
Height (m)	1.6526±0.0302	1.6630±0.0314	1.686	0.095
BMI (kg/m²)	25.72±1.34	25.77±0.15	0.244	0.806
Previous miscarriage	3.24±0.94	3.36±0.98	0.623	0.534

Table (2): Laboratory investigations among study groups

Variables	Nifedipine	Sildenafil	Test	p
RBCs x 10^6	4.344±0.554	4.286±0.450	0.573	0.567
WBCs x 10^3	5.05±0.628	4.974±0.472	0.683	0.496
Platelets x 10^3	268.94±47.79	256.20±26.21	1.652	0.102
Hct%	36.68±1.39	36.86±1.14	0.707	0.481
Hb (g/dl)	11.68±0.613	11.82±0.597	1.317	0.244
HbA1C%	5.75±0.372	5.68±0.246	1.013	0.313
TSH	3.058±0.545	3.208±0.649	1.250	0.214
Prolactin (ng/ml)	12.98±3.73	13.40±2.30	0.676	0.500
AST	17.00±2.61	17.18±2.24	0.370	0.712
ALT	13.10±2.25	12.50±1.72	1.497	0.137
Creatinine	0.62±0.17	0.67±0.21	1.250	0.214
Urea	16.16±2.10	16.66±2.28	1.095	0.276

Table (3): Comparison between study groups regarding ultrasound doppler indices before and after treatment

	Variables	Nifedipine	Sildenafil	Test	p
Uterine artery PI	Before	1.998±0.213	1.990±0.173	0.204	0.837
	After	1.453±0.208	1.413±0.170	1.042	0.300
Paired comparison	***Paired "p"***	***134.12***	***141.08***		
	Paired "t"	***<0.001****	***<0.001****		
Uterine artery RI	Before	1.066±0.117	1.067±0.111	0.045	0.965
	After	0.766±0.119	0.650±0.097	***5.38***	***<0.001****
Paired comparison	***Paired "p"***	***30.21***	***32.71***		
	Paired "t"	***<0.001****	***<0.001****		
Endometrial thickness	Before	6.636±0.733	6.741±0.628	0.796	0.444
	After	9.816±0.431	10.346±0.591	***5.125***	***<0.001****
Paired comparison	***Paired "p"***	***29.00***	***31.19***		
	Paired "t"	***<0.001****	***<0.001****		
PI difference		0.545±0.029	0.577±0.029	***5.483***	***<0.001****
RI difference		0.300±.001	0.417±0.090	***9.179***	***<0.001****
Endometrial thickness		3.180±0.775	0.3605±0.817	***2.667***	***<0.001****

Table (4): Comparison between study groups regarding side effects

Variables	Nifedipine	Sildenafil	Test	p
Headache	9 (18.0%)	12(24.0%)	0.54	0.46
Palpitation	5(10.0%)	8(16.0%)	0.796	0.372
Blurred vision	0(0.0%)	0(0.0%)	-	-
Flushing	5(10.0%)	8(16.0%)	0.796	0.372
Nausea/vomiting	0(0.0%)	0(0.0%)	-	-
Diarrhea	0(0.0%)	0(0.0%)	-	-

DISCUSSION

Unexplained recurrent pregnancy loss is a challenge of daily obstetric practice. No cause can be identified for the cases. However, it had been suggested the endometrial blood flow and endometrial thickness may play a role in the pathogenesis of the process [24]. Thus, this study was designed to examine the effectiveness and safety of vasodilator drugs with two different mechanisms (nifedipine and sildenafil) on the uterine blood flow and endometrial thickness in women with unexplained PRL. The results of the study showed that, both drugs were associated with improvement of uterine artery doppler indices and endometrial thickness after a first cycle of treatment. The group received sildenafil showed more improvement than nifedipine. However, with slight increase of side effects. But the difference regarding side effects did not reach statistical significance. These results are comparable to a previous study by **Saleh *et al.*** [25] who reported that sildenafil was more effective than nifedipine in improvement of endometrial thickness and uterine blood flow. In addition, the current results agree with previous studies carried out by **Huissoud *et al.*** [26] and **Firouzabadi *et al.*** [27], which demonstrated significant improvements of uterine artery blood flow and endometrial thickness with the use of nifedipine and sildenafil.

Furthermore, **Bahaa (24)** carried a randomized comparative trial to investigate the effects of adding small dose sildenafil citrate to aspirin and folic acid on the uterine blood flow and pregnancy rate in women with unexplained RPL. They reported significant reduction of PI and RI of the uterine artery in groups supported by sildenafil citrate than the non-supported group. In addition, the serum nitric oxide levels and conception rate, and cases completed their pregnancy beyond the first trimester were increased in the sildenafil treated group. They concluded that oral administration of low dose of sildenafil citrate (20 mg/day) is relatively safe and increased the possibility of conception in women with unexplained RPL. In addition, it could maintain their pregnancy beyond the first trimester.

To explain the possible effects of sildenafil and nifedipine with based mainly on their vasodilator actions, it was reported that sildenafil citrate rapidly decreases the mean arterial pressure, increases the heart rate and blood flow to the uterus [28]. Furthermore, sildenafil influences angiogenesis, platelet activation, proliferation of regulatory T cells, and production of proinflammatory cytokines and autoantibodies [29].

In line with our results, **Mostafa** [30] reported that the use of sildenafil citrate was significantly associated with lower uterine artery PI, RI and systolic/diastolic ratio compared to placebo group. Sildenafil citrate has an effective role in increasing the uterine arteries blood flow in patients with recurrent miscarriage. These results are expected because sildenafil citrate is NO donor and consequently increases serum NO of treated group, thus may explain the increase in uterine blood flow.

In addition, sildenafil citrate reduced the natural killer cell activity and improved the chance of successful pregnancy and endometrial thickness was significantly increased after such therapy in women with a history of RPL as reported by **Jerzak *et al.*** [31]. In addition, it was reported that sildenafil improved the measured antioxidants concentrations and reduced reactive oxygen species [32].

In conclusion, both oral nifedipine and Sildenafil demonstrated a good safety profile, with good effectiveness in improving uterine artery doppler indices and subsequently improved uterine blood flow and increased thickness in women with unexplained RPL. However, Sildenafil is associated with better results than nifedipine with nearly similar safety profile.

The current results, irrespective of their valuable addon effect to the known literature, must be treated cautiously and validated in future studies. This is due to study limitations, which include the small sample size, short duration of treatment, and its single-center nature with potential bias.

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