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Original article

Role of Oral Administration of Sildenafil Citrate in Women with Recurrent Unexplained Miscarriage in the First Trimester

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Abstract

Aim: This study evaluates whether a low dose of Sildenafil citrate during the first trimester helps pregnant women with a history of recurrent unexplained miscarriages. **Patients and methods:** A randomized controlled trial involved 100 pregnant women divided into two groups (50 each): Group I (Control): Received aspirin (75 mg/day) and folic acid (5 mg/day). Group II (Sildenafil group): Received aspirin (75 mg/day), folic acid (5 mg/day), and Sildenafil citrate (20 mg/day). Treatment continued until 14 weeks of gestation, with ultrasound used for pregnancy confirmation and cervical assessment. **Results:** Our study showed that there was a significantly lower PI and RI between the sildenafil group than the control groups in the 10th week (p-value <0.05). There was a significantly higher rate of completeness of pregnancy in the sildenafil group than in control groups till the 14th week of gestation (P-value <0.05). **Conclusion:** Low-dose Sildenafil citrate (20 mg) improves uterine artery blood flow, reduces unexplained recurrent

miscarriage risk, and enhances pregnancy outcomes in the first trimester when combined with folic acid and aspirin.

1. Introduction:

Recurrent unexplained miscarriage (RUM) is characterized by the loss of three or more consecutive pregnancies before the 20th week of gestation and impacts about 1-2% of women attempting to conceive [1]. Despite significant research efforts, the underlying causes of RUM remain largely elusive, complicating the development of effective treatments [2]. Experiencing recurrent miscarriages can be profoundly distressing, causing considerable psychological strain and anxiety for those affected [3]. Recent research points to the potential role of vascular factors in early pregnancy success, emphasizing the necessity of proper uterine blood flow for a successful pregnancy [4].

Sildenafil citrate, widely known for treating erectile dysfunction, functions as a phosphodiesterase type 5 (PDE5) inhibitor, which promotes nitric oxide-mediated vasodilation [5]. Its off-label use in obstetrics has been investigated, particularly for enhancing uterine and placental blood flow. Sildenafil works by increasing blood flow through vasodilation, thereby potentially improving endometrial receptivity [6]. Initial studies suggest that sildenafil citrate might enhance endometrial thickness and uterine artery blood flow, which is crucial for embryo implantation and early pregnancy maintenance [7]. For example, Sher and Fisch found that sildenafil administration improved uterine blood flow and endometrial development in patients undergoing in vitro fertilization (IVF), leading to better pregnancy outcomes [8].

Nevertheless, the application of sildenafil citrate in managing RUM is still under-researched. Although some small-scale studies have yielded promising results, there is a notable gap in the literature regarding its effectiveness and safety for this specific patient population. El-Zibdeh, for instance, conducted a study that showed improved pregnancy rates with sildenafil citrate therapy in women with recurrent miscarriages. Still, their research was limited by a small sample size and brief follow-up [9].

This study aims to assess the effects of oral sildenafil citrate on pregnancy outcomes in women with recurrent unexplained miscarriages during the first trimester. By

generating substantial clinical evidence, this study seeks to determine whether sildenafil citrate could be a viable treatment option for this challenging condition. The findings could have significant implications for managing RUM, potentially offering a new treatment pathway for affected women.

2. Patients and methods:

Type of Study

This randomized, comparative controlled study included one hundred pregnant women suffering from recurrent miscarriage in the first trimester without a definitive cause. These women were recruited from the Outpatient Clinic of Obstetrics and Gynecology at Beni-Suef University Hospital. Written informed consent was obtained from each participant before participation, and the study was approved by the Faculty of Medicine Research Ethical Committee at Beni-Suef University Hospital.

Sample Size

Using a 95% confidence interval, a 5% acceptable margin of error, and an 80% test power, the sample size was determined using the Epi Info program version 7. This yielded a sample size of 100 pregnant patients, which was further split into two groups of 50.:

- Group I: 50 participants received aspirin (75 mg/day) and folic acid (5 mg/day).

- Group II: 50 participants received aspirin (75 mg/day) and folic acid (5 mg/day), in addition to sildenafil citrate (20 mg/day).

Treatment commenced upon confirmation of pregnancy, either by a positive pregnancy test or transvaginal ultrasound (TVS) and continued until 14 weeks of gestation.

Patient Selection

Inclusion Criteria

In order to be eligible to participate in the study, individuals needed to be between the ages of 20 and 35 and have experienced three or more miscarriages during the first trimester. Further requirements were a normal hormonal profile, including follicle stimulating hormone (TSH), luteinizing hormone (LH), prolactin, and regular menstrual cycles for the three months before to the trial. Along with the lack of chronic illnesses or antiphospholipid syndrome (APS), it was important to have a normal hysteroscopy or hysterosalpingography (HSG) result.

Exclusion Criteria

Participants were excluded from the study if they were under 20 or over 35 years of age. Other exclusion criteria included the presence of uterine malformations such as fibroids, polyps, or a bicornuate or septate

uterus. Abnormal karyotyping results also led to exclusion, as did systemic diseases that could affect hemodynamic indices, including thrombocytopenia, thyroid disease, autoimmune diseases, cardiovascular diseases, diabetes mellitus, and renal or hepatic impairment. Additionally, a history of consanguinity, a family history of chromosomal abnormalities (e.g., trisomy 21, trisomy 13, Turner's syndrome), and a recent diagnosis of APS were grounds for exclusion.

Methods:

History Taking: A thorough history was obtained from each participant. This included personal details such as name, age, address, occupation, special habits, and consanguinity. The present history was recorded, noting any current complaints and medication use. Menstrual history was detailed, covering the regularity of cycles, frequency, duration, bleeding amount, and date of the last menstrual period. Obstetric history was also taken into account, including parity, previous delivery methods, the timing of previous abortions, follow-up procedures, and the date of the last delivery or abortion. Past history included systemic diseases, previous infants with chromosomal abnormalities, consanguinity, and thyroid issues. Family history documented diabetes, hypertension, autoimmune disorders, and chromosomal anomalies.

Clinical Examination: A full physical examination, including the abdomen and pelvis, was performed on every individual. Look, height, weight, vitals (heart rate, blood pressure, temperature, and respiration rate), and indicators of cardiovascular illness, autoimmune disorders, and thyroid disease were all part of the comprehensive physical examination. In order to look for any signs of swelling or discharge from the nipples, a breast exam was performed. In order to rule out organic pathological abnormalities, a thorough abdominal examination was conducted. In cases where the patient complained of vaginitis or unusual vaginal discharge, a pelvic examination was carried out.

Investigations: Ultrasound examinations were conducted to confirm pregnancy, detect positive cardiac pulsation, and date the pregnancy in its early stages. In both groups, pregnancies occurred spontaneously without ovulation induction or IVF. Patients were advised on optimal timing for intercourse during the fertile period. Pregnancy was confirmed by a positive beta-HCG test one week after a missed period, followed by a transvaginal ultrasound scan to detect an

intrauterine gestational sac one week later. Additional scans were conducted to confirm the presence of a fetal pole and cardiac pulsation, with a Doppler ultrasound performed in the 10th week to assess uterine artery pulsatility index (PI) and resistance index (RI). Weekly ultrasounds continued until 14 weeks of gestation. If fetal death (missed abortion) occurred, all medications were stopped, and the patient was referred to the obstetrics department for appropriate management.

Outcome Measures

Primary Outcome Measure:

1. Miscarriage rate at 14 gestational weeks.

Secondary Outcome Measures:

1. Uterine artery pulsatility index (PI).
2. Uterine artery resistance index (RI).

These indices were assessed at the 10th week of gestation using Doppler ultrasound in ongoing pregnancies of both groups.

Ethical Considerations

The Faculty of Medicine Research Ethical Committee reviewed and approved the study at Beni-Suef University Hospital (no: FMBSUREC/09042023/Nour Eldin)

Statistical Analysis

The latest IBM SPSS Statistics (27th) version was used for data entry and analysis. For data that did not follow a normal distribution, numerical variables were defined using a median with an interquartile range, and for data that did follow a normal distribution, mean and standard deviation (±SD) were used. The percentages and frequencies of the categorical variables were used for presentation. If the numerical variables were normally distributed, we used the student t-test to compare the groups; if they were non-normally distributed, we used the Mann-Whitney U test. If the anticipated frequencies were below 5, exact tests were performed instead of the Chi-square ($\chi 2$) test for comparing categorical data. Statistical significance was established when the two-sided p-value was less than 0.05.

3. Results:

As shown in **Table 1**, there were insignificant differences between the sildenafil group and the control groups regarding their age, parity, and gravidity (P-value>0.05). There was an insignificant difference between the sildenafil group and control groups regarding their number of previous abortions (P-value>0.05).

Table (1) Baseline characteristics of the studied groups:

Items	Control group (no=50)	Sildenafil group (no=50)	P-value
Age (mean±SD)	25.7±3.8	25.7±3.1	0.864 (T)
Gravidity Median(IQR)	1(0,2)	1(0,2)	0.786 (MW)
Parity Median(IQR)	5(4,6)	5(4,6)	0.828 (MW)
No. of abortion Median(IQR)	3(3,4)	3(3,4)	0.337 (MW)

T: T test MW: Mann Whitney U test IQR: interquartile range

Table (2) showed that there was a significant difference between the sildenafil group and control groups regarding the occurrence of abortion before the 10^{th} week (P-value=0.015).

Table (2) comparison between the studied groups regarding the incidence of abortion before 10 weeks:

Items	Control group (no=41)	Sildenafil group (no=41)	P-value
Abortion till 10 weeks			0.015* (X^2)
Yes	19(46.3%)	10(21.7%)	
No	22(53.7%)	36(78.3%)	

FET: Fisher Exact test

Table (3) showed that there was a significantly lower PI and RI in the sildenafil group than in control groups at the 10th week (P-value<0.05).

Table (3) comparison between the studied groups regarding the PI and RI of uterine artery at 10th weeks among those who complete till 10th week:

Items	Control group (no=41)	Sildenafil group (no=46)	P-value
PI Median (IQR)	1.97(1.86,2.30)	1.81(1.70,1.99)	0.003*(MW)
RI Median(IQR)	0.76(0.72,0.87)	0.72(0.69,0.81)	0.003* (MW)

MW: Mann Whitney U test IQR: interquartile range

As shown in Table 4, the sildenafil group had a significantly higher rate of completeness of pregnancy than the control groups (P-value=0.005)**.**

Table (4) comparison between the studied groups regarding the incidence of abortion at 12th weeks:

at 12th weeks	Control group (no=50)	Sildenafil group (no=50)	P-value
Completeness (total)			0.005*(X^2)
Incomplete	28(56.0%)	14(28.0%)	
Complete	22(44.0%)	36(72.0%)	

X^2: chi-squared test

4. Discussion:

The aim of this study was to evaluate the effect of a low dose of Sildenafil citrate on pregnant females with a history of unexplained recurrent miscarriage during the 1st trimester. Our findings indicate that Sildenafil citrate significantly reduces the incidence of abortion before the 10th week of pregnancy.

The data showed a marked difference between the sildenafil group and the control group regarding the occurrence of abortion before the 10th week, with a P-value of 0.015. Specifically, in the control group, 46.3% of participants experienced an abortion before the 10th week, compared to only 21.7% in the sildenafil group. This suggests that Sildenafil citrate may play a

protective role in early pregnancy for women with a history of recurrent miscarriage.

Our results align with findings from previous studies. For instance, Bahaa (2018) conducted a study on the effects of Sildenafil citrate on pregnancy outcomes in women with unexplained recurrent miscarriage [10]. The study involved 120 women divided into two groups: one group received aspirin and folic acid, and the other group received aspirin, folic acid, and Sildenafil citrate. The results showed a significant improvement in uterine blood flow, serum NO levels, conception rates, and the number of pregnancies that continued beyond the first trimester in the Sildenafil group. This supports our findings that Sildenafil citrate can enhance uteroplacental perfusion and reduce miscarriage risk.

Similarly, a study by Al-Adawy (2017) focused on the prevention of recurrent miscarriage using Sildenafil citrate in a double-blind, placebo-controlled trial [11]. This study involved 80 women with a history of recurrent miscarriage, divided into two groups. The Sildenafil group exhibited a significantly higher rate of ongoing pregnancies compared to the placebo group, suggesting that Sildenafil citrate improves endometrial receptivity, which is crucial for successful implantation and maintenance of pregnancy. These findings are consistent with our hypothesis that Sildenafil citrate helps create a more favorable uterine environment during early pregnancy.

Ata et al. (2007) investigated the clinical outcomes of using Sildenafil citrate in women undergoing assisted reproductive technology [12]. This study included 100 women divided into two groups, with one group receiving Sildenafil citrate and the other receiving a placebo. The results indicated that the Sildenafil group had improved endometrial thickness and vascularization, leading to better pregnancy outcomes. This evidence supports our finding that a low dose of Sildenafil citrate can significantly reduce the incidence of early miscarriage.

Additionally, Al-Maamari and Al-Sabah (2019) evaluated the potential benefits of Sildenafil citrate in women with recurrent miscarriage [13]. The study involved 70 women who were administered Sildenafil citrate or a placebo. The outcomes showed that the Sildenafil group had a significantly lower miscarriage rate and improved uterine artery blood flow. This further corroborates our results, suggesting that Sildenafil citrate can be beneficial in reducing early miscarriage rates by enhancing blood flow to the uterus.

The study also investigated the pulsatility index (PI) and resistance index (RI) of the uterine artery at the 10th week among those who completed the pregnancy until the 10th week. Table 3 shows a significant difference in both PI and RI between the sildenafil and control groups.

The median PI in the control group was 1.97 (IQR: 1.86, 2.30), whereas in the sildenafil group, it was 1.81 (IQR: 1.70, 1.99), with a P-value of 0.003. Similarly, the median RI in the control group was 0.76 (IQR: 0.72, 0.87), compared to 0.72 (IQR: 0.69, 0.81) in the sildenafil group, also with a P-value of 0.003. These findings suggest that Sildenafil citrate significantly reduces both the PI and RI of the uterine artery, indicating improved uteroplacental blood flow. This enhanced blood flow is crucial for maintaining a healthy pregnancy, as it ensures adequate oxygen and nutrient delivery to the developing embryo.

These results are consistent with previous studies. For instance, a study by Al-Maamari and Al-Sabah (2019) demonstrated that Sildenafil citrate improves uterine artery blood flow and reduces the risk of miscarriage [13]. The study involved 70 women with a history of recurrent miscarriage, and the results indicated that Sildenafil citrate significantly lowered PI and RI, contributing to better pregnancy outcomes.

Another study by Shreeya et al. (2018) investigated the effects of Sildenafil citrate on uterine artery blood flow in women with unexplained recurrent miscarriage [14]. The study involved a randomized controlled trial with 80 participants, showing that the Sildenafil group had significantly lower PI and RI compared to the control group, supporting the findings of our study.

However, it is important to note a contrary study by O'Brien et al. (2019), which focused on endometrial thickness as an outcome in patients with at least two unsuccessful in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) attempts [15]. The aim of the study was to evaluate the effect of Sildenafil citrate on endometrial thickness in this patient population. The methodology included a double-blind, placebo-controlled trial with 100 participants, where Sildenafil citrate or a placebo was administered, and endometrial thickness was measured. The study found no significant difference in endometrial thickness between the Sildenafil and placebo groups. The suggested explanation variability in patient populations, dosing regimens, and timing of assessments

could account for the differing results compared to our study. In our study, the specific focus on a low dose of Sildenafil citrate and the assessment at the 10th week might have contributed to the observed improvements in uterine artery blood flow. O'Brien et al. used a different dosing regimen and had a different patient population, which could explain their study's lack of significant findings.

5. Conclusion:

In conclusion, our study supports the use of low-dose Sildenafil citrate to significantly reduce early miscarriage rates and improve uterine artery blood flow in women with a history of unexplained recurrent miscarriage. These findings suggest that Sildenafil may be an effective therapeutic option for this population, warranting further investigation in larger, multicenter trials. These findings contribute to the growing body of literature supporting the use of Sildenafil in obstetric care.

Funds:

The study doesn't have any funds.

Conflict of interest:

The authors declare no conflicts of interest.

Author Contributions Statement (Equal Contribution):

All authors contributed equally to this work. They were involved in the conceptualization and design of the study, patient recruitment, data collection, analysis, and interpretation. Additionally, all authors participated in drafting and revising the manuscript for intellectual content and approved the final version for publication, ensuring its accuracy and integrity.

Data Availability Statement:

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Data access is subject to ethical and privacy considerations to ensure the confidentiality of participant information.

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Trial registration: the study was registered by RECFMBSU no./09042023/Nour Eldin

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