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The Effects of Nitric Oxide Patch Versus Oral Sildenafil Citrate on First Trimester Pregnant Women with a History of Recurrent Miscarriage

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Abstract

- The present cohort study was planned to investigate the clinical effect of sildenafil citrate (SC) tablets as well as nitric oxide (NO) patch for treatment of first trimester pregnant women with a history of unexplained recurrent spontaneous abortion.
- The survey was carried on 60 first trimester pregnant women with a history of recurrent miscarriage. The patientwas divided into two equal groups. The first patient group received SC 20 mg orally, 3 times/day and the second patient group received NO patch. We judged the effectiveness of this treatment on the patients.
- We establish that both oral SC and NO patch decreased the incidence of spontaneous recurrent first trimester abortion.
- In ending, we report evidence that both oral SC and NO patch can offer and optional therapy for cases of spontaneous recurrent first trimester abortion.

Keywords: Sildenafil citrate; Nitric oxide patch; Unexplained recurrent spontaneous miscarriage; Abortion.

Introduction

Recurrent miscarriage (RM) is a common pregnancy complication. It is defined as three or more consecutive pregnancy losses that take office before the fetus reaches viability, i.e., prior to 24 gestational weeks [1]. The etiology of RM is variable [2]. The mechanisms of early embryo loss observed are not yet fully realized [3].

Approximately 15 to 20% of clinically recognized pregnancies end in miscarriage, and approximately 1 to 5% of pregnant women experience the recurrent miscarriage (RM), of which 40 to 55% are caused by unknown causes [4].

A substantial body of experimental evidence suggests a relationship between nitric oxide (NO) and prostaglandins [5], particularly in pathophysiologic events associated with gestation. It is found that epidermal growth factor and IL-1enhance PG production by stimulating NO synthase (iNOS) activity [6].

El-Far et al., showed for the first time, in the preliminary report, that sildenafil citrate might be a novel, interesting, safe anti-abortive option in the treatment of threatened miscarriage in four patients with a history of unexplained recurrent spontaneous miscarriage [7].

The aim of this study was to evaluate the effects of nitric oxide patch versus oral sildenafil citrate in treating women with a history of unexplained first trimester recurrent fetal wastage.

Patients and Methods

The present cohort study was a comparative clinical study that included 60 first trimester pregnant women who had been selected from the outpatient high risk pregnancy clinic of the Obstetrics Department of Tanta University Hospital during the period from June 2017 to June 2018.

The inclusion criteria of the selected women were:Age ranged from (20-35) years old, BMI $\geq$ 25 kg/m^2, Frist trimester pregnant women with a history of two or more unexplained recurrent spontaneous first trimester miscarriage, Singleton pregnancy, gestational age (4-6 weeks) that was calculated from the first day of the last normal menstrual period and confirmed by transvaginal ultrasonography to detect intrauterine gestational sac.

The exclusion criteria were: patients that received any potential causes of abortion as: Congenital anomalies of the uterus, Luteal phase defect, Smokers, History of PCO or endometriosis, Abnormal karyotyping, Any chronic disorders including endocrine disorders, renal,cardiovascular, hepatic infectious disorders or immunological (APS).

A written informed consent from every patient included in this survey. The consent is turned out by the medical ethics committee of Tanta University Hospital.

Methods

All cases were subjected to the following:

1. Full history taking with special concern about the details of each abortion.
2. Through clinical general and abdominal exams.
3. Choosing blood pressure at booking and follow up in each visit using puppetry and auscultatory methods while patient in semi-sitting stance, then the average arterial blood pressure was estimated by MAP = 1/3 (SBP) + 2/3 (DBP) where (MAP is the mean arterial pressure, SBP is the systolic blood pressure, and DBP is the diastolic blood pressure.)
4. Investigations related to recurrent miscarriage including:
   - Routine laboratory investigations for pregnancy as (Rh factor, CBC, blood group and Urine analysis)
   - Immunological investigations (anticardiolipin, antinuclear and antiphospholipids antibodies).
   - Hormonal investigations (Thyroid function tests, fasting blood sugar, post prandial blood sugar, HbA1c and tests for thorombophilipitis)
5. Patients were randomly assigned into two groups:
   - Group A (SC group): Thirty patients received 20 mg sildenafil citrate (Respatio, Pharma Right Group) orally 3 times daily at booking till 14 weeks gestational age.
   - Group B(NO group): Thirty patients used (50 mg) Nitroglycerin transdermal patch (Novartis Pharma AG, Stein, Switzerland) on the abdominal skin below the umbilicus, releasing nitroglycerin at a rate of 0.4 mg/h, once daily for 12 hours from the day of booking till 14 weeks gestational age.
   - Both groups received folic acid 400 microgram/day.
   - Transabdominal pulsed wave color Doppler imaging was performed for each selected woman before treatment, two hours after beginning treatment, and was repeated every 2 weeks, according to the antenatal schedule of high risk pregnancy till 14 weeks gestational age. It was done to evaluate the uterine arteries bilaterally and sub-endometrial blood flow (pulsitility index (PI) and restrictive index (RI).
   - Ultrasound examination was performed for all selected women at the end of 14 weeks GA to exclude any fetal congenital anomalies.
   - Ethics committee: The study started after medical ethical committee approval. All included cases have been informed about aim and the nature of this study, risk elements, possible side effect of the drug.

Results

Among the cases of SC group success pregnancy occurred in 65% of cases (13 out of 20 patients). Among cases of NO group a success of pregnancy took place in approximately 55% of cases (11 out of 20 patients). Normal babies were delivered in all cases of the two groups. The other results are summarized in 6 tables.

In SC group 2 patients refused to take the drug and 3 patients complained of severe headache therefor stopped drug administration. Four patients of NO group refused the application of NO patch to abdominal skin and 2 suffered from skin rash and severe headache.

Discussion

Recurrent early pregnancy loss accounts for almost 20% of clinically recognized pregnancy losses. Apart from the well-known risk factors, the effect of pregnancy depends, to a great extent, on the success rate of early events, such as implantation, the establishment of fetomaternal circulation, maintenance of increased blood flow on the implantation site [8].

The mechanisms of early embryo loss observed are not yet fully realized. Most of our knowledge regarding the mechanism of early fetal resorption has been obtained by studying the cell biology of resorption prone matings [3].

The vasoactive drug, sildenafil citrate has proven useful in reducing adverse pregnancy events. An important biological function of its action is an inhibition of cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 activity, which could have beneficial effects on trophoblast survival [9].

Nitric oxide is required for trophoblast cell survival and appears to be critical for endovascular invasion necessary for normal placental perfusion and the associated phenotype switching [10].

The purpose of this work was to assess the effects of nitric oxide patch versus oral sildenafil citrate in first-trimester pregnant women with a history of spontaneous recurrent miscarriage.

In the current study, we found that among the cases of SC group success of pregnancy occurred in 65% of cases. This may be explicated by the fact that sildenafil citrate has been proven to be useful in increasing endometrial thickness and achieving pregnancy in women with varied uterine disorders. It is suspected that this medication causes selective vasodilatation, resulting in improved endometrial development [11].

The administration of sildenafil enhanced endometrial development in 70% of patients studied. High implantation and ongoing pregnancy rates were accomplished in a cohort with a poor prognosis for success [12].

Endometrial thickness is one of the most potent predictors of implantation rate and ongoing pregnancy success rate. The endometrial growth is dependent on the uterine blood flow and angiogenesis. Sildenafil citrate leads to smooth muscle relaxation and vasodilation. Because of these biological properties, it is a potential candidate for female infertility, especially in the management of thin endometrium, which leads to low implantation and pregnancy rates [13].

El-Far and associates in 2009 conclude that the sildenafil citrate tablets used as suppositories might be a safe anti-abortive option in the treatment of threatened miscarriage in patients with a history of unexplained recurrent miscarriage [7].

In addition, the contemporary study revealed that among cases of NO group a success of pregnancy took place in approximately 55% of cases. This can be ascribed to the reductive effects of NO on the contractile action of the human uterine cervix in early pregnancy [14].

The present study depicted a decrease in the average arterial blood pressure (MAP) of both studied groups 2 hours after the administration of the drug (table 2). Nevertheless, there was a substantial divergence between the two groups in MAP during the 2 hours after medication and 14 weeks pregnant after drug usage with more decrease among the SC group. This can be excused by the fact that sildenafil citrate induces vasodilation through inhibition of type 5 phosphodiesterase (PDE5) [15].

The Doppler study of this work indicated a strong reduction in sub-endometrial arteries RI and both uterine arteries RI in the two groups in the 2 hours after medication and at 14 weeks gestation (tables 3-6). EL-Far and associates set up similar effects.

Trapani and co-workers in 2015 found that the use of sildenafil citrate or transdermal nitroglycerin is associated with a substantial decrease in both uterine artery Doppler and uterine artery Pulsatility index, as well as maternal arterial blood pressure [16].

Recently, nitric oxide synthase (eNOS) has been reported to be over-expressed in the glandular and luminal epithelium of the endometrium in women with recurrent miscarriage and unexplained infertility, suggesting a detrimental effect of excess NO on endometrial receptivity and implantation [17]. Lastly, we close that both SC and NO patch are additional choices for treatment of unexplained recurrent spontaneous abortion.

Disclosure

We announce that we did not get any fund from whatever individual or establishment. If the patient refused to finish the field, she was taken out and replaced by another one from who are satisfying the inclusion criteria of the survey. We did not classify the patients according to their religious belief or civilization or race or any other unrelated points.

Conflict of interest

The authors declare no conflicts of interest in this study.

Table (1). The clinical data of the two study groups:

	Age (years)		**BMI** (kg/m²)		**Gestational age** (Weeks)		**Numberof previous abortions**		**HB%** (gm/dl)	
Groups	**SC (n=25)**	**NO patch (n=24)**	**SC (n=25)**	**NO patch (n=24)**	**SC (n=25)**	**NO patch (n=24)**	**SC (n=25)**	**NO Patch (n=24)**	**SC (n=25)**	**NO patch (n=24)**
Range	22 – 35	20 – 33	25 – 30	22-33	4-6	4-6	2-4	2-4	10.5 – 12.5	11-12.4
Mean ± SD	27.32 ±4.298	26.88±3.745	28.40±1.291	27.46±2.859	7.12±0.833	6.92±0.83	2.48±0.653	2.67±0.637	11.556±0.5276	11.471±0.3581
P. Value	**0.701**		**0.141**		**0.396**		**0.317**		**0.514**	

SC= **Sildenafil citrate** No = Nitroglycerine

Table (2). The mean arterial blood pressure (MAP) ((d*2) +s)/3, of the two study groups.

	Mean arterial blood pressure ((d*2) +s) /3 (mm Hg with sildenafil (n=25)						**Mean arterial blood pressure ((d*2) +s)/3) mmHg with nitrodermal patch (n=24)**					
	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)
Range (mm Hg)	87-102	80 –92	79-91	76-90	73-90	70 - 90	85-105	81– 97	80-95	78-92	76-90	75-95
Mean ± SD	94.8±4.664	79.52± 4.363	78.21± 4.253	77.42± 4.458	77.52 ±4.524	77.2±4.635	96.17±4.975	88.58± 4.742	87.92± 4.453	86.52± 4.668	85.38±4.763	84.92±4.80
P-value	<0.001*						<0.001*					
	0.1410											

GA = Gestational age

Table (3). The resistive index of the meanuterine artery of the two study groups.

	Mean uterine artery resistive index (RI) With sildenafil **(n=25)**						**Mean uterine artery resistive index (RI)** With nitrodermal patch **(n=24)**					
	Before	**2 hours after**	**8 weeks GA**	**10 weeks GA**	**12 weeks GA**	**14 weeks GA (n=23)**	**Before**	**2 hours after**	**8 weeks GA**	**10 weeks GA**	**12 weeks GA**	**14 weeks GA (n=23)**
Mean±SD	0.601±0.0435	0.488±0.0275	0.472±0.024	0.47±0.023	0.451±0.022	0.434±0.019	0.597±0.0406	0.453±0.027	0.434±0.026	0.429±0.025	0.411±0.02	0.4079±0.01793
P-value	<0.001*						<0.001*					
	0.024398											

GA = Gestational age

Table (4). The pulsatility index (PI) of the mean uterine artery of the two study groups.

	Mean uterine artery (PI) With sildenafil (n=25)					Mean uterine artery (PI) Withnitrodermal patch (n=24)					
	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)
Mean ± SD	1.98 ±0.14	1.5 ±0.09	1.32 ±0.08	1.24 ±0.062	1.15 ±0.059	1.1 ±0.055	1.85 ±0.124	1.35 ±0.0852	1.26 ±0.074	1.21 ±0.0598	1.15 ±0.053	0.92 ±0.0492
P-value	<0.001*					<0.001*						
	0.20678											

GA = Gestational age

Table (5). Sub-endometrial arteries resistive index (RI) of the two study groups.

	Sub-endometrial artery (RI) With sildenafil (n=25)						Sub-endometrial artery (RI) Withnitrodermal patch (n=24)					
	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)
Mean ± SD	0.872 ±0.0456	0.7648 ±0.035	0.744 ±0.0332	0.724 ±0.03125	0.708 ±0.02856	0.698 ±0.0245	0.925 ±0.052	0.829 ±0.0437	0.814 ±0.0421	0.78 ±0.0392	0.758 ±0.0375	0.727 ±0.0325
P-value	<0.001*						<0.001*					
	0.185223											

GA = Gestational age

Table (6). Sub-endometrial arteriespulsatility index (PI) of the two study groups.

	Sub-endometrial a. (PI) With sildenafil (n=25)						Sub-endometrial a. (PI) Withnitrodermal patch (n=24)					
	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)	Before	2 hours after	8 weeks GA	10 weeks GA	12 weeks GA	14 weeks GA (n=23)
Mean ± SD	2.88 ±0.62	1.98 ±0.58	1.89 ±0.54	1.85 ±0.51	1.83 ±0.49	1.79 ±0.472	2.92 ±0.65	2.15 ±0.612	1.92 ±0.584	1.872 ±0.542	1.852 ±0.529	1.819 ±0.518
P-value	<0.001*						<0.001*					
	0.784688											

GA = Gestational age

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