

## Vaginal Sildenafil: Role in Improving Endometrial Blood Flow in Women Undergoing IVF With Frozen- Thawed Embryo Cycles- A Study Over Three Cycles



### Medical Science

KEYWORDS :

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### ABSTRACT

**OBJECTIVE:** To investigate the effect of vaginal sildenafil on endometrial blood flow in infertile women with prior poor endometrial response.

**MATERIAL AND METHODS:** This study was carried out in the Department of Obstetrics and Gynecology of IKDRC-ITS, Ahmedabad from January 2014 to December 2014. A total of 55 infertile women with an antecedent poor endometrial vascularity and frozen embryos were included in this study. The women were given oral estradiol valerate tablets (6- 20 mg daily), and tablet ecospirin ( 75 mg daily) from day 2-14 of the cycle to prepare the endometrium . Women were advised to take sildenafil capsule intravaginally, 25 mg thrice a day, starting from day 5-13 of the cycle. Assessment of endometrial thickness, pattern and vascularity was done on day 14 of the cycle on voluson E8 using transvaginal probe (5-9 MHz).

**RESULTS:** Twenty seven (49.9%) women showed improvement in vascularity. Embryo transfer was done in 19 women, out of which 9(47.36%) conceived.

**CONCLUSION:** As our study shows, intravaginal use of sildenafil is a good way to improve endometrial vascularity and receptivity. We recommend the routine use of vaginal sildenafil in women with a previous failure of assisted reproductive technology cycles due to poor endometrial response.

### Introduction

The etiology of infertility is diverse. Despite the improvement in ovarian stimulation protocols and techniques, results of in vitro fertilization (IVF) has unfortunately reached a plateau. Diverse and unexplained factors affecting implantation rates have become a major limiting factor. Therefore, more attention needs to be focused on implantation and endometrial receptivity. Good embryo quality, appropriately timed and arranged endometrial receptivity, and efficient crosstalk between the embryo and the receptive endometrium are required for successful implantation. Impairment of any one of these factors may result in implantation failure (1).

Endometrial receptivity during the implantation window depends on various factors , the morphological markers are (2):

1. Endometrial thickness
2. Endometrial echogenic pattern
3. Endometrial and sub endometrial blood flow

To improve poor endometrial response, several regimens have been put forward, including treatment with estrogens and low dose aspirin (3,4). In the past few years, much interest has been focused on the role of nitrous oxide (NO) as a modulator of uterine blood flow (5)

Estrogen induced endometrial proliferation is, in large dependent upon blood flow to the basal endometrium (6). NO is a key signaling molecule involved in the vasodilatory response of smooth muscle cells. NO activates the cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway within smooth muscle cells to promote smooth muscle cell relaxation. Sildenafil citrate inhibits phosphodiesterase 5 (PDE5) maintaining activation of cGMP and PKG and maximizing the effect of existing NO, thus facilitating smooth muscle cell relaxation. The potent vasodilatory action of sildenafil has led researchers to evaluate sildenafil as a treatment in assisted reproduction where

low uterine blood flow is perceived to be a contributor to implantation failure (7,8). The current study was designed to investigate the effect of vaginal sildenafil on the subendometrial and endometrial blood flow.

### Materials and methods

This prospective study was carried out in the Department of Obstetrics and Gynecology of Institute of Kidney Disease and Research Centre, Ahmedabad from January 2014 to December 2014. A total of 55 women with frozen embryos with an antecedent poor endometrial vascularity were included in this study. The project was approved by the ethical committee of this institute. The women participating gave their informed written consent. The study was carried out over 3 continuous cycles.

### Inclusion criteria:

1. Age < 45 years
2. Have high quality frozen embryos

### Exclusion criteria:

1. History of endocrine diseases.
3. Cardiovascular, renal and liver diseases.
4. Hypotension (blood pressure <90/50 mmHg).
5. History of stroke or myocardial infarction.

Women who met these conditions were recruited in the study. The women were given oral estradiol valerate tablets (6 mg- 20 mg daily), dose depending upon the day-14 endometrial thickness in previous cycles and tablet ecospirin (75 mg daily) from day- 2- 14 of the cycle to prepare the endometrium . Women were advised to administer sildenafil capsule intravaginally, 25 mg thrice a day, starting from day-5 to day 13 of the cycle. Assessment of endometrial thickness, pattern and vascularity was done on 14<sup>th</sup> day of the cycle. Transvaginal Ultrasonography was done using transvaginal probe (5 to 9 MHz) on Voluson E8 ( GE medical systems). After obtaining a

true longitudinal view of the uterus, endometrial thickness and pattern were assessed on B-mode.

Endometrial morphology was classified as triple line, echogenic and intermediate. For assessing endometrial vascularity, power Doppler was applied in the longitudinal section of uterus keeping the gain setting at -10. We have followed Applebaum's zones of vascularity for categorizing endometrial vascularity (9).

Zone - 1 vascularity-When blood vessels reached the hypoechoic endometrio-myometrial junction. Zone - 2 vascularity- When the vessels reached the outer hyperechoic line of endometrium. Zone - 3 vascularity- When it reached the intervening hypoechoic area. Zone - 4 vascularity- When the vessels were seen reaching the central echogenic line.

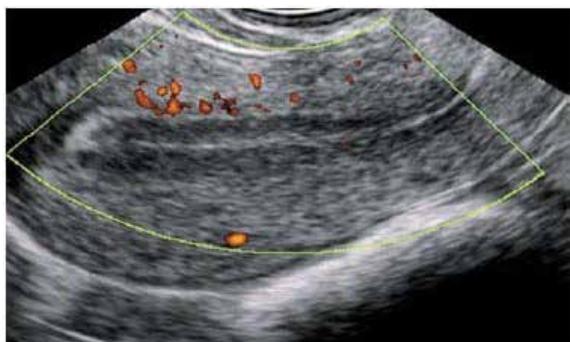


Fig 1. Zone 1 vascularity

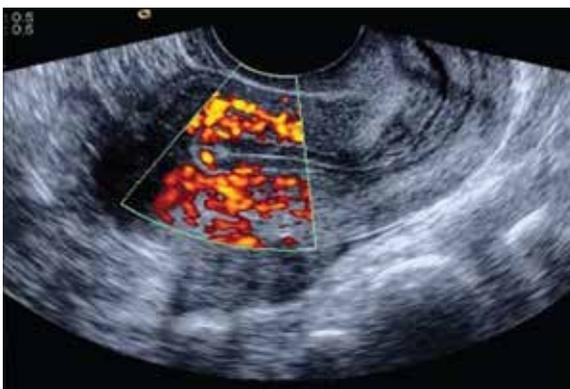


Fig 2. Zone4 Vascularity

**RESULTS**

A total of 55 women were recruited in the study, the basic demographic characteristics of whom were shown in Table 1,2 and 3. Out of 55 women,31(56.36%)women were in the age group of 30-40 years. Fifty one(92.72%)women had primary infertility. Twenty one (49.09%) women had infertility for 6-10 years. The endometrial vascularity was significantly higher after sildenafil treatment. Twenty one(38.18%) women showed improvement in endometrial vascularity (Table 4 and Fig 3).(P value<0.01). Embryo transfer was done in 19 women ,out of which 9(47.36%) women conceived.

**Table -1 : Distribution of women according to age**

Age in years	No. of women	%
< 30	15	27.27
30-40	31	56.36
40-45	09	16.36

**Table -2: Distribution of women according to type of infertility**

Type of infertility	No. of women	%
Primary	51	92.72
Secondary	04	7.27

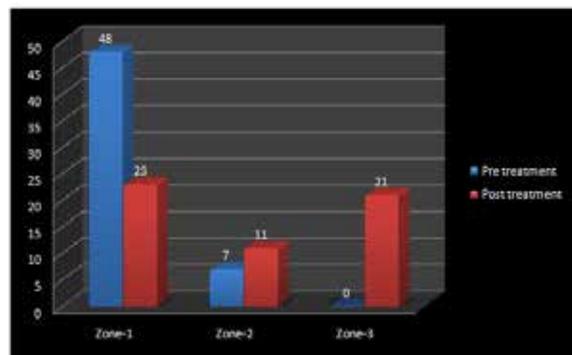
**Table -3: Distribution of women according to duration of infertility**

Duration of infertility (years)	No. of women	%
1-5	09	16.36
6-10	21	49.09
11-15	15	27.27
15	10	18.18

**Table -4: Effect of vaginal sildenafil on endometrial vascularity**

Zones	Pre treatment(N=55)	Post treatment(N=55)	P value
Zone 1	48	23	<0.01*
Zone 2	7	11	0.28(NS)
Zone 3	0	21	<0.01*

\*statically significant



**Fig.3 Effect of vaginal sildenafil on endometrial vascularity**

**Discussion:**

Implantation is the weakest link for the success of any ART procedure. Endometrial receptivity is crucial to implantation of an embryo. Several workers have presented several parameters and assessment techniques to assess the implantation potential of the endometrium. It is agreed that both endometrial thickness and endometrial pattern are useful prognostic parameter of endometrial receptivity. Adequate perfusion to endometrium seems vital to implantation. There are several reports by different groups that agree on the fact that implantation rates can be more correlated to the endometrial vascularity rather than its thickness and morphology. (10)

The effective treatment for improving endometrial perfusion in women with repeated poor endometrial vascularity in IVF cycles has not been widely studied. NO is recognized as a mediator of vascular smooth muscle relaxation in many areas of the body. NTG has long been used for its vasodilatory properties in the treatments of angina. Sheer et al used NTG successfully to improve uterine artery blood flow in IVF women with previous poor response. However, they experienced a high rate of side effects, including hypotension and headache. It has been possible to reduce the incidence of these side effects and delivery of the drug in close proximity to the target organ by use of intravaginal sildenafil (8).

Sildenafil, a phosphodiesterase-5 inhibitors, acts downstream of NO production and augments the vasodilatory effect of existing NO by inhibiting the hydrolysis of cyclic guanine monophosphate (cGMP) thus sustaining NO signaling.

Sildenafil citrate improves the uterine artery blood flow and the endometrial thickness in women with a prior failed assisted reproductive cycle due to poor endometrial response (11, 12, 13). Sildenafil citrate can be used orally to improve endometrial receptivity (14). Dehghani et al recommend the routine use of oral sildenafil citrate in women with a previous failure of assisted reproduction technology cycles (14). Sher et al have used sildenafil to improve the uterine artery blood flow with promising results, but have advocated further randomised studies. While improving uterine blood flow in proliferative phase, NO may have some detrimental effects on endometrium in the implantation window(15). Thus it is recommended to discontinue sildenafil 3-4 days before transfer.

While the number of the women in this study are too small to make generalizations, a definitive improvement in endometrial vascularity was seen in significant proportion of women but other factors like good quality of embryo, and endometrial receptivity also helps in implantation therefore this study does not prove that sildenafil improves the success rate of IVF cycle..

**Conclusion** – Use of vaginal sildenafil in endometrial preparation for patient with poor endometrial vascularity showed better endometrial development. We, therefore recommend the use of vaginal sildenafil for improving endometrial perfusion in IVF women with antecedent poor endometrial vascularity, though further larger randomized trial is warranted.

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