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Effects of tocopherol supplementation on endometrial thickness in subfertility patients.

Dr. Ruqia Fida
Associate Professor, Gynaecologist and Obstetrician at Dr Fida Painless and General Hospital, Peshawar

Dr. Shakeela Wahab
Consultant, Obstetrics & Gynaecology, Sonology, Dr Fida Painless and General Hospital, Peshawar
Corresponding Author e*mail: doctorshakeela@gmail.com*

Asiya Naz
Consultant Obstetrics and Gynecology, Dr Fida Painless and General Hospital, Peshawar

Noor E Hira
Nutritionist at Dr Fida Painless and General Hospital, MPhil Human Nutrition (Khyber Medical University), Peshawar

Amir Khan
Professor HOD Principal Medicine, Jinnah Teaching Hospital, Peshawar

Gullalay
Medical Officer at Dr Fida Painless and General Hospital.

Abstract---Background and Aim: Tocopherol is a vital nutrient for women during pregnancy, and multiple investigations revealed that a lack of tocopherol can cause preeclampsia, miscarriage, intrauterine growth restriction, and premature birth. There is scarcity of data regarding the effect of tocopherol on endometrial thickness. Therefore, the purpose of the present study was to assess the effect of tocopherol supplement on endometrial thickness. Methods: This randomized control clinical trial was conducted on 120 women with subfertility age group of 18 years to 37 years who visited the Obstetrics and Gynecology Department of Dr fida Painless Hospital Peshawar from January 2022 to June 2022. Patients were categorized into two groups: Group-I received Vit E supplements (800 IU) (n=60) and Group-II received placebo (n=60) for 12 weeks. The number of follicles and thickness of the endometrium were evaluated on ultrasound at day 2 and day 14. SPSS version 27 was used for data analysis.

Results: The overall mean age of group I and II was 30.4±2.6 and 29.8±2.5 respectively. A significant difference was observed in mean endometrial thickness between groups I and II on day 2 (4.6 mm versus 3.3 mm) and day 14 (8.4 mm versus 5.8 mm) (P<0.001). Ultrasound finding also showed that both groups had similar numbers of mature follicles without a statistically significant difference (Group-I 12.67 ±4.68 versus Group-II 11.76 ±3.82). Conclusion: The present study concluded that women who took tocopherol supplements during follicular phase had considerably higher endometrial thickness than placebo group women.

***Keywords*---**Tocopherol (Vit E), Supplement, Endometrial thickness

Introduction

A well-tolerated endometrium and embryo are two prime conditions for successful embryo implantation. Though, majority of infertile couples had widely used assisted reproductive technology (ART), the implantation failure due to poor endometrial receptivity is still a significant concern that should not be ignored [1].

Endometrial blood supply and morphology are two characteristics used to assess endometrial receptivity; however endometrial thickness is the most widely employed of the three. Surgical therapy, intrauterine perfusion, regenerative medicine, prolonged hormone therapy, and vasoactive medicine therapy are various approaches available to improve endometrial thickness [2-6]. The procedures described above for increasing endometrial receptivity are difficult to execute, invasive, or costly. In recent past, several researchers demonstrated a straightforward, efficient, and cost-effective approach for increasing endometrial thickness in reproductive age women by taking Vit E certain dose [7, 8].

Tocopherol is an exogenous lipid-soluble molecule that acts as a peroxyl radical scavenger in the body and is metabolized by the liver and kidney. According to study, tocopherol may boost endometrial secretory activity and improve endometrial thickness through anti-oxidation [9]. Numerous studies reported that favorable endometrium could be obtained by improved capillary blood flow [10, 11]. In contrast, another study by Zaffarin et al., [12] reported ineffectiveness of Vit E in improving the endometrial thickness.

Tocopherol appears to preserve embryo implantation by acting as an antioxidant and enhancing their movement throughout the menstrual cycle [13]. Protein tyrosine phosphatase, protein kinase C, lipoxygenases, and protein tyrosine kinase are different signal transduction modulation of enzymes influenced by the Tocopherol [14]. Till to-date, it has been debatable whether endometrial thickness and potentially improve pregnancy outcomes may be assisted by tocopherol supplementation. Raising endometrial thickness does not help an infertile woman to become pregnant, but it can improve pregnancy outcomes. As a result, the present study aimed to assess the effect of Vit E on endometrial thickness.

Methodology

Study design: Randomized control clinical trial

Study setting: Dr Fida Painless and General Hospital, Peshawar

Study duration: From January 2022 to June 2022 (6 months)

Sample size: 120 reproductive age women

Study criteria

Inclusion: 16 years to 38 years reproductive age female

Exclusion: Women having a polycystic ovary syndrome (PCOS) and uterine anomalies, glucose intolerance, thyroid disease, and smoking

This was conducted on aged 16 years to 38 years who visited the Obstetrics and Gynecology Department of Dr Fida Painless Hospital Peshawar, for the treatment of subfertility, Prior to study conduction, ethical approval was taken from institutional ethical committee. Each individual provided written informed consent.

Patients were categorized into two groups: Group-I received Vit E supplements (800 IU) (n=60) and Group-II received placebo (n=60), starting the intervention from 2^{nd} cycle day of their menstruation for 14 days during follicular phase. The number of follicles and thickness of the endometrium were evaluated prior to the initiation of intervention with ultrasound (TVS) at 2^{nd} cycle day of menstruation then 14^{th} cycle day of menstruation.

Statistical analysis:

ANOVA test was used for investigating the impact of Tocopherol consumption on different endometrial thickness. The ANOVA test was performed to adjust findings for confounders (age and baseline parameters). P-values of 0.05 were considered statistically significant in all analyses.

Results

The overall mean age of group I and II was 30.4±2.6 and 29.8±2.5 respectively. A significant difference was observed in mean endometrial thickness between groups I and II on days 2 (4.6 mm versus 3.3 mm) and day 14 (8.4 mm versus 5.8 mm) ($P<0.001$). Ultrasound (tvs) findings also showed that both groups had similar numbers of mature follicles without a statistically significant difference (Group-I 12.67 ±4.68 versus Group-II 11.76 ±3.82). Baseline characteristics of participants are shown in Table-I. Table-II represents the subfertility patients' metabolic profile and endometrial thickness adjusted for placebo and Tocopherol supplement group. Table-II represents the comparison of clinical characteristics of both groups.

Table-I
Baseline characteristics of participants

Parameters	Vit E group (N=60)	Placebo group (N=60)	P-value
Age (years)	30.4±2.6	29.8±2.5	0.29
BMI (kg/m^2) at baseline	24.9 ±3.5	25.5±2.2	0.32
BMI (kg/m^2) at end of study	24.7±3.8	25.9±2.8	0.51
BMI (kg/m^2) variation	-0.2±0.3	0.4±0.6	0.13

Table-II
Comparison of clinical characteristics of both groups

Variables	Group-I (N=60)	Group-II (N=60)	P-value
Endometrial thickness on 2nd cycle day (mm)	4.6 ±0.59	3.29 ±0.69	<0.001
Endometrial thickness on 14th cycle day (mm)	8.4 ±1.42	5.85 ±1.45	<0.001
Number of follicles (mm)	12.67 ±4.68	11.76 ±3.82	0.235

Discussion

The present study mainly focused on assessment of effect of Vit E on endometrial thickness and observed that the endometrial thickness was improved by tocopherol consumption in women undergoing the treatment of subfertility.

Moreover, when compared to the placebo, tocopherol administration for 14 days enhanced the endometrial thickness. The recommended role tocopherol showed improve blood flow and endometrial thickness as a result of their antioxidant properties.

A case series by Letur-Konirsch et al. Tocopherol were given to the patient with premature ovarian failure. They were examined for their endometrial thickness.

They also reported the outcome of increased endometrial thickness.

According to their hypothesis, this antioxidant therapy lessens subepithelial fibro sis, thickens the endometrium, and therefore overcomes uterine blood flow resistance. (16)

According to the current investigation, tocopherol oral supplementation promotes endometrial development in reproductive age women, particularly in women with thin endometrium lining.

The synchronous growth of the endometrium and the embryo is required for effective embryo implantation [17]. Functional and basal are two tissue layers

that form endometrium [18]. An adequate uterine blood flow would be required for hormones dependent endometrial growth [19]. The uterine blood flow encourages the epithelial cells proliferation. [20, 21].

In the female reproductive system reactive oxygen species (ROS) can destabilize intracellular equilibrium, impair the cellular activities and can even lead to cell damage. Excess ROS can affect early embryonic development by changing the major transcription factors that regulate gene expression. (22) Elevated ROS levels in the female reproductive system may also prevent embryonic implantation and negatively impact the oocyte fertilization [23,24].

Moreover, it has been shown that tocopherol works as a chain-breaking antioxidant to protect cellular membranes from ROS, for instance by preventing polyunsaturated fatty acids (PUFAs) from self-oxidation (25). Significant clinical trials have been conducted on the effectiveness of antioxidants such vitamin C and tocopherol, which have been used to treat problems associated to reproduction.

Based on these findings, it was determined that tocopherol administration could enhance endometrial response in women with unexplained subfertility through its anti-inflammatory and antioxidant properties, which enhance blood flow to the ovaries by increasing oestrogen synthesis, resulting in favorable endometrium (26). Besides, decrease in the vascular resistance and increase vascular development, endometrial glands, and VEGF protein expression increased in the endometrium detected in the interventional subjects [28], and an increase in uterine blood supply offers adequate nourishment for endometrial creation [29].

Any instability caused by free radicals increases or antioxidants generates oxidative stress reduction, which can result in anovulation and miscarriage [30].

Our findings revealed that tocopherol oral supplementation enhanced fertile women endometrial thickness, particularly those with thin endometrium.

Endometrial thickness may be important in achieving a successful pregnancy. A previous study reported that the endometrial thickness should be 7 mm for maximum pregnancy rate [31].

Conclusion

Women who took tocopherol supplements during follicular phase had considerably higher endometrial thickness than placebo group women. vitamins E play an important role in improving fertility outcomes by enhancing antioxidant and anticoagulant effects. This leads to an increase in endometrial receptivity and conception rates.

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