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Research Article

Autologous Blood Cell Derivative - ABCD-Endosera - A Next Generation Platelet Derivative Improves Endometrial Thickness and Pregnancy Outcome in Women with Thin Endometrium Undergoing IVF Procedure: A Prospective Self-Controlled Study

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Abstract

This study aimed to assess the efficacy of intrauterine instillation of Autologous Blood Cell Derivative (ABCD-Endosera) in improving endometrial receptivity among infertile women with thin endometrium undergoing Frozen Embryo Transfer (FET). A total of 123 women were initially assessed for eligibility, and 23 of them did not meet the inclusion criteria and were excluded from the study. Eventually, 100 patients with thin endometrium (<7mm) and previously canceled frozen embryo transfer (FET) cycles were recruited. ABCD-Endosera was prepared by concentrating growth factors and anti-inflammatory cytokines from selectively enriched platelets derived from autologous blood. Three 0.8ml doses of ABCD- Endosera were administered into the uterine cavity using a Tomcat catheter. The first dose was given between days 5-7 of the menstrual cycle, the second dose followed five days later, and the third dose was given 48 hours prior to the embryo transfer. Following ABCD- Endosera treatment, the thickness of the endometrium significantly increased from an average of 6.43 ± 0.42 mm before treatment to 7.85 ± 0.27 mm ($p < 0.05$). Among these 00 women, 59% (59 patients) achieved pregnancy after receiving ABCD-Endosera treatment. Out of the pregnant women, 21% (21 patients) successfully delivered healthy full-term babies, 20% (20 patients) had progressing pregnancies without complications, 10% (10 patients) experienced miscarriage before 10 weeks, and 8% (8 patients) had chemical pregnancies. No adverse effects, such as infection or anaphylaxis, were reported in any of the patients. This study highlights the significant potential of ABCD-Endosera as a promising solution to improve endometrial thickness, leading to better pregnancy outcomes for patients with persistently thin endometrium. Continued research is vital to fine-tune and maximize ABCD-Endosera's effectiveness in fertility procedures.

Keywords: Autologous Blood Cell Derivative; Endometrial Receptivity; Growth Factors; In vitro Fertilization; Recurrent Implantation Failure; Thin Endometrium

Introduction

The endometrium is a dynamic tissue that undergoes significant changes throughout the menstrual cycle in response to hormonal fluctuations. The ability of the endometrium to support embryo implantation and establish a successful pregnancy is known as endometrial receptivity [1]. An optimal endometrial thickness is considered a crucial factor for successful implantation and pregnancy outcomes. A thin endometrium, defined as endometrial thickness less than 7 mm, is associated with lower implantation and pregnancy rates in ART treatments [2,3]. Current therapeutic strategies for thin endometrium include long-term administration of exogenous estrogen [4], low-dose of aspirin [5], vaginal sildenafil citrate application [6], transvaginal endometrial perfusion of Granulocyte Colony-Stimulating Factor (G-CSF) [7] autologous Platelet-Rich Plasma Infusion (PRP) [8], stem cell therapy [9], vitamins C and E, and L-arginine supplement [10,11], electroacupuncture [12,13], steroid therapy [14], and endometrial scratching [15]. However, the effectiveness of these treatments remains controversial, and there is a need for alternative approaches that can improve IVF success rates. In recent years stem cells and PRP are being used to regenerate the endometrium and meta-reviews suggest beneficial effects of these add-on therapies to improve endometrial quality [16]. Platelet derived growth factor concentrate has been shown to be safe, reproducible, and effective in mimicking the natural processes of tissue repair and regeneration [17,18]. Platelet Derived Growth Factors (PDGFs) and play a crucial role in various physiological processes, including angiogenesis, cell proliferation, and tissue repair [19]. PDGFs promote angiogenesis by stimulating the proliferation and migration of endothelial cells and

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vascular smooth muscle cells [20]. PDGFs also regulate the extracellular matrix by controlling the synthesis and degradation of matrix components [21]. PDGFs have been implicated in endometrial growth and function due to their effects on angiogenesis, cell proliferation, and extracellular matrix remodeling [22]. PDGFs are expressed in the endometrium, with the highest levels detected during the proliferative phase of the menstrual cycle, suggesting a role in endometrial regeneration [23]. The role of PDGFs in endometrial angiogenesis is particularly relevant, as the formation of new blood vessels is essential for endometrial growth and receptivity.

Autologous Blood Cell Derivative (ABCD-Endosera) is a novel approach that contains implantation-friendly anti-inflammatory cytokines and regenerative growth factors concentrate derived from platelets [24,25]. In this study we aimed to evaluate the regenerative effect of ABCD-Endosera-Endosera on refractory thin endometrium in patients undergoing Frozen Embryo Transfer (FET). The primary outcome of this study was to evaluate the effect of intrauterine infusions of ABCD- Endosera-Endosera on EMT in patients presenting with refractory thin endometrium. The secondary outcomes encompassed assessing implantation rates, clinical pregnancy rates, live birth rates, and the reporting of adverse effects.

Materials and Methods

Study Design and Patients

This was a prospective self-controlled study, which was conducted in Altius Hospitals Rajajinagar Bangalore from May 2019 to February 2023. The study was approved by Independent Ethics Committee (NO: SGN/BLR/ETR/0119). A total of 123 women were initially assessed for eligibility, and 23 of them did not meet the inclusion criteria and were excluded from the study. Eventually, 100 women aged 27 to 39 years, suffering from primary or secondary infertility with thin endometrium (<7mm) and previously canceled frozen embryo transfer (FET) cycles were recruited. All of the participants were provided with informed consents after they were counselled for infertility treatments and routine IVF procedures. Patients with thin endometrium who met the following criteria were enrolled in this study:

Inclusion Criteria:

1. Patients in previous frozen embryo transfer cycles had their uterine lining which was persistently thin (characterized by endometrial thickness < 7mm), presented with inadequate response to treatments to increase blood flow to the endometrium include extended estrogen doses, low-dose aspirin, sildenafil, or Vitamin E and therapies like PRP and G-CSF .

2. Experienced one or more unsuccessful ART cycles (IVF or IUI), despite having good quality embryos ready for transfer.

3. Women with normal transvaginal ultrasounds and no significant issues in their uterus or nearby areas were included.

4. Patients tested negative for genital tuberculosis using Acid-Fast Bacillus (AFB) culture.

Exclusion Criteria:

1. Patients were excluded if she had a history of intrauterine adhesions, endometrial cavity infections, pelvic cancer, severe endometriosis, submucosal uterine myomas or endometrial polyps and adenomyosis.

Endometrial thickness was measured with vaginal ultrasound at its thickest part in the longitudinal axis of the uterus and was performed by the same investigator using a computerized vaginal ultrasound. This investigator was blind to the conditions of patients. Thin endometrium was defined as the endometrium thickness <7mm on the day when progesterone was given in HRT cycles [3].

Preparation of Endometrium

All the patients underwent standard Hormone Replacement Therapy (HRT) protocols for endometrial preparation. The protocol involved the incremental use of oral estradiol valerate 2 mg/day during days 1-7, 4 mg/day during days 8-12, 6mg/day during days 13 to embryo transfer [26]. Transvaginal ultrasound was used to monitor endometrial thickness, and once it reached 7 mm, 10 mg of micronized progesterone acetate was started. When endometrial thickness failed to reach over 7mm, patients were consulted to make decision to cancel the cycle, proceed to a new FET cycle or undergo embryo transfer regardless of thin endometrium. The decision to receive ABCD-Endosera treatment or not was based on the patients' preferences.

Embryo Transfer and Outcome Measures

In this study Single Embryo Transfer (SET) was employed as the chosen method for transferring embryos in all patients. The transferred embryos were blastocysts that had undergone the process of freezing and thawing. These blastocysts were of high quality, specifically graded as 4 AA/AB based on the guidelines outlined in the Istanbul Consensus workshop [3]. This approach not only minimizes the risks associated with multiple pregnancies but also ensures the transfer of the most viable embryos. SET allows for a precise evaluation of the individual embryos' potential for successful implantation, thereby optimizing the chances of achieving favorable pregnancy outcomes. Post-embryo transplantation, the luteal phase was supported through a combination of daily intramuscular injection of 50 mg progesterone and nightly administration of 200 mg vaginal progesterone soft capsules. Serum Human Chorionic Gonadotropin (HCG) levels were measured 14 days after embryo transfer. Vaginal ultrasonography was conducted 35 days after transfer in cases of biochemical pregnancy, while the presence of an intrauterine fetal heartbeat was used to define a clinical pregnancy. The primary outcome and endpoint of the study focused on endometrial thickness. The secondary endpoints included the clinical pregnancy rate, defined as the presence of a gestational sac and fetal heartbeat on transvaginal ultrasound five weeks after embryo transfer. Additional secondary outcome measures encompassed the miscarriage rate and ongoing pregnancy rate.

Autologous Blood Cell Derivative (ABCD-Endosera) Preparation

Platelet-Rich Fraction (PRF) was prepared from autologous blood following a previously reported method [17]. 30ml of autologous blood, obtained from the patient, was processed to isolate a concentrated platelet fraction with reduced lymphocytes and red blood cells (RBCs) to less than 1%. The platelet count in both whole blood and the PRF was measured using an automatic blood tester and immunophenotyping with antibodies specific to CD61 (a general platelet marker), CD63 and P selectin (markers of platelet activation), and an early stage platelet activation marker (Beckman Coulter PK7400 Automated Microplate System Analyzer). The platelet concentrate was stimulated to secrete growth factors and anti-inflammatory cytokines and processed through a proprietary filter to obtain ABCD-Endosera

using Seragen's proprietary selective growth factor enrichment protocol [25]. The final product contained growth factors, including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-Beta (TGF-β), Insulin-Like Growth Factor (IGF), Epithelial growth factor (EGF) and vascular endothelial growth factor (VEGF), as well as anti-inflammatory cytokines such as interleukin-10 (IL-10) and Interleukin-1 Receptor Antagonist (IL-1RA). To determine the levels of VEGF, EGF, IGF-1, PDGF, and TGF-β in both the whole blood and ABCD-Endosera, an Enzyme-linked Immunosorbent Assay (ELISA) was performed following the manufacturer's instructions (R&D Systems, Minneapolis, MN). Prior to detection, the samples were appropriately diluted up to 25 times to ensure the assay range was within 1000-2000 pg/ml. For patients receiving ABCD-Endosera treatment, the infusion protocol involved administering the first dose of 0.8 ml of ABCD-Endosera intrauterine infusion between days 5-7 of the menstrual cycle. The second dose was administered five days after the first dose, and the third dose was given 48 hours before embryo transfer. The ABCD-Endosera infusion into the uterine cavity was performed using a Tomcat catheter for each administration [24].

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to summarize the data, and the results were expressed as means ± Standard Deviation (SD) or percentages.

Results

123 women were assessed for eligibility, 23 of them were excluded as they did not meet the inclusion criteria. A total of 100 patients with thin endometrium (<7mm) and previously canceled FET cycles were recruited. Out of the 100 women included in the study, 59 (59%) became pregnant following ABCD-Endosera treatment (Table 1). Of these, 21 (21%) had a delivered healthy full term babies and in 20 women (20%) pregnancy is progressing uneventfully, while 10 women (10%) miscarried before 10 weeks and 8 women (8%) had a chemical pregnancy. After ABCD-Endosera treatment, endometrium thickness was 7.85±0.27mm, which was significantly thicker than before treatment (6.43 ± 0.42 mm, P <. 05). In the subgroup analysis of patients with more than 5 cycles of IVF failure (n=22), 11 out of 22 (50%) women conceived after ABCD-Endosera treatment. No patients were reported to have infection, anaphylaxis or any other side effects.

Stage of the Study	Number of Women	Percentage (%)
Assessed for Eligibility	123	
Excluded (Did Not Meet Inclusion Criteria)	23	
Recruited for Study	100	
Endometrial Thickness Before ABCD-Endosera Treatment (mm)	6.43 ± 0.42	
Endometrial Thickness After ABCD-Endosera Treatment (mm)	7.85 ± 0.27	P <.05
Pregnancy Outcomes After ABCD-Endosera Treatment		
- Total Pregnant	59	59
- Full-Term Deliveries	21	21
- Ongoing Pregnancies	20	20
- Miscarriages	10	10
- Chemical Pregnancies	8	8
Subgroup Analysis (Patients with >5 IVF Failures):	22	
- Conceived after ABCD-Endosera Treatment	11	50
Reported Adverse Effects		
- Infection, Anaphylaxis, or Other Side Effects	None	

Table 1: Outcome Analysis.

In order to prove our hypothesis that the therapeutic outcome may be attributed to growth factors and final product composition and stability for longer duration, we have analyzed the whole blood and ABCD-Endosera aliquots saved before delivery for administration. The average platelet concentration in platelet concentrate was 8.2 folds higher than that in whole blood (1935.2 ± 71.21x103/mL vs 236.65 ± 51.40x103/mL, P< 0.0001). Samples in triplicates were used to evaluate the growth factor levels in ABCD-Endosera immediately after preparation and after storage duration of 1week, 4 weeks, 8weeks, 12 weeks and 24 weeks at -20°C. Mean levels of VEGF, FGF, PDGF-BB, and TGF-b1 were significantly higher in ABCD-Endosera than whole blood (PDGF-BB, 15.2 ± 1.29 ng/ml vs 1.39 ± 0.08ng/ml, TGF-β, 52 ± 4.15 ng/ml vs 11 ± 1.19 ng/mL, FGF, 1.39 ± 0.08 ng/ml vs 0.3475 ± 0.08 ng/ml VEGF 63.21 ± 8.51 ng/ml vs 11.09 ± 2.51 ng/ml, all P<.001) .No significant difference was observed in IGF-1 levels between ABCD-Endosera and whole blood.

Discussion

Our study presents preliminary evidence supporting the utilization of ABCD-Endosera for enhancing endometrial receptivity and improving pregnancy outcomes in infertile women with thin endometrium. The use of ABCD-Endosera, which contains growth factors and anti-inflammatory cytokines, is a novel and alternate approach to improve endometrial thickness and receptivity [24,25]. The growth factors contained in ABCD-Endosera, such as PDGF, TGF-β, IGF, and VEGF, are known to play a critical role in tissue repair and regeneration, and their use in improving endometrial receptivity has been previously reported [27,9]. Furthermore, anti-inflammatory cytokines such as IL-10 and IL-1RA are known to suppress the local immune response, thereby reducing inflammation and improving implantation [28].

Strengths and Limitations

Our study exhibits several strengths, including relatively large sample size and the adoption of a standardized protocol for endometrial preparation. The extraction of growth factors concentrate from platelets presents several potential benefits over the use of conventional PRP. This process allows for an increased concentration of these growth factors, possibly amplifying their therapeutic effects. Additionally, the ability to selectively extract specific growth factors allows treatments to be more precisely tailored to the individual patient's needs, potentially improving outcomes [12]. Using these growth factors in combination with an appropriate delivery system can provide controlled and sustained release [29]. The extraction process could also potentially reduce risks related to platelet activation, such as coagulation or inflammation, by removing lymphocytes [30]. Isolated growth factors might offer better stability and ease of storage compared to PRP, which usually necessitates fresh preparation and immediate use [31]. The use of isolated growth factors can provide clearer insights into their mechanisms of action, enabling more

precise treatment protocols [32]. Also, the feasibility of preparing multiple doses from a single blood draw reduces the burden on healthcare providers and decreases patient discomfort associated with multiple blood pricks [33]. Despite these potential benefits, it's important to consider that using individual growth factors may not provide the synergistic effects of conventional PRP. Furthermore, the extraction, purification, and utilization of these growth factors present its own challenges and it is crucial to establish the most effective and safe practices for leveraging the therapeutic potential of PRP and its components [32]. However, our study also acknowledges several limitations, including its self controlled design, lack of randomization and absence of a control group, and the utilization of subjective measures to assess endometrial receptivity.

Conclusion

In conclusion, our study presents preliminary evidence endorsing the efficacy of ABCD- Endosera in improving endometrial receptivity and pregnancy outcomes in infertile women with thin endometrium and recurrent implantation failure. The use of ABCD-Endosera, which contains growth factors and anti-inflammatory cytokines, is a novel and alternate promising intervention to improve endometrial thickness and receptivity. Further randomized controlled trials with larger sample sizes are needed to validate the effectiveness of ABCD-Endosera and to determine its optimal dosing and timing of administration.

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