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Breakthrough Bleeding Following Missed Doses of Estradiol Valerate in a Surrogate Undergoing Endometrial Preparation 8 Days Prior to Embryo Transfer: A Case Report

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Abstract

Background: Endometrial preparation is an important step in the *in vitro* fertilization procedure. It involves the use of estradiol valerate. Once endometrial preparation has commenced, there should be no bleeding and the endometrial thickness should be between 7 mm and 12 mm for optimal embryo implantation. **Case Presentation:** A 24-year-old P 1 + 0 petty trader presented to St Elizabeth Hospital and Fertility Centre Limited, Enugu for surrogacy. She subsequently commenced the IVF procedure and during the endometrial preparation, she missed three doses of estradiol valerate. Following this, she started bleeding 8 days before embryo transfer. She was re-evaluated and was given a stat dose of leuprolide acetate 3.75 mg and the dose of estradiol valerate was increased as well. The bleeding stopped. Following embryo transfer, pregnancy was confirmed two weeks later. Pregnancy was uneventful until 11 weeks + 5 days when she had a threatened miscarriage which was managed and she got well. She had antenatal steroids at 30 weeks of gestation and delivered via elective caesarean section at 37 weeks + 2 days of gestation with a good feto-maternal outcome. **Conclusion:** Breakthrough bleeding before embryo transfer affects endometrial thickness which also affects implantation. A cycle that was complicated by breakthrough bleeding was successfully salvaged with a specific intervention leading to a live child.

Keywords

Breakthrough Bleeding, Estradiol Valerate, Surrogate, Endometrial Preparation, Embryo Transfer

1. Introduction

Currently, *in vitro* fertilization (IVF) has become a successful method for helping infertile couples become pregnant [1]. An essential part of this process is the endometrial preparation for embryo transfer [1]. The endometrium consists of three layers. The basal layer resting above the myometrium is the stratum basalis. The stratum compactum and stratum spongiosum lie above the basalis and together form the stratum functionalis. The functionalis layer undergoes cyclic change in response to hormone fluctuations and is shed with menstruation leaving the basalis to regenerate a new functionalis layer the following cycle. [2]. The stroma and the epithelium within the functional layer aid in embryo nurturing and embryo adhesion respectively [2]. Conventionally, gonadotropin releasing (GnRH) hormone agonists were used for down regulation to suppress luteinizing hormone (LH) surge during endometrial preparation prior to transfer followed by estrogen administration. In addition to suppressing the LH surge, it also plays a role in suppressing endogenous ovarian hormone production to create a controlled cycle. [3]. Five days prior to the planned embryo transfer, daily progesterone administration is commenced while estrogen is continued [3]. Live birth rates in cycles involving a fresh embryo transfer rise sharply until the endometrial thickness reaches 10 - 12 mm whereas in frozen embryo transfer (FET) cycles, they level off after 7 - 10 mm [4]. The aim of this report was to document a case of breakthrough bleeding following missed doses of estradiol valerate in a surrogate undergoing endometrial preparation 8 days prior to embryo transfer.

2. Case Presentation

A 24-year-old P 1 + 0 presented to our facility for the purpose of surrogacy. She was counseled following which she was evaluated.

Her evaluations include: hormonal profile, HIV 1 & 2, HBsAg, HCV, VDRL, abdominopelvic ultrasound scan, trans-vaginal ultrasound scan, and mock embryo transfer. All her evaluation results were normal and she was counseled on the results.

She was commenced on levofem (levonogestrel 0.15 mg and Ethinylestradiol 0.03 mg) 2 tablets daily for 3 weeks. During this period, she was downregulated with Leuprolide acetate 3.75 mg. She subsequently bled for 4 days following the withdrawal of levofem. Confirmation of down-regulation was done on the first day of bleeding and she was commenced on tablet estradiol valerate 4 mg thrice daily. Subsequently serial abdominopelvic (ABDS) and transvaginal (TVS) scans were done to measure the endometrial thickness as shown in **Table 1**.

Table 1. Showing endometrial thickness.

Day 1		Day 7		Day 10		Day 14	
ABDS	TVS	ABDS	TVS	ABDS	TVS	ABDS	TVS
6.9 mm	6.2 mm	11.2 mm	10.6 mm	-	-	-	-

Patient failed to come for the day 10 scan and started bleeding per vaginal a day before the day 14 scan following missed doses of her medication (estradiol valerate). She was re-evaluated and was commenced on a stat dose of Leuprolide acetate 3.75 mg. Also, her dose of estradiol valerate was increased to 6 mg thrice daily. A transvaginal scan done after the bleeding and before embryo transfer showed an endometrial thickness of 7.6 mm and 10.8 mm respectively. A day 5 embryo transfer was done.

A positive pregnancy test (blood and urine) was recorded 2 weeks post embryo transfer. An abdominopelvic scan done about 6 weeks post transfer showed a singleton fetus with cardiac activity.

Pregnancy was uneventful until 11 weeks + 5 days when she had a threatened miscarriage which was managed and she got well. She had antenatal steroids at 30 weeks of gestation and delivered via elective caesarean section at 37 weeks + 2 days of gestation with good feto maternal outcome.

3. Discussion

The normal endometrial thickness for optimal embryo implantation is between 7 mm - 12 mm, though some authorities have mentioned 6 mm - 12 mm [5].

Following fertilization of the ovum, successful implantation requires a viable blastocyst to communicate effectively with the receptive endometrium, which can support the growing embryo until the placenta is able to supply adequate nutrition. The endometrium is considered receptive for a relatively short period of time each cycle, likely several days. This period is called the window of implantation beyond which the blastocyst cannot adhere and menstruation results [6] [7]. The optimization of pregnancy rates is directly related to the synchronization of the developing endometrium and the embryo [5].

The bleeding following the withdrawal of estrogen otherwise called withdrawal bleeding results from the shrinkage of the glandular endometrium. This was reported by Sedar E. B., in Williams Textbook of Endocrinology, where he said that discontinuation of exogenous estrogen therapy almost invariably leads to uterine bleeding [8]. The patient was on an estrogen tablet, missed three doses and started bleeding. Withdrawal of the estrogen tablet can lead to breakthrough bleeding as seen in the index patient. This bleeding is an indication for the cancellation of the IVF cycle.

The adequate endometrial thickness should be between 6 mm - 12 mm. In this index patient who missed three doses of estradiol valerate, which resulted in shrinkage of the endometrium, withdrawal bleeding and which was supposed to

lead to the cancellation of the procedure, was salvaged by giving Leuprolide acetate 3.75 mg and increasing the dose of estradiol valerate. This intervention led to cessation of the bleeding and also it helped to regenerate the endometrium as the endometrial thickness before the embryo transfer was 10.8 mm which is within the normal range of endometrial thickness needed for implantation to occur. This intervention is a novel one that has not been reported previously as there are few literatures if any concerning the intervention that was done to continue with the IVF process.

Furthermore, the threatened miscarriage that was experienced by the index patient at 11 weeks + 5 days could have resulted from any other causes of miscarriage such as hormonal imbalance, issues with implantation resulting from poor vascular development in the uterus and not necessarily from suboptimal uterine preparation as the endometrial thickness before embryo transfer was within the normal range.

For this patient that had this novel intervention, achieving implantation and delivery with good feto maternal outcome is worthy of note.

4. Conclusion

Breakthrough bleeding can greatly influence the progress of the IVF procedure and can lead to cancellation of the cycle. Patients should be adequately counselled on compliance with their medications.

Consent

Informed consent was obtained from the patient before publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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