A Review of The Causes, Pathophysiological Mechanisms and Clinical Consequences of Second-Trimester Breakthrough Bleeding (BTB)

ARTICLE INFO

DOI: 1052547/sjrm.11.1.2

Article Type

Editorial letter

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Received: 04 February 2026
Accepted: 16 March 2026
e Published: 19 May 2026

Article History

Abstract: Bleeding during pregnancy is a major clinical challenge and can range from benign to life-threatening for both maternal and fetus. In the second trimester, breakthrough bleeding (abnormal vaginal bleeding in the presence of an ongoing normal pregnancy and in the absence of signs of labor or miscarriage) is a relatively rare but significant phenomenon.
Possible causes include hormonal changes, cervical abnormalities, early placental lesions, or damage to the decidua. Given the lack of scientific literature focused on BTB in this period of pregnancy, a comprehensive review and analysis of the available literature is necessary to clarify the underlying factors and clinical management.

Keywords: Second-Trimester Breakthrough Bleeding (BTB); Causes; Pathophysiological Mechanisms; Clinical Consequences; Review Article.

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[DOI: 10.66224/sjrm.11.1.1]

Editorial

Introduction

In recent years, significant advances in the field of stem cell biology, especially the development of induced pluripotent stem cell (iPSC) technology, have provided new avenues for studying germ cell development and their clinical applications. These cells, which are obtained from somatic cell reprogramming, have similar properties to embryonic stem cells, including the ability to self-renew and differentiate into all three germ layers. These properties have made them an attractive option for disease modeling, regenerative medicine, and especially infertility treatment [1]. The process of differentiating iPSCs into germ cells is a complex and multi-step process that is attempted to be recreated in vitro, similar to the natural pathway of gametogenesis. This process usually involves two major steps: first, differentiation into primary germ-like cells (PGC-LCs) and then entry of these cells into meiosis and formation of mature germ cells. Although the generation of PGC-LCs has been relatively successful in various studies, the full induction of meiosis and the production of functional gametes still face major challenges [2, 3].

Among them, the role of inducing factors in directing stem cell differentiation towards the germ line is very important. One of the most important of these factors is retinoic acid (RA), which is known as a key signaling molecule in the initiation of meiosis. RA regulates the meiotic entry pathway through the activation of genes such as *STRA8* and plays a fundamental role in regulating the timing of germ cell differentiation. In addition, RA can increase the proliferation of primary germ cells and prevent their apoptosis, which is very effective in improving the efficiency of differentiation. Experimental evidence shows that the combined use of RA with hormones such as 17β-estradiol can significantly improve germ cell differentiation. In particular, increased expression of key genes related to meiosis and spermatogenesis, such as *SYCP3* and *AKAP3*, has been reported in the presence of these compounds [4]. Studies have also shown that these compounds can lead to the formation of a population of haploid cells, which indicates a relative improvement in the reconstruction of the gametogenesis process in vitro. In addition to RA, growth factors and cytokines such as *BMP4*, *GDNF*, *SCF* and *EGF* also play an important role in the differentiation of germ cells. These molecules are involved in the induction of germ cell differentiation and proliferation by activating specific signaling pathways, such as the Smad pathway. For example, *BMP4* initiates the process of germ cell fate determination by inducing the expression of key transcription factors such as *Blimp1* and *Prdm14*. Together, these factors attempt to reconstruct the gonadal microenvironment, which is essential for the proper progression of gametogenesis [5].

Despite these advances, one of the fundamental challenges in this field is the precise reconstruction of the natural testicular niche or microenvironment in vitro. Studies have shown that the use of 3D culture systems, coculture with somatic gonadal cells, and conditioned media can help improve germ cell differentiation. These approaches create conditions closer to the in vivo environment by providing cell-to-cell interactions and paracrine signals that are essential for the progression of meiosis and maturation of germ cells. From a clinical application perspective, the differentiation of iPSCs into germ cells could revolutionize the treatment of infertility. Especially in patients with non-obstructive azoospermia who lack viable sperm, this technology could allow the production of functional sperm from the patient's own cells. This not only reduces the need for the use of donated gametes, but also addresses the ethical and psychological issues associated with it [6].

However, the path to clinical application of this technology faces several obstacles. These include the risk of tumorigenesis due to the presence of undifferentiated cells, genetic and epigenetic instability, and incomplete meiotic progression. Also, the use of reprogramming methods based on oncogenes such as c-Myc can pose potential risks to patient safety, which requires the development of safer methods. Finally, although significant progress has been made in the field of differentiation of iPSCs into germ cells, there is still a significant distance to the widespread clinical application of this technology. Future research should focus on optimizing culture conditions, gaining a deeper understanding of the molecular and epigenetic mechanisms, and developing safe and reliable methods for the production of functional gametes. Given the growing importance of this field in regenerative medicine and infertility treatment, it is expected that further research in this field will pave the way for fundamental developments in assisted reproductive technologies and provide new treatment solutions for infertile patients**.**

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[DOI: 10.66224/sjrm.11.1.1]