Progesterone-Induced Blocking Factor (PIBF) as a possible Early Diagnostic Marker of Pregnancy

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Abstract

Background: Pregnancy loss is one of the main issues of contemporary Reproductology with the prevalence 12%, amounting to 55% in case of 3 consecutive miscarriages. Presumably, 50% of miscarriages occur before the delay of menstruation.

Pregnancy seems to be a purely immunological phenomenon. Embrioprotective factors are being activated from the first day of pregnancy. One of them is progesterone-induced blocking factor (PIBF), which is produced in CD56+ cells and mononucleocytes. It impairs pro-inflammatory cytokines' production, suppresses constriction of the myometrium, shifts the production of Th1 towards Th2, and blocks the natural killer (NK) cells degranulation.

Aim: The purpose of this article is to summarize the extant knowledge on the effects of PIBF and to estimate its significance as a possible early diagnostic marker of pregnancy.

Method: The data were collected from NCBI, PubMed, ScienceDirect databases by using the keywords: progesterone-induced blocking factor, immunology of pregnancy, progesterone, pregnancy. The years for the search were between 1985 and 2021.

Conclusions: The level of PIBF increases soon after conception, contributes to the modulation of the mother's immunity and pregnancy maintenance. Its significance, as an early diagnostic marker of pregnancy, is not defined, though it may be informative at the first two weeks of gestation. Therefore, the studies must be continued in this connection.

Keywords: Early pregnancy loss; Progesterone-induced blocking factor (PIBF); Miscarriage; Immunity of pregnancy; Progesterone (P4).

Introduction

Pregnancy loss is one of the most important issues of contemporary Reproductology. The frequency of it is 12%, but in case of 3 consecutive miscarriages is rated at 55%. 90% of miscarriages occur in the first trimester (Fig. 1) (1).

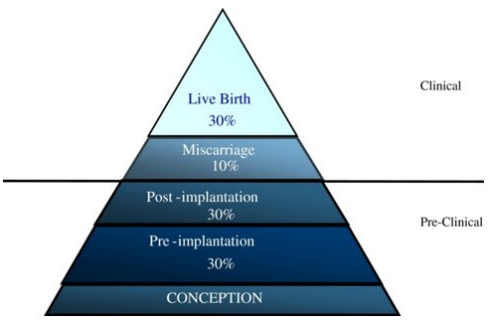

Fig. 1. The pregnancy loss iceberg: an overview of the outcome of spontaneous human conceptions (Larsen et al. 2013).

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The causes of spontaneous miscarriages are multiple: genetic and immunological causes, infectious factors, hormonal disturbances, anatomical defects and etc. 50% is caused by feto-maternal factors (fetal - chromosomal anomalies, maternal - anatomical anomalies, synechias, leiomyomas, advanced age, chronic diseases, immunological diseases, endocrine disturbances). The reason of pregnancy loss often is unknown as 50% occurs in the first two weeks of gestation – before the delay of period and the first blood beta chorionic gonadotropin (βhCG) determination.

The Role of PIBF in Immunity of Pregnancy

During the pregnancy, the complex neuro-endocrinological and immunological mechanisms are activated, which contributes to normal development of pregnancy. In 1953, Peter Medawar first used the term "Tolerogenic Immunity". He suggested that maternal immunity recognizes the fetus as a foreign body, but does not harm it due to activated immunosuppressive mechanisms. In 2019 Jabren-Ferrat noted that during pregnancy protective mechanisms are activated as well. She called this phenomenon the "Immunological Paradox of Pregnancy". One of the main roles in these processes has PIBF, properly:

- Suppresses constriction of the myometrium, impairing pro -inflammatory cytokines'

production;

- Suppresses the activation of pro-inflammatory cytokines, thus increasing the differentiation and proliferation of T helpers; Blocks the natural killer (NK) cells degranulation and thus reduces their cytolytic function (2).

Effects of PIBF

The scientists' attention to the PIBF has been increased during the last several decades. PIBF consists of 757 amino acids and the molecular mass is 90kDa (3). There are also shorter forms – 30, 43, 57 kDa, which are localized in the cytoplasm. They are associated with cell-specific intra and extracellular expression (4). It is thought that the short ones act as PIBF's receptor ligands (5). PIBF is produced in the γδ T lymphocytes at the early stage of pregnancy (soon after conception) (6). The lymphocytes are activated by the feto-paternal antigen. γδ + T lymphocytes' concentration in the peripheral blood of pregnant women is higher than in non-pregnant, but is considerably less than in decidua. After binding progesterone (P4) to the T lymphocytes' receptors, the PIBF level increases in the peripheral blood. PIBF then connects to its receptor, which activates phosphorylation of janus kinase 1 (Jak1) and of the proteins – signal transducer and activator transcription 6 (STAT 6) and suppressor of cytokine signaling 3 (SOCS 3). Ultimately production of Th2 cytokines is started (7). SOCS 3 binds to interleukin-12R (IL-12R) and inhibits STAT 4 phosphorylation (7) (Fig. 2).

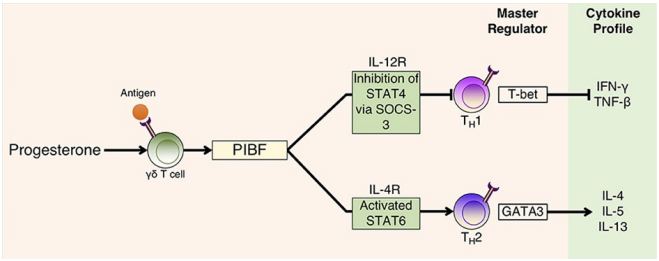

Fig. 2. PIBF action on the T cells differentiation and production of cytokines (Shah et al. 2019).

PIBF suppresses the T and NK cells activity and synthesis of arachidonic acid (2). It must be noted that inhibiting an immune response is a reliable sign for maintaining pregnancy, but also may contribute to the tumor growth, due to local immunosuppression (8). Szekeres-Bartho et al. has first demonstrated that in lymphocytes of women, who take P4, PIBF is produced, which blocks the cytotoxic activity and synthesis of prostaglandin F2α (PGF2α). Thus, in women with threatening preterm delivery, PIBF synthesis was reduced (9). In other studies, considerable reduction of PIBF and increase of pro-inflammatory cytokines – IL-6 and γ interferon (γIFN) - was demonstrated in urine and plasma of women with threatening preterm delivery (10), (11). Pro-inflammatory cytokines are associated with RPL and preterm delivery. Besides, the PIBF level in urine and plasma is significantly lower in women with threatening miscarriage (10). Hereby, Szekeres-Bartho et al. in their study have noted that PIBF inhibits PGF2α synthesis by decreasing the activity of phospholipase A2. As a result, the concentration of arachidonic acid is decreased (9). PGF2α contracts the smooth muscles of the myometrium. Thus, reduction of PGF2α by PIBF maintains the normal tonus of the uterus. PIBF's antitoxic activity during pregnancy occurs by its effect on NK cells. In the in vitro studies, it was shown that P4 and PIBF reduce decidual lymphocytes' cytotoxic activity and increase the production of perforins (2). Thus, it turned out, that PIBF is very important in the maintenance of pregnancy because it participates in the modulation of the immune response. It is remarkable that PIBF occurs in the lymphocytes of the pregnant soon after implantation (12), but at the same time, Check JH et al. have revealed that the corpus luteum is not a reliable sign for producing the PIBF (13). PIBF and P4 have immunomodulatory effects on the membrane progesterone receptors (mPR) of CD4+ T cells. In one study it was concluded that PIBF was able to significantly increase mPR expression on the surface of peripheral CD4+ T cells. Thus, a decrease in PIBF concentration during abnormal pregnancy can modulate mPR expression and regulatory performance of P4 on T cells. Rafiee M. et al. have concluded that the researches must be continued to open up a new understanding of the aetiology of pregnancy loss (14).

Besides all the mentioned above, the relation between mother and fetus is based on the extracellular vesicles (EVs). Preimplanted embrio produces EVs. PIBF is transported by these vesicles from the fetus to the mother's lymphocytes, stimulates the production of IL-10, and thus activates Th2 mediated immune response. In this process, the P4 participates as well, which:

Acts as "immunosteroid";

Determines the differentiation of T cells toward to Th2;

Regulates uterine NK (uNK) cells activity.

Most of the immunological effects of P4 is mediated by PIBF (Fig. 3).

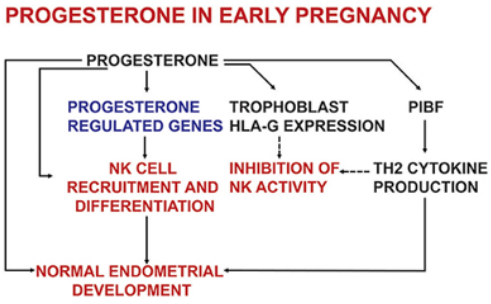

Fig. 3. Progesterone's (PG) effect on endometrium and immune system at the early stage of pregnancy (Szekeres-Bartho, Šućurović, and Mulac-Jeričević 2018).

PIBF as a predictor of pregnancy outcome

PIBF has become more popular after its determination in different tissues of the reproductive system and meanwhile in tumor tissues (4), (15). Several studies have shown the association between PIBF level and pregnancy outcome. In the prospective, cohort study of pregnancy loss, Polgar et al. have revealed that PIBF was the one, most important, associated risk factor. During the normal pregnancy PIBF concentrations in urine and plasma increase, while in women with miscarriage or preterm delivery the high level of PIBF is not noticed (16). On the assumption of PIBF activates P4's effects, in one of the studies the effect of dydrogesterone on the hormonal profile and PIBF concentration in women with threatening miscarriage has been evaluated. The results have revealed, that the induction of PIBF by the dydrogesterone may improve the outcome of pregnancy (17). Low PIBF level is the predictor of preterm delivery at the 24-28 weeks of gestation, but not at the 11-13 weeks, which shows, that the predictive index depends on the interval between the sampling and labor (18). PIBF, also, is expressed on the surface of the trophoblast and participates actively in its invasion. Miko E, Halasz M. Et al. have described that PIBF is expressed by the normal placenta, also by the hydatidiform moles, but its

expression is considerably decreased during the complete mole and is not expressed at all during the choriocarcinoma (19). PIBF increases from the first days of conception and progresses with the pregnancy (20). The role of PIBF is very important in the in vitro fertilization (IVF) and in the pathogenesis of RPL. During IVF determining PIBF level at the early stage of pregnancy may be used as the predictive value for the pregnancy outcome (21).

Conclusion

The level of PIBF increases soon after conception, contributes to the modulation of the mother's immunity and pregnancy maintenance. Its significance, as an early diagnostic marker of pregnancy, is not defined, though it may be informative at the first two weeks of gestation. Therefore, the studies must be continued in this connection.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interest regarding the publication of this article.

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