GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 4 (349) Апрель 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 3 (348) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 4 (349) 2024

EARLY PREGNANCY LOSS: INVESTIGATING THE ROLE OF PROGESTERONE-INDUCED BLOCKING FACTOR

Nina Davidova[1,2], Lali Pkhaladze[1,3], Nana Kvashilava[4], Ludmila Barbakadze[5], Archil Khomasuridze[1,6].

[1]*Gynaecologist, reproductologist at Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia.*

[2]*Doctorate of Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*

[3]*Professor at Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*

[4]*The head of the laboratory department at Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia.*

[5]*Gynaecologist, reproductologist at Leader Med clinic, Tbilisi, Georgia.*

[6]*Professor, the head of the department of reproductology, gynaecology and obstetrics of Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*

Abstract.

Aim of the study: The assessment of the diagnostic value of Progesterone-Induced Blocking Factor (PIBF) in Early Pregnancy Loss (EPL), in naturally conceived women and in women who underwent In Vitro Fertilization (IVF).

Materials and Methods: In the prospective and retrospective study 50 naturally conceived women were divided into three groups: Group I – patients with progressive pregnancy; Group II- patients with EPL; Group III – patients with biochemical pregnancy (BP). 36 pregnant women after IVF were divided into three groups: Group IV - patients with progressive pregnancy, Group V – patients with EPL, and Group VI - patients with BP. β human Chorionic Gonadotropin (βhCG), PIBF and Progesterone (PG) were assessed in the women conceived naturally and after IVF on the 12th to 14th day after ovulation and embryo transfer (ET), respectively.

Results: PG and PIBF levels were significantly higher in the progressive and significantly lower in the biochemical pregnancy groups as in the naturally conceived women, so after IVF. PIBF was not significantly different in EPL and BP groups of naturally conceived and IVF pregnant, opposite to the PG, which was significantly lower in the BP group. Thus, PIBF is more informative in the prognosis of EPL and PG – in the diagnosis of clinical pregnancy.

Conclusions: PIBF emerges as a prognostic indicator for early pregnancy loss, encompassing even its preclinical stage.

Key words. Early Pregnancy Loss (EPL), Progesterone-induced blocking factor (PIBF), preclinical stage of pregnancy, Progesterone (PG), biochemical pregnancy.

Introduction.

Prevalence of infertility worldwide reaches 17.5%, in favour of primary infertility (10.5%). Due to this fact Pregnancy Loss (PL) is one of the most important issues of Reproductology. Its frequency is 13.5%, but in the case of 3 consecutive miscarriages - it is rated at 55%. 60% of miscarriages occur in the first trimester [1,2]. The causes of spontaneous miscarriages are multiple: genetic and immunological causes, infectious factors, hormonal disturbances, anatomical defects, etc. It must be mentioned, that 30% of couples suffer from unexplained infertility problem [3]. In such cases In Vitro Fertilization (IVF) is often used and its success rate is 30.7% [4]. All patients mentioned above may even conceive, but these pregnancies remain undiagnosed as 60% is lost in the first two weeks of gestation - before the delay of period and the first blood beta chorionic gonadotropin (βhCG) determination [5]. Additionally, it must be noted, that the incidence of EPL increases and IVF effectiveness decreases along with advancing maternal age [6-8].

During pregnancy complex neuro-endocrinological and immunological mechanisms are activated, which contributes to the normal development of pregnancy. In these processes, one of the main is the Progesterone-Induced Blocking Factor (PIBF). Properly, PIBF 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 [9].

The scientists' attention to the PIBF was increased during the last several decades. PIBF consists of 757 amino acids and the molecular mass is 89 kDa [10,11]. There are also shorter forms – 30, 43, and 57 kDa, which are localized in the cytoplasm. They are associated with cell-specific intra and extracellular expression [12]. It is thought that the short forms act as PIBF's receptor ligands [13]. PIBF is produced in the γδ T lymphocytes at the preclinical stage of pregnancy (soon after conception) [14,15]. It must be noted that inhibiting an immune response is a reliable sign for maintaining pregnancy but also may contribute to other pathologies, such as tumour growth, due to local immunosuppression [16]. Szekeres-Bartho et al. first demonstrated that in the lymphocytes of women, who take PG, 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 [17]. In other studies, a considerable reduction of PIBF and an increase of pro-inflammatory cytokines – IL-6 and γ interferon (γIFN) - was demonstrated in the urine and plasma of women with threatening preterm delivery [18,19]. Pro-inflammatory cytokines, also, are associated with Recurrent Pregnancy Loss (RPL) and preterm delivery. Besides, the PIBF level in urine and plasma is significantly lower in women with threatening miscarriages [19]. Hereby, Szekeres-Bartho et al. in their study have noted that PIBF maintains the normal tonus of the uterus [17]. Thus, it turned out, that PIBF is very important in the maintenance of pregnancy as it participates in the modulation of the immune response. PIBF and PG have immunomodulatory effects on the membrane progesterone receptors (mPR) of CD4+ (Cluster differentiation) 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 PG on T cells.

Hence, Rafiee M. et al. have concluded that the research must be continued to open up a new understanding of the aetiology of pregnancy loss [20].

PIBF has become more popular after its determination in different tissues of the reproductive system and meanwhile, in tumour tissues [12,21,22]. PIBF, is, also, 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, and also by the hydatidiform moles. Still, its expression is considerably decreased during the complete mole and is not expressed at all during the choriocarcinoma [23]. PIBF has an important role in the maintenance of pregnancy, it increases from the first day of conception [11]. According to Hudic et al., during IVF determining PIBF level at the early stage of pregnancy may be used as the predictive value for the pregnancy outcome [24].

Therefore, the aim of our research became the assessment of the diagnostic value of PIBF in early pregnancy loss.

Materials and Methods.

The prospective study included 86 patients and was conducted at "Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology" and "LiderMed" clinic, Tbilisi, Georgia. The study was approved by the local ethical committee. The informed consent was obtained from the patients. 50 patients conceived naturally, and 36 women – after IVF. The inclusion criteria were unexplained infertility, one or more EPL in anamnesis, normal ovulation, and positive βhCG (>25 mIU/ml) level in the blood on the 12th to 14th day after ovulation and ET. The exclusion criteria contained all causal factors of EPL: tubal, endocrine disorders, ovarian dysfunction, endometriosis, congenital and acquired anomalies of the pelvic organs, confirmed genetical disorders, congenital and acquired thrombophilia, sexually transmitted diseases, acute and chronic inflammatory diseases of pelvic organs, uterine fibroids and polyps, abnormal uterine bleedings, infertility caused by male factor.

After analyzing the results of natural conception and IVF procedure, retrospectively the patients were divided into the following manner: From 50 naturally conceived patients, aged 18-35 (29.50±5.59), in 13 women menstruation started in a time, which, in our belief, probably indicates that in those cases the pregnancy was lost in the preclinical stage. Other 37 women had delayed menstruation and pregnancy was diagnosed clinically. However, pregnancy loss occurred in 18 women at different weeks of gestation (3-8 weeks). 19 patients had progressive pregnancies, which lasted in the term delivery. Retrospectively, these patients were divided into three groups according to the course of pregnancy: Group I – patients with progressive pregnancy (n=19); Group II- patients, with early pregnancy loss (n=18); Group III – patients with biochemical pregnancy (n=13). Similarly, in the IVF group, based on timely menstruation and clinically diagnosed pregnancy, 36 patients, aged 21-35 (30.97±3.78), were also divided into three groups: Group IV - patients with progressive pregnancy (n=15); Group V – patients with EPL (n=10), and Group VI - patients with biochemical pregnancy (n=11). Along with βhCG, PIBF and PG were assessed in all women conceived naturally or after IVF on the 12-14th day after ovulation and ET, respectively. The blood was collected in a fast state and the analysis was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) method (for PIBF level measurement - Human PIBF ELISA kit, catalogue No.: EH1818). Statistical analysis was performed using the One-Way ANOVA test of the SPSS software package, version 26.0 for Windows.

Results.

The study has revealed the following results: In the naturally conceived group the mean level of PIBF was statistically significantly higher in patients with progressive pregnancy (15.94±5.0 ng/ml) compared to patients with EPL (7.13±5.04 ng/ml) and biochemical pregnancy (5.62±2.76 ng/ml) P<0.05, but no significant difference was found in PIBF level between women with EPL and biochemical pregnancy P>0.05. (Table 1). Similarly, after IVF, PIBF was statistically higher in patients with progressive pregnancy (30.14±10.21 ng/ml) than in the EPL (21.11±5.37 ng/ml) P<0.05, and biochemical pregnancy groups (20.72±4.24 ng/ml) P<0.05, but no statistically significant difference was found in PIBF level between women with EPL and biochemical pregnancy P>0.05. (Table 2). Besides, PIBF was statistically higher in IVF than in the natural cycle women in all groups (P<0.05).

Table 1. *The comparison rates of Progesterone Induced Blocking Factor (PIBF), Progesterone (PG) and beta-Human Chorionic Gonadotropin (βhCG) of Group I (patients with progressive pregnancy) with Group II (the patients with Early Pregnancy Loss) and Group III (patients with biochemical pregnancy). All values are performed as the mean ± SD (standard deviation).* **- significant difference between groups I and II (P<.05);* $^{\Psi}$ *- significant difference between groups I and III (P<.05);* $^{¥}$*- significant difference between groups II and III (P<.05).*

	Groups		
	I (n=19)	**II (n=18)**	**III (n=13)**
PIBF (ng/ml)	15.94±5.0	7.13±5.04*	5.62±2.76 $^{\Psi}$
PG (ng/ml)	25.13±8.93	24.97±12.42	6.55±4.08 $^{\Psi ¥}$
βhCG (ng/ml)	274.91±551.45	754.30±2558.44	48.62±8.86

Table 2. *The comparison rates of Progesterone Induced Blocking Factor (PIBF), Progesterone (PG) and beta-Human Chorionic Gonadotropin (βhCG) in In vitro groups: Group IV (patients with progressive pregnancy), group V (women with Early Pregnancy Loss), group VI (women with biochemical pregnancy). All values are performed as the mean ± SD (standard deviation).* **- significant difference between groups IV and V(P<.05).* † *- significant difference between groups IV and VI (P<.05).* § *- significant difference between groups V and VI (P<.05).*

	Groups		
	IV (n=15)	**V (n=10)**	**VI (n=11)**
PIBF (ng/ml)	30.14±10.21	21.11±5.37*	20.72±4.24†
PG (ng/ml)	61.32±7.76	57.76±5.15	32.30±6.32†§
βhCG (ng/ml)	182.43±215.52	103.86±10.70	77.64±13.92

In the naturally conceived women, the mean PG level also was significantly higher in the patients with progressive pregnancy (25.13±8.93 ng/ml) compared to women with biochemical pregnancy (6.55±4.08 ng/ml) P<0.05; The PG level was significantly lower in the patients with biochemical pregnancy in the natural cycle compared to EPL (24.97±12.42 ng/ml) (P<0.05). In IVF women PG level was not statistically

different between progressive pregnancy (61.32±7.76 ng/ml) and EPL (57.76±5.15 ng/ml) groups, P>0.05, but was statistically significantly lower in the biochemical pregnancy group (32.30±6.32 ng/ml) (P<0.05). Additionally, the PG level was statistically significantly higher in the IVF groups than in the appropriate natural cycle groups (P<0.05).

There was no statistically significant difference in βhCG level between all groups.

There was no significant correlation between PIBF and PG in the groups, (I group – r = -0.04 (P>0.05), III group – r = -0.16 (P>0.05), IV group – r = 0.42 (P>0.05), group V – r = -0.12 (P>0.05), group VI– r = 0.30 (P>0.05)), except group II, where a moderate negative correlation was revealed (group II – r = -0.64 (P<0.05).

Discussion.

The prevalence of infertility worldwide is rather high, estimated at 17.5%, indicating that approximately one in every six adult experiences infertility [25]. Several studies suggest that primary infertility rates are higher in various countries compared to secondary infertility rates, with figures ranging from 6% to 16% (average 10.5%) for primary infertility and approximately 2% for secondary infertility [26,27]. However, from 1990-2010 the rate of secondary infertility was higher than primary – 8.7-32.6% vs 0.6-3.4%, respectively [28]. The rates mentioned above, are confusing and it is essential to consider, that in developing countries, they may be much higher. All data concern clinically approved pregnancies, but considering the number of pregnancies we may lose before delaying menstruation, the rate will increase significantly, which is already alarming. The reason for infertility, at least in half of the cases, is, obviously, undetectable, which is called "unexplained infertility" [29]. Theoretically, those patients, maybe, even get pregnant, but these pregnancies are lost within the first two weeks of pregnancy, remaining undiagnosed. In our consideration, the majority of these cases are linked to the women's immune responses, which can become activated after conception. One of them is the PIBF.

PIBF levels start rising from the early stages of conception and continue to increase throughout pregnancy [11]. The significance of PIBF is particularly notable in IVF. Monitoring PIBF levels during IVF can serve as the predictive indicator of pregnancy outcomes [24]. All these mechanisms underscore the critical role of PIBF in supporting of pregnancy progression.

In a study assessing the effects of Dydrogesterone on hormonal profiles and PIBF concentrations in women facing the threat of miscarriage, the findings indicated that Dydrogesterone-induced elevation of PIBF could potentially enhance pregnancy outcomes [30]. Additionally, low levels of PIBF have been identified as predictive of preterm delivery occurring between 24 to 28 weeks of gestation. [31].

However, regarding the absence of diagnostic markers for the preimplantation and early implantation stage, the rate of undiagnosed pregnancy and thus, the rate of EPL remains still very high.

Due to this reason, we decided to assess the diagnostic value of PIBF in EPL, in women who conceived naturally and after IVF.

The findings from our study align with those of Lim et al., indicating that PIBF and PG levels are notably higher in naturally conceived women with ongoing, progressive pregnancies compared to women experiencing EPL or biochemical pregnancies. This correlation supports the notion that PIBF levels increase throughout trimesters in healthy pregnant women [11]. Also, Szekares-Bartho et al., declared that PIBF synthesis was reduced in women with threatening preterm delivery [17].

Quite interesting was the result concerning PIBF, which was equally lower in both - EPL and biochemical pregnancy groups compared to the progressive pregnancy group and there was no statistically significant difference between them. This result implies that a low PIBF level in the preclinical stage of pregnancy could potentially serve as an indicator of miscarriage risk, not only in cases of biochemical pregnancy but also in clinically recognized pregnancies. Our results are proven in other studies. According to Polgar et al. PIBF was the one most important associated factor to pregnancy outcome, as its concentrations in both - urine and plasma increase with pregnancy progression. Conversely, in cases of miscarriage or preterm delivery, they noted a lack of the expected rise in PIBF levels [32]. Sahin ME et al., have revealed that a significantly low PIBF level was found in women with unexplained infertility compared to the fertile control group [33]. These findings may match our results, as in our study we have included patients with unexplained infertility and with EPL in anamnesis.

Contrary to PIBF, the PG rate was significantly lower in biochemical pregnancy compared to the EPL group, and there was no significant difference in PG levels between progressive pregnancy and the EPL groups. This suggests that PG levels may not be as informative in predicting EPL outcomes, especially considering the instances where early pregnancy loss occurred at 5-8 weeks of gestation, despite relatively high PG levels in naturally conceived patients.

Our results are different from Ku et al., according to whom serum PG level is increased linearly during 5-13 weeks of gestation and a low level of PG is associated with a threatened miscarriage and a complete miscarriage at 16 weeks of gestation [34].

According to one study, PIBF is released by the lymphocytes in the presence of PG, also, the percentage of these lymphocytes increases in the luteal phase [35] and both – PG and PIBF are promising biomarkers for predicting pregnancy viability [11]. However, in our research, we did not find a linear correlation between PIBF and PG in the progressive and BP groups. We found only a moderate negative correlation in the EPL group. This fact may be related to a small sample size or may point that PG is not the only factor for PIBF induction. There may be other possible factors involved in this process. Our results are similar to Check et al., who revealed that corpus luteum is not a reliable sign for producing PIBF [36].

The same tendency was maintained after the IVF procedure - the PIBF level was higher in women with progressive pregnancy than in patients with EPL and a biochemical pregnancy. Thus, the high PIBF level may point to a favourable outcome after IVF. Our suggestion is confirmed in a study by Adamczak R. et al., who revealed that higher PIBF1 concentration in follicular fluid may indicate a greater possibility of successful IVF [37]. Hudic et al., consider that PIBF taken in early pregnancy predicts the pregnancy outcome in women undergoing IVF procedures [24].

PG in IVF group patients, similarly to naturally conceived women, was significantly lower in biochemical pregnancy compared to the EPL group, and there was no significant difference between progressive pregnancy and the EPL groups.

Ku C. et al. revealed that low PG and PIBF concentrations in blood predict spontaneous miscarriage among women with threatened miscarriages between 6-10 weeks of gestation [38]. The similar results we get in our study concerning the PIBF level, but not the PG level.

Interestingly was the finding that PIBF and PG were statistically higher in IVF groups than in the naturally conceived women groups, which may be related to the hormonal therapy in IVF cycles. Despite this, the prognostic value of PIBF in naturally conceived women and IVF was similar, as it was similar regarding PG levels, as well.

There was no linear correlation between PIBF and PG in IVF groups as in naturally conceived women groups. All the above reinforces the notion, that PIBF regulation involves a network of additional factors beyond just PG.

The importance of βhCG is high in the diagnosis of pregnancy. According to Macklon et al., βhCG was significantly lower in the women with a miscarriage compared to the uncomplicated pregnant women group [5]. Albeit, in our study, there was no statistically significant difference in βhCG levels between groups. This may be related to its large deviation which is contributed by the study's small sample size.

Thus, PG is more informative in clinical pregnancy occurrence. PIBF is more informative in the prognosis of early pregnancy loss, including biochemical pregnancy.

While these markers are undoubtedly important, it is crucial to acknowledge the potential influence of other factors contributing to unexplained infertility and early pregnancy loss and more large-scale studies must be continued in this connection.

Conclusion.

PIBF emerges as a prognostic indicator for early pregnancy loss, encompassing even its preclinical stage.

REFERENCES

1. Larsen E.C, Christiansen OB, Kolte AM, et al. New insights into mechanisms behind miscarriage. BMC Medicine. 2013;11:154.
2. Wang X, Chen C, Wang L, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertility and Sterility. 2003;79:577-584.
3. Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertility and Sterility. 2020;113:305-322.
4. Reindollar R.H, Regan MM, Neumann PJ, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertility and Sterility. 2010;94:888-899.
5. Macklon N.S, Geraedts JPM, Fauser BCJM. Conception to ongoing pregnancy: the "black box" of early pregnancy loss. Human Reproduction Update. 2002;8:333-343.
6. Andersen AMN, Wohlfahrt J, Christens P, et al. Maternal age and fetal loss: population-based register linkage study. BMJ. 2000;320:1708-1712.
7. Li Y.H, Marren A. Recurrent pregnancy loss: A summary of international evidence-based guidelines and practice. Australian Journal of General Practice. 2018;47:432-436.
8. Pierce N, Mocanu E. Female age and assisted reproductive technology. Global Reproductive Health. 2018;3:e9-e9.
9. Laškarin G, Tokmadzić VS, Strbo N, et al. Progesterone induced blocking factor (PIBF) mediates progesterone induced suppression of decidual lymphocyte cytotoxicity. American Journal of Reproductive Immunology. 2002;48:201-9.
10. Cohen R.A, Check JH, Dougherty MP. Evidence that exposure to progesterone alone is a sufficient stimulus to cause a precipitous rise in the immunomodulatory protein the progesterone induced blocking factor (PIBF). Journal of Assisted Reproduction and Genetics. 2016;33:221-9.
11. Lim M.K, Ku CW, Tan TC, et al. Characterization of serum progesterone and progesterone-induced blocking factor (PIBF) levels across trimesters in healthy pregnant women. Scientific Reports. 2020;10:3840.
12. Lachmann M, Gelbmann D, Kálmán E, et al. PIBF (progesterone induced blocking factor) is overexpressed in highly proliferating cells and associated with the centrosome. International Journal of Cancer. 2004;112:51-60.
13. De La Haba C, Palacio JR, Palkovics T, et al. Oxidative stress effect on progesterone-induced blocking factor (PIBF) binding to PIBF-receptor in lymphocytes. Biochimica et Biophysica Acta - Biomembranes. 2014;1838:148-157.
14. Check J.H, Arwitz M, Gross J, et al. Detection of progesterone induced blocking factor (PIBF) in very early pregnancy correlates more with successful implantation than mere conception. Journal of the Society for Gynecologic Investigation. 1996;3:201A.
15. Check J.H, Arwitz M, Gross J, et al. Evidence that the expression of progesterone-induced blocking factor by maternal T-lymphocytes is positively correlated with conception. American Journal of Reproductive Immunology. 1997;38:6-8.
16. Szekeres-Bartho J, Polgar B. PIBF: The Double-Edged Sword. Pregnancy and tumor. American Journal of Reproductive Immunology. 2010;64:77-86.
17. Szekeres-Bartho J, F Kilaŕ, G Falkay, et al. The Mechanism of the Inhibitory Effect of Progesterone on Lymphocyte Cytotoxicity: I. Progesterone-Treated Lymphocytes Release a Substance Inhibiting Cytotoxicity and Prostaglandin Synthesis. American Journal of Reproductive Immunology and Microbiology. 1985;9:15-18.
18. Hudić I, Szekeres-Bartho J, Stray-Pedersen B, et al. Lower Urinary and Serum Progesterone-Induced Blocking Factor in Women with Preterm Birth. Journal of Reproductive Immunology. 2016;117:66-9.
19. Hudić I, Fatusić Z, Szekeres-Bartho J, et al. Progesterone-induced blocking factor and cytokine profile in women with threatened pre-term delivery. American Journal of Reproductive Immunology. 2009;61:330-7.
20. Rafiee M, Rezaei A, Alipour R, et al. Progesterone-induced blocking factor (PIBF) influences the expression of membrane progesterone receptors (mPRs) on peripheral CD4+ T lymphocyte cells in normal fertile females. Hormones. 2021;20:507-514.

21. Shah N.M, Lai PF, Imami N, et al. Progesterone-related immune modulation of pregnancy and labour. Frontiers in Endocrinology. 2019;10:198.
22. Szekeres-Bartho J. Progesterone induced blocking factor in health and disease. Exploration of Immunology. 2021:406-417.
23. Miko E, M Halasz, B Jericevic-Mulac, et al. Progesterone-induced blocking factor (PIBF) and trophoblast invasiveness. Journal of Reproductive Immunology. 2011;90:50-57.
24. Hudic I, Szekeres-Bartho J, Vrtacnik EB, et al. Progesterone induced blocking factor (PIBF) taken in early pregnancy predicts the pregnancy outcome in women undergoing in vitro fertilization procedure. Journal of Reproductive Immunology. 2020;140:103150.
25. 1 in 6 people globally affected by infertility: WHO. 2023. https://www.who.int/news/item/04-04-2023-1-in-6-people-globally-affected-by-infertility.
26. Chaubey L, T B. Singh, Kirti Kaithwas, et al. Risk factors associated with primary and secondary infertility in eastern part of north India: A pilot study. The Journal of Community Health Management. 2020;5:188-191.
27. Mascarenhas M.N, Flaxman SR, Boerma T, et al. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLoS Medicine. 2012;9:e1001356.
28. Borumandnia N, Majd HA, Khadembashi N, et al. Worldwide trend analysis of primary and secondary infertility rates over past decades: A cross-sectional study. International Journal of Reproductive BioMedicine (IJRM). 2022;20:37-46.
29. Buckett W, Sierra S. The management of unexplained infertility: an evidence-based guideline from the Canadian Fertility and Andrology Society. Reproductive BioMedicine Online. 2019;39:633-640.
30. Kalinka J, Szekeres-Bartho J. The impact of Dydrogesterone supplementation on hormonal profile and progesterone-induced blocking factor concentrations in women with threatened abortion. American Journal of Reproductive Immunology. 2005;53:166-171.
31. Beta J, Szekeres-Bartho J, Skyfta E, et al. Maternal serum progesterone-induced blocking factor at 11-13 weeks' gestation in spontaneous early preterm delivery. Fetal Diagnosis and Therapy. 2011;29:197-200.
32. Polgár B, Nagy E, Mikó E, et al. Urinary progesterone-induced blocking factor concentration is related to pregnancy outcome. Biology of Reproduction. 2004;71:1699-705.
33. Sahin M.E, Madendag IC, Sahin E, et al. The role of serum progesterone-induced blocking factor on unexplained infertility. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020;252:15-18.
34. Ku C.W, Allen Jr JC, Lek SM, et al. Serum progesterone distribution in normal pregnancies compared to pregnancies complicated by threatened miscarriage from 5 to 13 weeks gestation: a prospective cohort study. BMC Pregnancy and Childbirth. 2018;18:360.
35. Check J.H, J Szekeres-Bartho, A O'Shaughnessy. Progesterone induced blocking factor seen in pregnancy lymphocytes soon after implantation. American Journal of Reproductive Immunology. 1996;35:277-80.
36. Check J.H, Szekeres-Bartho J, Nazari P. A corpus luteum is not a prerequisite for the expression of progesterone induced blocking factor by T-lymphocytes a week after implantation. Journal of Assisted Reproduction and Genetics. 2001;18:603-607.
37. Adamczak R, Ukleja-Sokołowska N, Lis K, et al. Progesterone-induced blocking factor 1 and cytokine profile of follicular fluid of infertile women qualified to in vitro fertilization: The influence on fetus development and pregnancy outcome. International Journal of Immunopathology and Pharmacology. 2022;36:039463202211111.
38. Ku C.W, Allen Jr JC, Malhotra R, et al. How can we better predict the risk of spontaneous miscarriage among women experiencing threatened miscarriage? Gynecological Endocrinology. 2015;31:647-651.

Абстракт

Введение и цели исследования: Определение диагностической ценности Прогестерон-Индуцирующего Блокирующего Фактора (ПИБФ) при Раннем Прерывании Беременности (РПБ), в натуральном цикле и после Экстракорпорального Оплодотворения (ЭКО).

Материалы и методы: В проспектно-ретроспективрое исследование 50 женщин, забеременевших в натуральном цикле были распределены в трех группах: I – женщины с прогрессирующей беременностью, II – женщины с РПБ, III - женщины с биохимической беременностью (ББ). 36 женщин после процедуры ЭКО также были распределены в группах: IV группа – пациентки с прогрессирующей беременностью, V - женщины с РПБ, VI - женщины с ББ. ПИБФ, ПГ и β Хорионический Гонадотропин Человека (βХГЧ) были определены на 12-14-й день после овуляции и змбриотрансфера (ЭТ).

Результаты: Показатели ПИБФ и ПГ были статистический значимо выше в группе I и статистический значимо ниже в группе III как в натуральном цикле, так и после ЭКО. Не выявилась значимая разница в показателях ПИБФ между женщин с РПБ и ББ, как в натуральном цикле, так и после ЭКО. Однако, концентрация ПГ была статистический значимо ниже в группе с ББ. Следовательно, ПИБФ был информативнее в РПБ, ПГ – в диагностике клинической беременности.

Выводы: ПИБФ может быть рассмотрен как возможный прогнозирующий маркер РПБ, в том числе на преклинической стадии.

Ключевые слова: Раннее прерывание беременности (РПБ), Прогестерон-Индуцирующий Блокирующий Фактор (ПИБФ), преклиническая стадия беременности, Прогестерон (ПГ), биохимическая беременность.

აბსტრაქტი

კვლევის მიზანი:. პროგესტერონით ინდუცირებული მაბლოკირებელი ფაქტორის (პიმფ) დიაგნოსტიკური მნიშვნელობის შეფასება ორსულობის ადრეული დანაკარგების დროს, როგორც ბუნებრივი გზით, ისე ინ ვიტრო განაყოფიერების (ივგ) შედეგად მიღებულ ორსულობებში.

მასალა და მეთოდები: პროსპექტულ-რეტროსპექტულ კვლევაში ჩართული ბუნებრივი

გზით დაორსულებული 50 ქალი დაიყო სამ ჯგუფად: I ჯგუფი - ქალები პროგრესირებადი ორსულობით; II - ქალები ორსულობის ადრეული დანაკარგით (ოად); III - პაციენტები ბიოქიმიური ორსულობით; ივგ-ის შედეგად დაორსულებული 36 ქალი განაწილდა, ასევე, სამ ჯგუფში: IV ჯგუფი - ქალები პროგრესირებადი ორსულობით; V - ქალები ოად-ით, VI - ქალები ბიოქიმიური ორსულობით. პიმფ, პროგესტერონი (პგ) და ადამიანის ბეტა ქორიონული გონადოტროპინი (ბქგ) განისაზღვრა ბუნებრივ და ივგ ციკლებში ოვულაციიდან და ემბრიონის ტრანსფერიდან მე-12-14 დღეს, შესაბამისად.

შედეგები: პიმფ და პგ მაჩვენებლები სარწმუნოდ მაღალი იყო პროგრესირებადი ორსულობის და სარწუმუნოდ დაბალი - ბიოქიმიური ორსულობის ჯგუფებში, როგორც ბუნებრივი, ისე ივგ-ით მიღებული ორსულობის დროს. პიმფ არ განსხვავდებოდა ბუნებრივ და ივგ შედეგად მიღებულ ორსულებში ადრეული დანაკარგების და ბიოქიმიური ორსულობების ჯგუფებში მაშინ, როდესაც პგ იყო სტატისტიკურად სარწმუნოდ მაღალი ადრეული დანაკარგების ჯგუფში. ამდენად, პიმფ იყო უფრო ინფორმაციული ოად-ის, ხოლო პგ კლინიკური ორსულობის დიაგნოსტირების თვალსაზრისით.

დასკვნები: პიმფ შეიძლება განიხილოს როგორც ორსულობის ადრეული, მათ შორის, პრეკლინიკურ სტადიაზე შეწყვეტის შესაძლო პროგნოზული მარკერი.

საკვანძო სიტყვები: ორსულობის ადრეული დანაკარგი (ოად), პროგესტერონით ინდუცირებული მაბლოკირებელი ფაქტორი (პიმფ), ორსულობის პრეკლინიკური სტადია, პროგესტერონი (პგ), ბიოქიმიური ორსულობა.