INTRODUCTION
About 60% of human zygotes are eliminated during the preimplantation and early postimplantation stages of embryogenesis; 15% to 20% of clinically confirmed pregnancies are spontaneously terminated during the first trimester, mostly due to teratonasia [1–3] (Table 1).

Recurrent miscarriages, defined as 2 or more spontaneous miscarriages in a row, are seen in 2% of all pregnancies. In the structure of all pregnancy losses, the recurrent miscarriages comprise 5% to 20% [3].

REPRODUCTIVE LOSSES AND THEIR CAUSES
The etiology of the recurrent miscarriage includes genetic, anatomic, infectious, endocrine, and immune factors. In addition, in clinical practice the major contradictions remain with regards to the contribution of specific factors and causes of reproductive losses. Many studies have shown that most (50% to 76%) early losses are caused by the embryonic aneuploidy [4–13] (Table 2). It should be noted that earlier gestational age at the moment of the miscarriage corresponds to higher frequency of chromosomal abnormalities (CA) [14–18] (Table 3).

As N. Fabricant once said, some doctors keep making the same mistakes for 20 years and call it clinical experience [19]. The author was right about the medicine based on expert opinion and personal experience. In the light of the current development of diagnostics and treatment for a wide range of diseases, as well as of the medical informational processes globalization, evidence-based approach becomes more important in medicine. Its principles are aimed to help the physician choose optimal treatment for an individual patient.

REVIEWING EFFICACY OF PROGESTAGENES IN RECURRENT EARLY REPRODUCTIVE LOSSES
ANALYSIS OF PUBLISHED DATA

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of the study</th>
<th>Miscarriage / Missed miscarriage, absolute number</th>
<th>Chromosomal abnormalities, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Boue</td>
<td>1975</td>
<td>1,498</td>
<td>61.5</td>
</tr>
<tr>
<td>T. Hassold</td>
<td>1985</td>
<td>2,264</td>
<td>50.4</td>
</tr>
<tr>
<td>J. Kline</td>
<td>1987</td>
<td>2,098</td>
<td>37.6</td>
</tr>
<tr>
<td>J. Menasha</td>
<td>2005</td>
<td>1,203</td>
<td>65.8</td>
</tr>
<tr>
<td>N.P. Veropotvelyan, L.A. Kodunov</td>
<td>2012</td>
<td>1,208</td>
<td>57.1</td>
</tr>
<tr>
<td>S. Mathew</td>
<td>2014</td>
<td>1,599</td>
<td>63.2</td>
</tr>
<tr>
<td>N.P. Veropotvelyan, L.A. Kodunov</td>
<td>2016</td>
<td>1,808</td>
<td>54.97</td>
</tr>
</tbody>
</table>

Table 3. Frequency and types of aneuploidy in reproductive losses of different stages

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>Frequency of chromosomal abnormalities, %</th>
<th>Dominant chromosomal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losses during preimplantation</td>
<td>20</td>
<td>Wide range</td>
</tr>
<tr>
<td>Preclinical losses</td>
<td>50</td>
<td>Different</td>
</tr>
<tr>
<td>Embryo death during the first 5 weeks after the conception</td>
<td>35</td>
<td>Tetraploidy, triploidy, all kinds of trisomy, mostly +16, +22</td>
</tr>
<tr>
<td>Embryo death at 6–10 weeks after the conception</td>
<td>20</td>
<td>45, X+; +14; 15; +16; +22; +8; +21; +13; +18; +20; 69, XYY; 92, XXXX</td>
</tr>
<tr>
<td>Miscarriage in the early fetal period (11–14 weeks)</td>
<td>10–15</td>
<td>45, X; +21; +13; +18; +22; 69, XYY</td>
</tr>
<tr>
<td>Late miscarriage (16 weeks)</td>
<td>4</td>
<td>45, X; +21; +13; +18; +22</td>
</tr>
<tr>
<td>Early premature birth (22–28 weeks)</td>
<td>1–2</td>
<td>+21; +13; +18; 45, X</td>
</tr>
<tr>
<td>Live births</td>
<td>0.5–0.7</td>
<td>+21; +13; +18; 47, XXX; 47, XYY; 47, XXXY; 45, X</td>
</tr>
</tbody>
</table>

DOI: http://dx.doi.org/10.18370/2309-4117.2016.31.22-33
When studying the reasons of the reproductive losses, groups with different levels of evidence were formed. The assessment was based on the probability of the difference between the study groups which is equal or higher than the difference which could be explained by a chance (Table 4).

Although the lutein phase insufficiency (LPI) is not a confirmed reason of reproductive losses (evidence level 3 – unlike causes), the attention of obstetricians/gynecologists is mostly concentrated on this pathology. Interestingly, a significant number of publications and scientific presentations are focused not on the confirming the LPI as a reason of early reproductive losses, but on the use of progesterone for the reproductive losses treatment. In addition, the most controversial aspect is the comparison of efficacy of micronized progesterone and dydrogesterone.

This publication is not focused on tocolytic, neuroprotective, immunomodulatory, antiinflammatory, antiandrogenic, and other effects of progesterone. Instead, it is focused on the therapy of early reproductive losses with progesterone drugs.

The main objective of this work is to summarize and analyze the existing data of clinical aspects of progestagens use aimed to decrease early reproductive losses in the context of evidence-based approach.

OPINIONS AND DISCUSSIONS
Terminology issues
Classification of progestagene medications into natural and synthetic still results in significant confusion. For example, one very popular claim is for the term natural to mean that in the manufacturing process, the plant-based materials are used. In reality, though, the term natural does not define the source of material (almost all hormones are produced on the base of soy or wild yam), but the structural similarity of the synthetized hormone molecule with the endogenous hormone molecule.

In relation to this, it should be noted that all progestagens are pharmaceutical substances synthetized in the conditions of pharmaceutical manufacturing, and may be divided into the medications based on the natural progesterone, and synthetic progestines [20].

The natural progesterone has the same chemical formula and molecular structure as the hormone synthetized in the human body. In other worlds, the best term to explain the meaning of natural in this case is bioidentical.

Synthetic progestagens (or progestines) are compounds with chemical formula and/or structure which in some degree differ from those of the endogenous hormone.

Opinions of professional associations
Micronized progesterone in vaginal form is approved by the USA Food and Drug Administration (FDA) for the support of lutein phase during the first trimester of pregnancy. Dydrogesterone is not approved in the USA and, thus, is not used there in the obstetric-gynecological practice.

The true progesterone deficit is the main cause of the recurrent miscarriages only in 12% women. In the opinion of some investigators, progesterone medications are prescribed not to replenish its deficit but to correct the immune disorders, as there are evidences of immunomodulatory effect of exogenous progesterone on the endometrial tissue [21, 22].

In 2015, the Practice Committee of the American Society for Reproductive Medicine published its opinion on the clinical significance, diagnostics and treatment principles for the LPI [23]. In this document, it is said that the first step is the exclusion of possible primary reasons of the LPI, i.e., disorders of the central (hypothalamic-pituitary) regulation, thyroid gland disorders, hyperprolactinemia. After the exclusion of such endocrine disorders, there may be considered an empiric therapy which can improve the implantation processes, increase the endometrial susceptibility, support the development of pregnancy in the early phase.

In the Early pregnancy loss: Obstetric evidence-based guidelines published in New York [24], it is said that the routine progesterone use during the second phase of the menstrual cycle until the pregnancy, as well as during the first 8 to 10 weeks after the conception, is recommended to all women with the history of recurrent miscarriages. It is also noted that the number of menstrual cycles to support with progesterone during the second phase is unlimited and individual [25].

According to the official opinion of the European Progestin Club (EPC), only dydrogesterone is recommended for the treatment and prevention of the threatened miscarriage [26].

PROMISE (2015), Kumar (2014), and other studies
Among the publications on the efficacy of different progestagens in the treatment of miscarriages, most discussions in recent years are dedicated to the results of the dydrogesterone and micronized progesterone use.

The scientific base of progestagens efficacy in women with threatened miscarriage was built on the data of the 2011 Cochrane review [27]. It is clear that the significance of the results of any meta-analysis is defined by the quality and the quantity of included studies. According to the opinion of the review authors, only one of the four studies met the predefined criteria on some level (Pandian, 2009). The resting 3 studies were methodologically weak and did not have sufficient statistical power due to small sample sizes. These reasons do not permit to interpret the meta-analysis results correctly from the point of view of the evidence-based medicine [27].

Table 4. The significance of different reproductive loss reasons from the point of view of the evidence-based medicine

<table>
<thead>
<tr>
<th>Degree of significance</th>
<th>Reproductive loss reasons</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>Antiphospholipid syndrome, chromosomal pathology</td>
<td>I</td>
</tr>
<tr>
<td>Probable</td>
<td>Uterine abnormalities, thrombophilia</td>
<td>II</td>
</tr>
<tr>
<td>Possible</td>
<td>Endocrine (polycystic ovarian syndrome, lutein phase insufficiency, hypothyroidism), infectious factors</td>
<td>III</td>
</tr>
<tr>
<td>Unknown</td>
<td>Allergenic factors, endometrial pathology, psychological factors</td>
<td>Are being studied</td>
</tr>
</tbody>
</table>
Published results of the studies focused on the efficacy of dydrogesterone (Kumar, 2014) and vaginal micronized progesterone (PROMISE, 2015) in women with recurrent miscarriages led to many discussions among the obstetricians/gynecologists [28, 29]. The comparative characteristics of these studies are presented in the Table 5.

In both cases, during the enrolment stage, possible known reasons of miscarriage (anatomical factors, endocrine factors, chromosomal abnormalities in parents, autoimmune diseases etc.) were excluded for all patients.

It should be noted that patients with the history of recurrent miscarriage, who received progestagens in both studies, did not have confirmed diagnosis of the progesterone (lutein phase) insufficiency. Thus, the prescription was not based on the pathogenic mechanism but rather driven by empirical approach.

PROMISE (Progesterone in recurrent miscarriages) was the first randomized controlled study with the adequate statistical power where the frequency of live births was assessed as the primary endpoint [28]. In earlier studies of progestagens use [29, 30], the relative risk of miscarriage was used.

According to the results of the multicenter study PROMISE, there were no statistically significant differences from the point of view of miscarriage and live birth values between the groups of vaginal progesterone and placebo (65.8% (262/398) vs 63.3% (271/428), respectively, difference 2.5%). The authors have not found any increase in the risk of congenital abnormalities in children of the women who received micronized progesterone during the pregnancy, there were no statistically significant differences from the group of dydrogesterone, there were trends for lower frequency of premature births, cesarean sections, lower number of newborns with low body weight, less cases of the retardation of fetal development. The publication does not contain data on the medication effects of the congenital abnormalities risk.

At the same time, another study published in 2015 has shown a triple increase in the frequency of babies born with congenital heart abnormalities among the women who received dydrogesterone during the first trimester of their pregnancies [32].

In a cohort study of the health and development evaluation in twins aged 3–6 years, who were born to mothers receiving micronized progesterone during the pregnancy, there were no findings about any adverse effects of micronized progesterone [33].

### Meta-analysis of the studies of the dydrogesterone and micronized progesterone use

During the most recent search of online publications (October 2015), total of 343 publications on progestagens use for the treatment of reproductive losses were found [34]. For the meta-analysis, 8 studies which met specific criteria, were selected. Total number of women included in these studies was 3809; 1523 were selected to use dydrogesterone, 1288 to use vaginal progesterone in capsules, 898 to use vaginal progesterone in gel. All 8 studies assessed the use of oral dydrogesterone in the doses of 20 to 40 mg daily. In 6 studies, oral dydrogesterone was compared with vaginal progesterone in capsules in the doses of 600 to 800 mg daily [35–40]. In the study by V. Tomic et al. (2015), the efficacy of dydrogesterone and vaginal progesterone gel in the dose of 90 mg daily was compared. In the publication by A. Ganesh and colleagues (2011), there were 3 studies on the comparison of oral dydrogesterone and vaginal progesterone in capsules and gel [42].

The authors of the meta-analysis concluded that in the treatment of reproductive losses, the oral dydrogesterone

<table>
<thead>
<tr>
<th>Study</th>
<th>PROMISE, 2015</th>
<th>Kumar, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>The investigators</td>
<td>Dr. Arri Coomarasamy, Birmingham, UK</td>
<td>Dr. Ashok Kumar, Delhi, India</td>
</tr>
<tr>
<td>The Sponsors</td>
<td>Imperial College, London, UK</td>
<td>Maulana Azad Medical College &amp; Lok Nayak Hospital, India</td>
</tr>
<tr>
<td>Study design</td>
<td>Multicenter, randomized, placebo-controlled</td>
<td>Double blind, randomized, placebo-controlled, in parallel groups</td>
</tr>
<tr>
<td>Investigational centers</td>
<td>United Kingdom (36 centers), the Netherlands (9 centers)</td>
<td>Medical College Maulana Azad clinic, New Delhi, India</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Unexplainable miscarriages ≥ 3 Age 18–39 years Spontaneous pregnancy</td>
<td>Unexplainable miscarriage ≥ 3 Age 18–35 years Spontaneous pregnancy</td>
</tr>
<tr>
<td>Total number of subjects in the study</td>
<td>836</td>
<td>348</td>
</tr>
<tr>
<td>Number of subjects in the main group</td>
<td>404</td>
<td>175</td>
</tr>
<tr>
<td>Start of the therapy</td>
<td>After the positive urine pregnancy test, not later than 6 weeks of gestation</td>
<td>After the confirmation of fetal heart beating, weeks 4–8 of gestation</td>
</tr>
<tr>
<td>Medication and way of administration</td>
<td>Vaginal micronized progesterone</td>
<td>Oral dydrogesterone</td>
</tr>
<tr>
<td>Daily dose</td>
<td>800 mg (400 mg BID)</td>
<td>20 mg (10 mg BID)</td>
</tr>
<tr>
<td>Duration of the therapy</td>
<td>Until 12 weeks of the pregnancy</td>
<td>Until 20 weeks of the pregnancy</td>
</tr>
</tbody>
</table>
seems equally effective as the vaginal micronized progesterone, but less women complained on inconvenience of the use in case of the former. Due to the differences in the ways of administration and routes of entry, the subgroup analysis has provided important information. At the authors mentioned, oral dydrogesterone did not influence the frequency of pregnancies. The observed benefit was small, and its assessment was still inaccurate. Nevertheless, the authors consider the obtained data sufficient to conclude that dydrogesterone caused no clinically significant worsening of ongoing pregnancy parameters or clinical outcomes. During the comparison with the vaginal progesterone gel, the authors observed the lack of the oral dydrogesterone effect on the ongoing pregnancy or its clinical outcomes. Preventive effect against miscarriage remains weak, preluding any reliable conclusions for either subgroup.

**DISCUSSION**

A more detailed comparison of the PROMISE (2015) and Kumar (2014) studies shows that, despite apparent resemblance, the studies are actually similar no more than their author’s last names are – written quite differently albeit sharing common syllables (Coomarasamy and Kumar).

Although the inclusion criteria of these studies were identical, the important differences include not only administrative, territorial, climatic and geographical conditions, but also the timing of the therapy starting and ending.

Without preferring any of the discussed progestagenes, we believe that the optimistic results of the study by Kumar [29] should be treated skeptically, as the timing of the start of the dydrogesterone treatment was later than the most critical phase for the natural elimination of abnormal embryos (as 35% embryos are eliminated before the week 6 of gestation). The treatment was prescribed after the confirmation of the heart beating; thus, cases of anembryonic gestation and embryonic death before the start of the study were excluded. For example, in the randomized sample of missed miscarriages at the gestational age 5 to 11 weeks, 30.6% cases were composed by anembryonic gestations, half of which were caused by aneuploidy [43]. Another important issue is the fact that only 13% of all miscarriages happen at the gestational age of 12 to 20 weeks, and 84% happen before the 11 weeks [44]. Frequency of miscarriages is shown in the figure below by the gestational age.

According to the statistical analysis of the data obtained since 1997 until 2008, the percentage of pregnant women older than 35 years has increased from 8% to 20% in the UK (up to 60% in the USA, and to 15% in the Netherlands) [45]. Among the women with the history of reproductive loss, this percentage is even higher due to unimplemented maternity. Taking these data into account, in the PROMISE study the percentage of women aged 35 to 39 years might reach 25% (mean age 32.5 years vs 25.3 years in the study by Kumar). At the same time, the percentage of chromosomal abnormalities in miscarriages in the age range of 18 to 35 is in average 48%, reaching 74% in the age range of 35–39 years [46]; furthermore, in women with a history of more than 3 miscarriages the probability of chromosomal abnormalities beyond the age of 35 would further increase by 1.68-fold [42], i.e. PROMISE study subjects had higher level of reproductive losses caused by aneuploidy in women older than 35 years. Thus, at least for 65 to 70 pregnancies in the PROMISE study, adverse outcomes were prevented irrespectively of the prescription of any supporting therapy, including progestagenes. Therefore we believe claims by some experts that micronized progesterone is administered too late, advocating its earlier use, are inappropriate [31], as administration of dydrogesterone only after the registration of the fetal heartbeat in the study by Kumar was, on the contrary, shown to be more effective.

This may be explained by the fact that in the study by Kumar, a group of patients with inherently higher changes of the positive pregnancy outcome was formed, in comparison to the PROMISE study, where the treatment was started at the moment of the positive pregnancy test. The embryonic death happened 2–3 weeks later (gestational age 10.1 weeks [6–18 weeks] in the study by Kumar and 7.5 weeks [6–8 weeks] in the PROMISE study), so the difference in the miscarriages number between the study by Kumar (16.8%) and the PROMISE (32.8%) was quite expected. If we excluded 65 patients with initially poor prognosis (taking into account the proportion of anembryonic cases and chromosome abnormalities in women older than 35) from the total number of PROMISE study subjects who had taken micronized progesterone and whose outcome was a miscarriage, the remaining percentage of losses (68/404 – 16.8%) will be the same as in the Kumar study.

Therefore it is by far inappropriate to compare efficacy of dydrogesterone and micronized progesterone based on the results of those two studies.

According to the results of meta-analysis by MW Barbosa and colleagues [32], the comparison of the two groups of progestagenes results in the demonstration of the convenience of oral dydrogesterone in comparison to vaginal progesterone. Nevertheless, the progesterone might also be administered orally and sublingually, and this aspect is not so important compared to the efficacy and safety of these medications. It should be noted that an orally
administered hormone is subjected to the first-pass effect, which is different for the vaginal form. In case of the vaginal administration, the progesterone concentration is maximal in the target area (uterine body layers) due to the reverse osmosis mechanism. In addition, progesterone is absorbed into the systemic circulation in significantly less quantities, which decreases the pharmacological burden for the liver.

In our opinion, progestagenes should be administered after the confirmation of the embryo viability. During the earlier stages of the pregnancy, they should be used only in cases of clinically confirmed lutein phase insufficiency, as well as in patients participating in the cycles and programs of assisted reproductive technologies in order to ensure synchronized transformation of endometrial receptors within the "implantation window". A separate point of consideration is whether to administer progestagenes in histologically verified chronic endometritis to women with recurrent miscarriages in order to intensify endometrial regeneration responses [48].

Once the gestational sac can be imaged, in patients with the recurrent miscarriages progestagenes should be prescribed taking into account its growth, as a decrease in the gestational sac growth rate below 0.7 mm per day might be a sign of a threatened miscarriage, and below 0.2 mm per day – of a missed miscarriage [49, 50]. If the pregnancy does not develop, the persistence of the unviable embryo in the uterine cavity may be associated with the presence of continuous hormone production by the trophoblast which blocks uterine contractions after the embryonic death [43, 51]. Thus, the additional progestagenes administration in case of the embryonic death may promote the gestational sac persistence for several days or even weeks, rather than rescuing the pregnancy.

The issue of the correct dosing of progestagenes used in the therapy of reproductive losses is also not highlighted enough. The risk factors associated with the administration of excessive doses of the exogenous progesterone include the endometrial receptors block, when they become less susceptible, as well as other negative effects [52], which require additional investigation. In such a case, the efficacy of the treatment will depend not only on the fact of progestagenes administration, but also on the optimal doses for each individual patient.

Currently, the patients are being enrolled into a randomized, double blind, placebo-controlled study (PRISM) which will include 4000 patients with the spotting during the early stages of pregnancy; the results are expected in 2018. The study objective is to evaluate the hypothesis that vaginal progesterone started as earlier as possible after the confirmation of a visible intrauterine pregnancy and continued to 16 full weeks of gestation, increases the frequency of the live births after 34 full weeks for at least 5% compared to placebo.

We hope that during the conduct of this study, all evidence-based medicine criteria will be adhered, and the results will reflect an accurate picture of progestagenes use for the treatment of miscarriages during the early stages of pregnancy.

**Literature/References**


К ВПРОСУ ОБ ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ ПРОГЕСТАГЕНОВ ПРИ ПОВТОРНЫХ РАННИХ РЕПРОДУКТИВНЫХ ПОТЕРАХ

Анализ данных литературы

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Приведенное невынашивание беременности, определяемое как самопроизвольное прерывание беременности два и более раза подряд, составляет 2% от числа всех беременностей, при этом в структуре невынашивания в целом частота прерывания составляет от 5 до 20%. Вместе с тем в практической медицине существуют большие противоречия относительно доминирования факторов и причин невынашивания. Несмотря на то, что недостаточность лютеиновой фазы не относится к доказанным причинам невынашивания беременности, применение препаратов прогестерона в ее терапии посвящено значительное число публикаций и научных работ.

В статье представлен собственный критический взгляд автора на исследования последних лет, посвященные применению прогестагенов с целью предотвращения повторных репродуктивных потерь.

Анализированны методология, дизайн экспериментов и результаты ряда исследований по определению эффективности терапии невынашивания беременности микронизированным прогестероном и дидрогестероном. Сделаны общебиологические выводы и определены критически значимые моменты данных исследований.

Среди прочего, пристальное внимание уделено результатам двойного слепого рандомизированного параллельного плацебо-контролируемого исследования Kumar (2014) и многоцентрового рандомизированного плацебо-контролируемого исследования PROMISE (2015). В частности, по мнению автора, сравнение эффективности применения дидрогестерона и микронизированного прогестерона по результатам этих двух исследований является как минимум некорректным. В статье, за независимости автора от результатов этих исследований, применение прогестагенов нужно начинать после установления жизнеспособности эмбриона, при этом применять их на ранних сроках беременности следует только в случае клинически доказанной недостаточности лютеиновой фазы, а также у пациенток в циклах и программах вспомогательных репродуктивных технологий.

Анализ данных о привычном невынашивании вагиности, которое составляет 2% от числа всех вагиностей, при этом в структуре невынашивания в целом частота привычного выкидыша составляет от 5 до 20%. Вместе с тем в практической медицине также существуют большие противоречия относительно доминирования факторов и причин невынашивания. Несмотря на то, что недостаточность лютеиновой фазы не относится к доказанным причинам невынашивания беременности, применение препаратов прогестерона в ее терапии посвящено значительное число публикаций и научных работ.

Автор статьи выражает надежду, что истинную картину в области применения прогестагенов для лечения невынашивания в ранние сроки беременности отобразят результаты рандомизированного двойного слепого плацебо-контролируемого исследования PRISM, которые ожидаются в 2018 году.

Ключевые слова: прогестагены, микронизированный прогестерон, дидрогестерон, невынашивание беременности, ранние репродуктивные потери.

REVIEWING EFFICACY OF PROGESTAGENES IN RECURRENT EARLY REPRODUCTIVE LOSSES

Analysis of published data

N.P. Veropotvelyan, PhD, Chief Physician of the Multiregional Center of Medical Genetics and Prenatal Diagnostics, Kryvyi Rih

Recent miscarriages, defined as 2 or more spontaneous miscarriages in a row, are observed in 2% of all pregnancies. In the structure of all pregnancy losses, the recurrent miscarriage compositions 5% to 20%. In addition, in clinical practice, there are large contradictions related to the domination of some factors and causes of reproductive losses. Although the lutein phase insufficiency (LPI) is not a confirmed reason of reproductive losses, there is a significant number of publications and scientific presentations which are focused on the use of progesterone for the reproductive losses treatment.

This article presents the author's critical view on recent studies dedicated to the use of progesterone therapy with the objective of the prevention of early reproductive losses. Methodology, design and results of several studies of the efficacy of micronized progesterone and dydrogesterone have been analyzed. Generalized conclusions and critically important points of these studies have been defined.

Among other things, special attention was dedicated to the results of the double blind, randomized, parallel-groups, placebo-controlled study by Kumar (2014), and the multicenter, randomized, placebo-controlled study PROMISE (2015). For example, in the author's opinion, the comparison of the efficacy of dydrogesterone and micronized progesterone on the base of these studies can not be correct. As outlined in this article, progesterone should be administered after the confirmation of the embryo viability. They should be used during the earlier stages of the pregnancy only in cases of clinically confirmed lutein phase insufficiency, as well as in patients participating in cycles and programs of assisted reproductive technologies. The issue of the correct dosing of progesterone is also not highlighted enough. This issue requires additional investigation, as the efficacy of the treatment will depend not only on the fact of progesterone administration, but also on the optimal doses for each individual patient.

The author expects that the accurate picture of progesterone use for the treatment of miscarriages during the early stages of pregnancy will be reflected by the results of a randomized, double blind, placebo-controlled study (PRISM) which are expected in 2018.

Keywords: progesterone, micronized progesterone, dydrogesterone, miscarriage, early reproductive losses.

ДО ПИТАННЯ ЩОДО ЕФФЕКТИВНОСТІ ЗАСТОСУВАННЯ ПРОГЕСТАГЕНОВ ПРИ ПОВТОРНИХ РАННИХ РЕПРОДУКТИВНИХ ВТРАТАХ

Аналіз даних літератури

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Значне невишивання вагітності, яке визначається як самовільне переривання вагітності два і більше разів поспіль, становить 2% від числа всіх вагітностей, при цьому в структурі невишивання в целому частота звичного викидня становить від 5 до 20%. Водночас у практичній медицині йснують великі суперечності щодо домінування факторів і причин невишивання. Незважаючи на те, що недостатність лютеинової фази не відноситься до доказаних причин невишивання вагітності, застосуванню препаратів прогестагенів треба ставити під суперечку, так як не відомо, що саме впливає на результати терапії.


Серед іншого, автор зазначає, що доказано відсутність ефективності прогестагенів для терапії невишивання вагітності залежно від відповідного режиму застосування. Проблема втручання залежить від відповідного режиму застосування.

Автор статті висловлює сподівання, що справжню картину в області застосування прогестагенів для лікування невишивання в ранніх термінах вагітності відобразять результати рандомізованого двохступненого плацебо-контрольованих досліджень PRISM, які очікуються у 2018 році.

Ключові слова: прогестагени, микронизований прогестерон, дидрогестерон, невишивання вагітності, ранні репродуктивні втрати.