REVIEWING EFFICACY OF PROGESTAGENES IN RECURRENT EARLY REPRODUCTIVE LOSSES

ANALYSIS OF PUBLISHED DATA

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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.

Table 1. Reproductive losses as a way of natural selection

Stages of development	Reproductive losses, %
Non-implanted fertilized egg	10–15
Preclinical pregnancy termination	22
Embryo death during the first 5 weeks after the conception	20–25
Embryo death during the final weeks of embryogenesis (6–10 weeks)	15–20
Miscarriage in the early fetal period (11–14 weeks)	10–15

Table 2. Population studies of fetal chromosomal abnormalities in missed abortions

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

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

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

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

Degree of significance	Reproductive loss reasons	Level of evidence
Confirmed	Antiphospholipid syndrome, chromosomal pathology	I
Probable	Uterine abnormalities, thrombophilia	II
Possible	Endocrine (polycystic ovarian syndrome, lutein phase insufficiency, hypothyroidism), infectious factors	III
Unknown	Alloimmune factors, endometrial pathology, psychological factors	Are being studied

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 progestagenes 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 progestagenes 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 progestagenes (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 progestagenes 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 progestagenes 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 5. Comparative characteristics of the PROMISE and Kumar studies [28, 29]

Study	PROMISE, 2015	Kumar, 2014
The investigators	Dr. Arri Coomarasamy, Birmingham, UK	Dr. Ashok Kumar, Delhi, India
The Sponsors	Imperial College, London, UK	Maulana Azad Medical College & Lok Nayak Hospital, India
Study design	Multicenter, randomized, placebo-controlled	Double blind, randomized, placebo-controlled, in parallel groups
Investigational centers	United kingdom (36 centers), the Netherlands (9 centers)	Medical College Maulana Azad clinic, New Delhi, India
Inclusion criteria	Unexplainable miscarriages ≥ 3 Age 18–39 years Spontaneous pregnancy	Unexplainable miscarriage ≥ 3 Age 18–35 years Spontaneous pregnancy
Total number of subjects in the study	836	348
Number of subjects in the main group	404	175
Start of the therapy	After the positive urine pregnancy test, not later than 6 weeks of gestation	After the confirmation of fetal heart beating, weeks 4–8 of gestation
Medication and way of administration	Vaginal micronized progesterone	Oral dydrogesterone
Daily dose	800 mg (400 mg BID)	20 mg (10 mg BID)
Duration of the therapy	Until 12 weeks of the pregnancy	Until 20 weeks of the pregnancy

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 progestagenes 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 progestagenes 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 800 mg daily compared to placebo. The expert opinion is that the PROMISE study has shown that starting the therapy at weeks 5–6 of the pregnancy in patients with the recurrent miscarriages of unknown etiology is already belated; most patients had miscarriages at the gestational age of 6–7 weeks, just barely after the inclusion into the study [31].

In the study conducted by Kumar [29], a significant decrease of the miscarriages number was shown for the dydrogesterone compared to placebo (miscarriage frequency was 6.9% and 16.9%, respectively, p = 0.004). In addition, in 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 resent search of online publications (October 2015), total of 343 publications on progestagenes 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

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 routs 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.

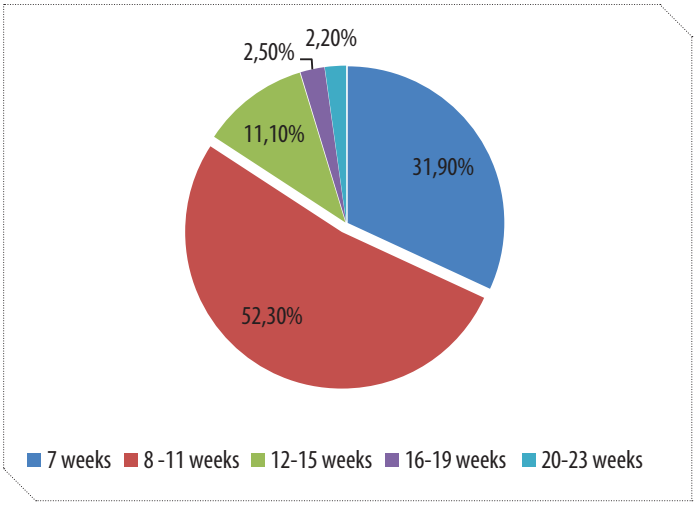

Figure. Frequency of miscarriages by the gestational age [44]

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 losses, 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.

ЛИТЕРАТУРА/REFERENCES

1. Сосніна, К.О.
Імуногенетичні передумови ранніх репродуктивних втрат у людини/ К.О. Сосніна // Автореф. дис. ... к. біол. н. – Київ, 2014.
Sosnina, K.O.
Immunogenetic prerequisites of early reproductive losses in human. Thesis abstract for PhD degree. Kyiv (2014).

2. Ранние сроки беременности.
Под ред. В.Е. Радзинского и А.А. Оразмурадова. – М. – 2005. – 448 с.
Early stages of pregnancy.
Ed. by V.E. Radzinskyi, A.A. Orazmuradova. Moscow (2005): 448 p.

3. Доброхотова, Ю.Э., Джобава, Э.М., Озерова, Р.И.
Неразвивающаяся беременность. – М.: ГЭОТАР-Медиа. – 2010. –144 с.
Dobrokhotova, Y.E., Jobava, E.M., Ozerova, R.I.
Non-developing pregnancy. Moscow. GEOTAR-Media (2010):144 p.

4. Bessho, T., Sakamoto, H., Shiotani, T., et al.
"Fetal loss in the first trimester after demonstration of cardiac activity: relation of cytogenetic and ultrasound findings." Hum Reprod 10.10 (1995): 2696–9.

5. Eiben, B., Bartels, I., Bahr-Porsch, S., et al.
"Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage." Am J Hum Genet 47.4 (1990): 656–63.

6. Guerneri, S., Bettio, D., Simoni, G., et al.
"Prevalence and distribution of chromosome abnormalities in a sample of first trimester internal abortions." Hum Reprod 2.8 (1987): 735–9.

7. Hogge, W.A., Byrnes, A.L., Lanasa, M.C., Surti, U.
"The clinical use of karyotyping spontaneous abortions." Am J Obstet Gynecol 189.2 (2003): 397–400.
DOI: 10.1067/S0002-9378(03)00700-2

8. Lathi, R.B., Milki, A.A.
"Tissue sampling technique affects accuracy of karyotype from missed abortions." J Assist Reprod Genet 19.11 (2002): 536–8.
DOI: 10.1023/A:1020916003666

9. Minelli, E., Buchi, C., Granata, P., et al.
"Cytogenetic findings in echographically defined blighted ovum abortions." Ann Genet 36.2 (1993): 107–10.

10. Strom, C.M., Ginsberg, N., Applebaum, M., et al.
"Analyses of 95 first-trimester spontaneous abortions by chorionic villus sampling and karyotype." J Assist Reprod Genet 9.5 (1992): 458–61.
DOI: 10.1007/BF01204052

11. Spandorfer, S.D., Davis, O.K., Barmat, L.I., et al.
"Relationship between maternal age and aneuploidy in in vitro fertilization pregnancy loss." Fertil Steril 81.5 (2004): 1265–9.
DOI: 10.1016/j.fertnstert.2003.09.057

12. Schmidt-Sarosi, C., Schwartz, L.B., Lublin, J., et al.
"Chromosomal analysis of early fetal losses in relation to transvaginal ultrasonographic detection of fetal heart motion after infertility." Fertil Steril 69.2 (1998): 274–7.
DOI: 10.1016/S0015-0282(97)00497-4

13. Веропотвелян, М.П.
Визначення первинної популяційної частоти хромосомної патології і ранньої ембріональної летальності в Україні / М.П. Веропотвелян, Л.О. Кодунов, П.М. Веропотвелян та ін. // Здоровье женщины. – 2012. – № 9. – С.108–114.
Veropotvelyan, M.P., Kodunov, L.O., Veropotvelyan, P.M., et al.
"Determining the primary population frequency of chromosomal aberrations and early embryonic mortality in Ukraine." Women's Health 9 (2012): 108–114.

14. Веропотвелян, Н.П., Кодунов Л.А., Погуляй Ю.С.
Генетические причины ранних репродуктивных потерь. Анализ свыше 1800 наблюдений / Н. П. Веропотвелян, Л.А. Кодунов, Ю.С. Погуляй // Репродуктивная медицина. – 2016. – № 2–3 (27–28). – С. 61–67.
Veropotvelyan, N.P., Kodunov, L.A., Poguliai, Y.S.
"Genetic causes of early reproductive losses. An analysis of more than 1,800 observations." Reproductive medicine 2–3.27–28 (2016): 61–7.

15. Chromosome abnormalities and genetic counseling. Fourth edition.
Oxford monographs on medical genetics. Ed. by R.J. McKinlay Gardner (2011).

16. Harvey, H.J.
"Stern preimplantation genetic diagnosis: prenatal testing for embryos finally achilving its potential." J Clin Med 3.1 (2014): 280–309.

17. Wells, D., Delhaty, J.D.
"Comprehensive chromosomal analysis of human preimplantation embryos using whole genome amplification and single cell comparative genomic hybridization." Mol Hum Reprod 6.11 (2000): 1055–62.

18. Vollaire, L., et al.
"Chromosome analysis of blastomeres from human embryos by using comparative genomic hybridization." Hum Genet 106.2 (2000): 210–7.

19. Ачкасов, Е.Е., Мискарян, И.А.
Медицина в афоризмах и крылатых выражениях от истоков до наших дней. – М.: «Профиль 2С». – 2009. – 448 с.
Achkasov, E.E., Miskarian, I.A.
Medicine in aphorisms and popular expressions from the beginnings to the present day. Moscow. Profile 2C (2009): 448 p.

20. Stanczyk, F.Z.
"Pharmacocinetics and potency of Progestins used in Hormone Replacement Therapy and contraception." Review in Endocrine & Medical disorders 3 (2002): 211–24.

21. Giordano, G.
Value of immuhistochemistry in uterine pathology: common and rare diagnostic dilemamas." Pathol Res Pract 205.10 (2009): 663–76.

22. Радзинский, В.Е.
Угроза спонтанного аборта: старые контраверсии – новые возможности / В.Е. Радзинский, И.М. Ордиянц, О.С. Побединская, Э.А. Алиева // Репродуктивное здоровье. Восточная Европа. – 2014. – № 5 (35). – С. 164–173.
Radzinskyi, V.E., Ordiyants, I.M., Pobedinskaya, O.S., Alieva, E.A.
"The threat of spontaneous abortion: old kontraversions – new opportunities." Reproductive Health. Eastern Europe 5.35 (2014): 164–73.

23. American Society for Reproductive Medicine.
"Current clinical irrelevance of luteal phase deficiency: a committee opinion, Practice Committee of the American Society for Reproductive Medicine." Fertil Steril 103 (2015): 27–32.

24. Berghella, V.
Early pregnancy loss: Obstetric evidence based guidelines. 2nd edition. New York. CRC (2012): 142–9.

25. Van der Linden, M., Buckingham, K., Farquhar, C., et al.
"Luteal phase support for assisted reproduction cycles." Cochrane Database Syst Rev 10 (2011): CD009154.
DOI:10.1002/14651858.CD009154.pub2

26. Schindler, A.E., et al.
"European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens." Gynecol Endocrinol 31 (2015): 447–9.

27. Wahabi, H.A., Abed Althagay, N.F., Elawad, M.
"Progestogen for treating threatened miscarriage (Review)." Cochrane Database Syst Rev 12 (2011): CD005943.
DOI: 10.1002/14651858.CD005943.pub4

28. Coomarasamy, A., et al.
"A Randomized Trial of Progesterone in Women with Recurrent Miscarriages." N Engl J Med 373 (2015): 2141–8.
DOI: 10.1056/NEJMoa1504927

29. Kumar, A., Begum, N., Prasad, S., et al.
"Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial." Fertil Steril 102.5 (2014): 1357–63.
DOI:10.1016/j.fertnstert.2014.07.1251

30. Haas, D.M., Ramsey, P.S.
"Progestogens for preventing miscarriage." Cohrane Database Syst Rev 10 (2013): CD003511.

31. Carpentier, P.A., Stanford, J.B., Boyle, P.C.
"Progesterone in women with recurrent miscarriages." N Engl J Med 374 (2016): 894.
DOI: 10.1056/NEJMc1600491

32. Zaqout, M., Aslem, E., Abuqamar, M., et al.
"The Impact of Oral Intake of Dydrogesterone on Fetal Heart Development During Early Pregnancy." Pediatr Cardiol 36.7 (2015): 1483–8.
DOI: 10.1007/s00246-015-1190-9

33. McNamara, H.C., Wood, R., Chalmers, J., et al.
"STOPPIT Baby Follow-up Study: the effect of prophylactic progesterone in twin pregnancy on childhood outcome." One 10.4 (2015): e0122341.
DOI: 10.1371/journal.pone.0122341

34. Barbosa, M.W., Silva, L.R., Navarro, P.A., et al.
"Dydrogesterone vs progesterone for luteal-phase support: systematic review and meta-analysis of randomized controlled trials." Ultrasound Obstet Gynecol 48.2 (2016): 161–70.
DOI: 10.1002/uog.15814

35. Chakravarty, B.N., Shirazee, H.H., Dam, P., et al.
"Oral dydrogesterone versus intravaginal micronised progesterone as luteal phase support in assisted reproductive technology (ART) cycles: results of a randomised study." J Steroid Biochem Mol Biol 97 (2005): 416–420.

36. Saharkhiz, N., Zamaniyan, M., Salehpour, S., et al.
"A comparative study of dydrogesterone and micronized progesterone for luteal phase support during in vitro fertilization (IVF) cycles." Gynecol Endocrinol 32 (2016): 213–7.

37. Salehpour, S., Tamimi, M., Saharkhiz, N.
"Comparison of oral dydrogesterone with suppository vaginal progesterone for luteal-phase support in in vitro fertilization (IVF): A randomized clinical trial." Iran J Reprod Med 11 (2013): 913–8.

38. Chakravarty, B.N., Dam, P., Goswami, S.K., et al.
"Oral dydrogesterone versus vaginal micronised progesterone as luteal phase support in ART cycles – evaluation based on correction of hormone profile and clinical outcome." Hum Reprod 20 (2005): i139.

39. Chakravarty, B.N., Sharma, S., Ghosh, S., et al.
"Oral dydrogesterone vs. vaginal micronized progesterone as luteal support in art cycles: evaluation based on hormone profile and clinical outcome." Hum Reprod 21 (2006): I83.

40. Patki, A., Pawar, V.C.
"Modulating fertility outcome in assisted reproductive technologies by the use of dydrogesterone." Gynecol Endocrinol 23 Suppl 1 (2007): 68–72.

41. Tomic, V., Tomic, J., Klaic, D.Z., et al.
"Oral dydrogesterone versus vaginal progesterone gel in the luteal phase support: randomized controlled trial." Eur J Obstet Gynecol Reprod Biol 186 (2015): 49–53.

42. Ganesh, A., Chakravorty, N., Mukherjee, R., et al.
"Comparison of oral dydrogestrone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study." Fertil Steril 95 (2011): 1961–5.

43. Веропотвелян, М.П.
Особливості співвідношення хромосомних аномалій та термінів персистенції плодового яйця серед вагітностей, що не розвиваються, у випадках анембріоній і за наявності ембріона (аналіз 1328 випадків) / М.П. Веропотвелян, Л.О. Кодунов // Здоровье женщины. – 2015. – № 5. – С. 74–80.
Veropotvelyan, M.P., Kodunov, L.O.
"Features of the ratio of chromosomal abnormalities and terms of persistence gestational sac of non-developing pregnancies in non-embrionyc and embrionyc cases (analysis of 1328 cases)." Women's Health 5 (2015): 74–80.

44. Makino, T., Iwasaki, K., Sugi, T., et al.
"Statistical analysis of possible causes of repeated spontaneous abortions." Nihon Sanka Fujinka Gakkai Zasshi 43.12 (1991): 1642–6. Article in Japanese.

45. Sheldon, T.
"Rising age of starting family in Netherlands reflects fall in younger not rise in older mothers." BMJ 19.337 (7662) (2008): 134.
DOI: 10.1136/bmj.a773

46. Веропотвелян, Н.П.
Ассоциация возраста матери с ранними репродуктивными потерями хромосомной этиологии / Н.П. Веропотвелян, Л.А. Кодунов // Здоровье женщины. – 2015. – № 2. – С. 44–48.
Veropotvelian, N.P., Kodunov, L.A.
"Association of maternal age with early reproductive losses of chromosomal etiology." Women's Health 2 (2015): 44–8.

47. Munne, S., Sandalinas, M., Magli, C., et al.
"Increased rate of aneuploidy embryos in young women with previous aneuploidy conception." Prenat Diagn 24 (2004): 638–43.

48. Маринкин, И.О.
Невынашивание беременности и хронический эндометрит: определяем приоритеты / И.О. Маринкин, С.В. Айдагулова, В.М. Кулешов // Репродуктивная медицина. – 2016. – № 2–3 (27–28). – С. 49–57.
Marinkin, I.O., Aidagulova, S.V., Kuleshov, V.M.
"Miscarriage and chronic endometritis: defining the priorities." Reproductive medicine 2–3.27–28 (2016): 49–57.

49. Aboallah, Y., et al.
"Gestational sac and embryonic growth are not useful as criteria to define miscarriage: a multicentre observational study." Ultrasound Obstet Gynecol 38 (2011): 503–9.

50. Pankaj Desai.
Recurrent spontaneous miscarriges. Second edition. Jaypee brothers medical publishers (2007).

51. Гутикова, Л.В.
Причины, приводящие к развитию невынашивания беременности / Л.В. Гутикова, Т.В. Янушко // Репродуктивное здоровье. Восточная Европа. – 2014. – № 5 (35). – С. 75–86.
Gutikova, L.V., Yanushko, T.V.
"The reasons that lead to the development of miscarriage." Reproductive Health. Eastern Europe 5.35 (2014): 75–86.

52. Lanari, C., et al.
"The MPA mouse breast cancer model: evidence for a role of progesterone receptors in breast cancer." Endocr Relat Cancer 16/2 (2009): 333–50.
DOI: 10.1677/ERC-08-0244

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К ВОПРОСУ ОБ ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ ПРОГЕСТАГЕНОВ ПРИ ПОВТОРНЫХ РАННИХ РЕПРОДУКТИВНЫХ ПОТЕРЯХ

Анализ данных литературы

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Привычное 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 привычного выкидыша 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, применению препаратов прогестерона в ее терапии посвящено значительное число публикаций и научных докладов.

В статье представлен собственный критический взгляд автора на исследования последних лет, посвященные применению прогестагенов с целью предотвращения ранних репродуктивных потерь. Проанализирована методология, дизайн экспериментов и результаты ряда исследований по определению эффективности терапии невынашивания беременности микронизированным прогестероном и дидрогестероном. Сделаны обобщенные выводы и определены критически значимые моменты данных исследований.

Среди прочего, пристальное внимание уделено результатам двойного слепого рандомизированного параллельного плацебо-контролируемого исследования Kumar (2014) и мультицентрового 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. Как подчеркивается в статье, назначение 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. Кроме того, в исследованиях Kumar и PROMISE остался неосвещенным вопрос корректной дозировки прогестагенов, применяемых при терапии невынашивания. Эта проблема требует дальнейшего изучения, поскольку эффективность терапии зависит не только от самого факта приема прогестагенов, но и от подбора оптимальной дозировки индивидуально для каждой пациентки.

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

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Recurrent 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 composes 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 progestagenes 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, progestagenes 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 progestagenes used in the therapy of reproductive losses is also not highlighted enough. This issue requires additional investigation, as 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.

The author expects that the accurate picture of progestagenes 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: progestagenes, micronized progesterone, dydrogesterone, miscarriage, early reproductive losses.

ДО ПИТАННЯ ЩОДО ЕФЕКТИВНОСТІ ЗАСТОСУВАННЯ ПРОГЕСТАГЕНІВ ПРИ ПОВТОРНИХ РАННІХ РЕПРОДУКТИВНИХ ВТРАТАХ

Аналіз даних літератури

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Звичне невиношування вагітності, яке визначається як самовільне переривання вагітності два і більше разів поспіль, становить 2% від числа всіх вагітностей, при цьому в структурі невиношування в цілому частота звичного викидня становить від 5 до 20%. Водночас у практичній медицині існують великі суперечності щодо домінування факторів і причин невиношування. Незважаючи на те, що недостатність лютеїнової фази не відноситься до доведених причин невиношування вагітності, застосуванню препаратів прогестерону в її терапії присвячено значну кількість публікацій і наукових доповідей.

У статті представлений власний критичний погляд автора на дослідження останніх років, присвячені застосуванню прогестагенів із метою запобігання раннім репродуктивним втратам. Проаналізовано методологію, дизайн експериментів і результати низки досліджень щодо визначення ефективності терапії невиношування вагітності мікронізованим прогестероном і дидрогестероном. Зроблені узагальнені висновки та визначені критично значущі моменти даних досліджень.

Серед іншого, пильну увагу приділено результатам подвійного сліпого рандомізованого паралельного плацебо-контрольованого дослідження Kumar (2014) і мультицентрового рандомізованого плацебо-контрольованого дослідження PROMISE (2015). Зокрема, на думку автора, порівняння ефективності застосування дидрогестерону і мікронізованого прогестерону за результатами цих двох досліджень є щонайменше некоректним. Як підкреслюється в статті, призначення прогестагенів потрібно починати після встановлення життєздатності ембріона, при цьому застосовувати їх на ранніх термінах вагітності слід тільки в разі клінічно доведеної недостатності лютеїнової фази, а також у пацієнток у циклах і програмах допоміжних репродуктивних технологій. Крім того, в дослідженнях Kumar і PROMISE залишилося невисвітленим питання коректного дозування прогестагенів, які застосовуються при терапії невиношування. Ця проблема вимагає подальшого вивчення, оскільки ефективність терапії залежить не тільки від самого факту прийому прогестагенів, а й від підбору оптимального дозування індивідуально для кожної пацієнтки.

Автор статті висловлює сподівання, що справжню картину в області застосування прогестагенів для лікування невиношування в ранні терміни вагітності відобразять результати рандомізованого подвійного сліпого плацебо-контрольованого дослідження PRISM, які очікуються в 2018 році.

Ключові слова: прогестагени, мікронізований прогестерон, дидрогестерон, невиношування вагітності, ранні репродуктивні втрати.