EVALUATION OF RATIONALITY OF PHARMACOTHERAPY IN CASE OF THREATENED MISCARRIAGE AND DEVELOPMENT OF A MODEL OF PHARMACEUTICAL CARE AS AN INFORMATION-AND-EXPLANATORY SUPPORT

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Abstract: The comprehensive study was conducted to evaluate the rationality of pharmacotherapy of pregnant women with the threat of miscarriage in real clinical practice. In 27 patients 328 drug-related problems (DRPs) were identified, the largest part among which were the problems of drugs choice (39.9%), the problems of modern native Ukrainian clinical practice for the proper drugs prescription (29.0%), and dosing problems (18.0%). At the same time, only 15.9% of the 44 prescribed medicines, belonged to the category A (safe during pregnancy) according to the FDA classification. For 29.5% of medicines, no category was established (the risk for pregnancy is not defined). According to the obtained results of the study, we formed 11 key elements/messages of pharmaceutical care, directed on the physician to eliminate the identified typical system DRPs. The model of the pharmaceutical care for pregnant women with a threat of miscarriage was developed.

Keywords: pharmacotherapy assessment, pharmaceutical care, drug-related problems, threat of miscarriage in the first half of pregnancy.

Introduction

The problem of rational approaches to pharmacotherapy (PhT) of habitual miscarriage (HM) in general and the threat of miscarriage, especially in the first half of pregnancy, in particular, is becoming increasingly relevant both in the world and in Ukraine [7, 8, 12, 18, 19]. The maximum number of spontaneous abortions (81.1%) is observed in the 1st trimester of pregnancy. The results of the demographic indicators analysis for the last 15-20 years show that Ukraine is in the deep demographic crisis. Direct reproductive losses from HM annually result in 36-40 thousand of unborn desired children. At the same time, the frequency of premature termination of pregnancy varies between 10-25% [3, 6]. Habitual miscarriage is a universal, integrated response of the female body to any expressed disorder in the state of health of a pregnant woman, the fetus, the environment and many other factors [11]. Despite a significant number of studies devoted to prevention and PhT of HM, the incidence of premature delivery is 5-10% [9, 13, 16]. So, the striving to reduce morbidity and mortality associated with the problem of HM should motivate to the increased attention in the monitoring of women exactly in the early stages of pregnancy, because it is in the first trimester when a fetoplacental complex is formed, the fetal organs and tissues are laid, hence it

determines the further course of pregnancy [1].

Taking into account that prescription of any medicines during pregnancy can be potentially dangerous and as a rule requires a number of warnings, in case women are threatened with the miscarriage, they require a particularly careful monitoring and processing of clear recommendations (elements of pharmaceutical care (PhC)) for the safe, effective and rational use of medicines. The integrated approach to PhT and the need to simultaneously prescribe several medicines should be taken into account. Thus, in the practical activity of the physician, there is a need to find the most suitable evidence-based approach to overcoming the risks of HM in certain clinical situations. For this purpose, in our opinion, it is expedient and necessary, to develop an optimal model of PhC of pregnant women with a threat of miscarriage, and consequently a professional awareness of the prospect of obtaining positive results from PhT.

In Ukraine, the substantiation of rational PhT of pregnant women with the threat of miscarriage remains one of the most urgent problems of modern obstetric and gynecological care. The practical value of it is extremely important, so determined the relevance, purpose, and design of our study.

Materials and methods

The subjects of the study were 27 inpatient medical cards and medication prescription-and-administration records (MPARs) of the gynecological department of the multidisciplinary hospital in Lviv; the State Drug Formulary, 7th Edition [5]; the adapted methodology of PhT assessment for DRPs detection [10, 17]; instructions for medical use (IMU) of the analyzed medicines [4]; current clinical protocols (CPs), approved by the Ministry of Health of Ukraine as a standard of good practice of PhT prescription [2]; drug-drug interaction checker [14]. Retrospective analysis of the 27 MPARs of patients with a threat of miscarriage for up to 20 weeks of pregnancy, who were discharged in a satisfactory condition, in order to assess the rationality of the medication use in the intended PhT schemes was the design of our study. In 27 patients, whose records were included into the study, the following diseases were identified: the main – the threat of miscarriage/abortion (gestation term varied from 4 to 20 weeks), retrochorionic hematoma, early gestosis, as well as the concomitant diseases – pyelonephritis, iron deficiency anemia, intraperitoneal bleeding. It should be noted that the threat of termination of pregnancy had been diagnosed in all of the 27 patients, and three of them had a burdened gynecological history. Descriptive statistics of the main parameters of the study are represented in Table 1. In the course of the research, the following methods were applied: system analysis, bibliographic, modern information retrieval, analytical, clinical-and-pharmaceutical, clinical-and-pharmacological, modeling. Conflict of interest: none.

Table 1. *Descriptive statistics of the main parameters of the study*

Characteristics	Value
Number of pregnant women, N	27
Average age, years ±SD*	27.3±4.5
Age range, years min-max	19-38
Average number of took medicines ±SD	6.5±1.9
Average number of detected DRPs ±SD	12.4±4.1
Average length of hospital stay, days ±SD	11.7±5.6

*SD – standard deviation

Results

In general, 27 pregnant women were prescribed 44 different medicines, repeating in combinations for 169 times. Standardization of medicines according to the ATC-classification showed that medicines, prescribed in 27 MPARs, belonged to 8 PhT groups. The largest share (34.1%) belonged to "Medicines that affect the alimentary tract and metabolism", in particular, Vitamin E, Drotaverine, Papaverine and others; 20.4% belonged to "Medicines that affect the blood and blood-forming organs". Among them: Magnesium sulfate (injectable solution), Folic acid, Etamsylate etc. Also, 18.2% were "Medicines that affect the genitourinary system and sex hormones", for example, Dydrogesterone, "Divigel" (Estradiol) etc. (Fig.1).

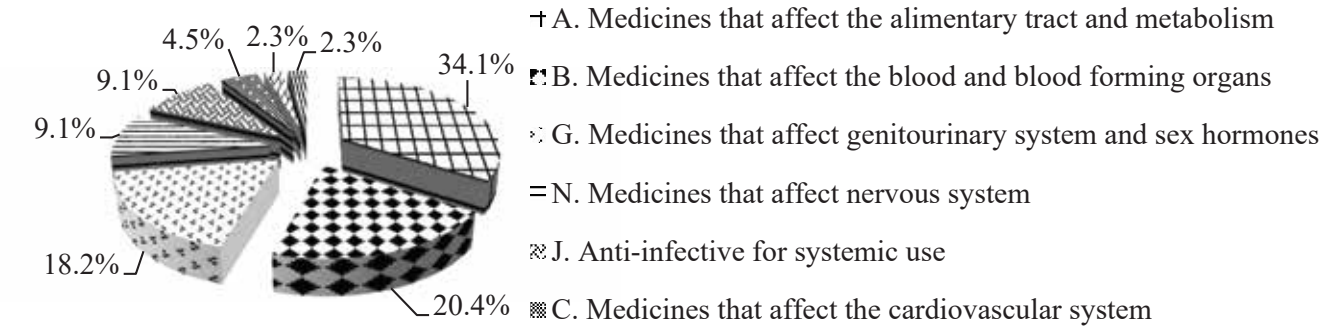

Fig. 1. *Distribution of medicines (n=44) according to the ATC-classification*

At the same time, a significant share (45.5%) belonged to medicines (Etamsylate, Metamizole sodium, Belladonna extract, Nitroxoline, "Orcipol" (*Ciprofloxacin/Ornidazole*),"Novo-Passit"(*Guaifenesin/Sambusi flos/Crataegi folium cum flore/Hyperici herba/Melissae herba/ Passiflorae herba/Lupuli flos/Valerianae radix*), etc.)) of non-established purpose of prescription, since they were not included into any of the current CPs for either the main or the concomitant pathology (and the latter serve as a standard for the proper prescribing of medicines in a specific clinical case).

Further, we determined the safety of PhT according to the FDA classification, which is used most often and provides the distribution of medicines into 5 categories of risk and/or safety precisely during pregnancy. The results of our study showed that only 15.9% of medicines were classified as category A (safe, it can be used without restrictions during any gestation period); the largest share (31.8%) – as category B (relatively safe, the risk to the fetus is not established); 15.9% – as category C (potentially dangerous, controlled clinical trials of which are not completed or conducted); 4.6% – as category D (dangerous medicines, with a proven risk for the fetus), and 2.3% namely 1 medicine: "Divigel"i.e. Estradiol – as category X (contraindicated during pregnancy, because of the proven teratogenic effect). At the same time, a fairly significant share of medicines (29.5%) – was not included into the FDA classification, its risk during pregnancy had not been established, and since safety studies of these medications use are still insufficiently conducted (Fig.2).

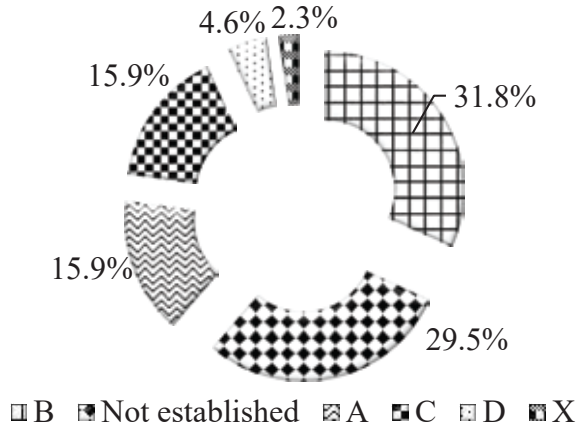

Fig. 2. *Distribution of drugs (n=44), prescribed to 27 patients in the context of FDA categories*

The next stage of PhT according to MPARs included the use of the adapted PCNE European classification system for the detection of DRPs according to V 5.01 [10]. It was found that for 27 patients 328 DRPs were identified, among which the largest share belonged to the problem of drug choice (code P.2) – 39.9%; the problems of modern native Ukrainian clinical practice for the proper drugs prescription (P.8) – 29.0%; dosing problems (P.3) – 18.0% (Fig. 3).

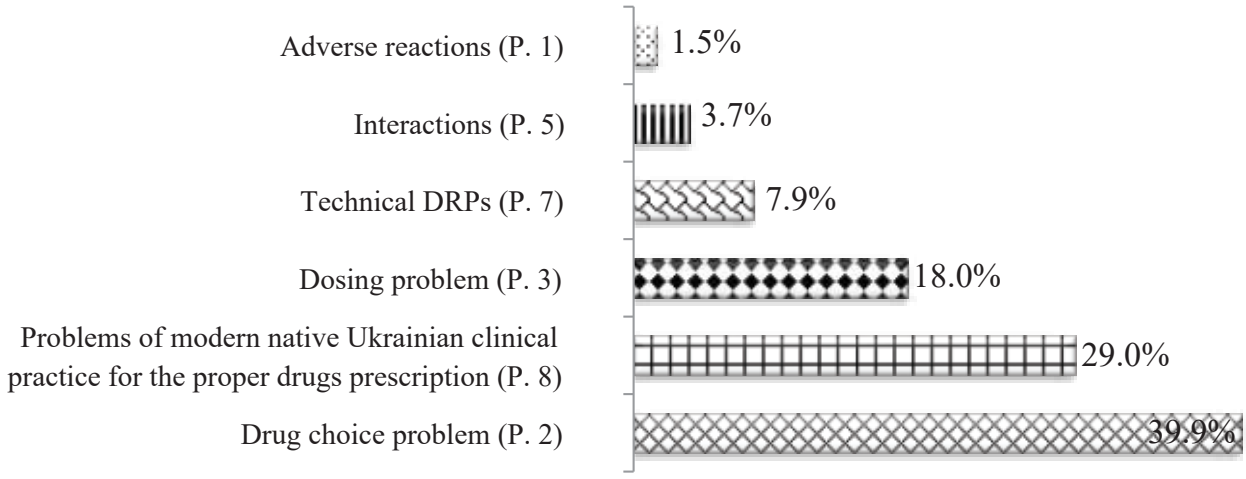

Fig. 3. *The share of the detected DRPs (n=328), in 27 analyzed MPARs*

Detailed analysis with the standardization of DRPs, using secondary categorization, as well as results of detection of DRPs according to the adapted PCNE classification system version 5.01 in the analyzed cohort of patients are represented in Table 2.

Table 2. *The detailed distribution of the identified DRPs (n=328), standardized using secondary categorization*

No.	Primary category	DRPs code	Detailed problem	n=328	100%
1	Drug choice problem	**P.2**	**Total**	**131**	**39.9**
		P2.1	Inappropriate drug (not most appropriate for indication)	22	6.7
		P2.3	Inappropriate duplication of the PhT group or active ingredient	6	1.8
		P2.4	Contraindication for drug use	23	7.0
		P2.5	No clear indication fordrug use	19	5.8
		P2.6	No drug prescribed but clear indication	61	18.6
2	Problems of modern native Ukrainian clinical practice for the proper drugs prescription	**P.8**	**Total**	**95**	**29.0**
		P8.1	Absence of current CP on certain nosology	2	0.6
		P8.2	Absence of drugs in available CPs in a particular clinical case	54	16.5
		P8.3	Absence of drugs in the State Drug Formulary	39	11.9
3	Dosing problem	**P.3**	**Total**	**59**	**18.0**
		P3.1	Drug dose too low or dosage regime not frequent enough	23	7.0
		P3.2	Drug dose too high or dosage regime too frequent	18	5.5
		P3.4	Duration of PhT too long	18	5.5
4	Technical DRPs	**P.7**	**Total**	**26**	**7.9**
		P7.1	Detected technical DRPs	26	7.9
5	Interactions	**P.5**	**Total**	**12**	**3.7**
		P5.1	Potential drug-drug interactions (DDIs)	12	3.7
6	Adverse drug reactions (ADRs)	**P.1**	**Total**	**5**	**1.5**
		P1.3	Toxic effects	5	1.5

The following stage of research focuses on the detailed analysis of the detected DRPs. First of all, the largest share of DRPs (n=131) P.2 belonged to the problem of drugs choice: **1. P2.6 code** of "No drug prescribed but clear indication" takes more than ½ (61 DRPs) of all problems for this paragraph. Thus, 6 medicines (i.e. Folic acid, oral Magnesium, Vitamin E, Tranexamic acid, Progesterone, Iron Supplements), recommended according to the CPs and approved by the relevant acting orders of the Ministry of Health of Ukraine, were not intended in the MPARs, despite the required indications for use (Fig. 4).

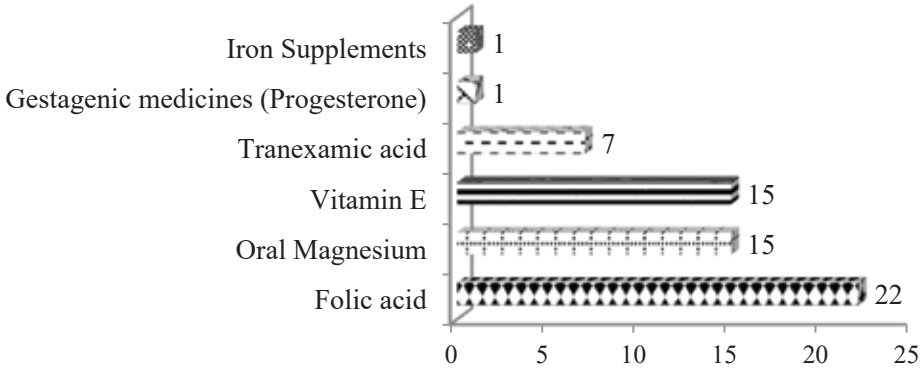

Fig. 4. *Frequency (in abs. numbers) of medicines non-prescribing, despite the required indications in 27 MPARs*

In particular, the medicines recommended according to the current CPs in case of a threat of pregnancy termination: 1) Oral Magnesium – 1 tablet 4-6 times daily (200-300 mg of magnesium per day); 2) Vitamin E oral capsules, tablets or oily solution 200 mg per day may be administered as a single dosage form or as a component of a multivitamin complex (e.g. "Pregnavit", "Prenatal", "Undevit" etc.); 3) Prescription of Folic acid 0.4 mg per day up to 12 weeks positively affects the formation of the fetal neural tube under the condition of the threat of abortion. For women with a history of such a deficiency in fetal development (e.g. neural tube defect) Folic acid is prescribed at a dose of 4 mg per day. 4) Gestagenic medicines: Progesterone 10-25 mg per day; "Utrogestan" (micronized Progesterone) 100 mg oral or intravaginal 2 times per day (up to 27 weeks). At the same time, in 1 of the analyzed MPARs, the patient with concomitant anemia was not prescribed an Iron supplement. Therefore, it would be obligatory to use one of the Iron supplements from FDA categories A or B (safe and relatively safe) as follows: Iron(III)-hydroxide polymaltose complex (level of evidence A); Iron(II) gluconate (B); Iron(II) fumarate (B); saccharated iron oxide (B).

2. P2.4 code of "Contraindication for drug use" included 9 medicines (e.g. Etamsylate, Metamizole sodium, Ciprofloxacin/Ornidazole, etc.).The frequency of this DRP in 27 MPARs amounted to 23 cases in total.

3. P2.1 code of "Inappropriate drug" included 6 medicines (22 cases of not the most appropriate indications). As far as Etamsylate is concerned, according to its IMU, there was no reliable information about the effect on the fetus during pregnancy. So, the medicine is contraindicated in the 1st trimester. However, it would be more expedient to prescribe Tranexamic acid instead of Etamsylate. According to numerous available research data, its use for hemostatic PhT in the 1stand 2nd trimesters of pregnancy with the risk of miscarriage allows to rapidly prevent the threat of abortion and contributes to its successful course.

4. P2.5 code of "No clear indication for drug use" included 13 medicines (in particular, Belladonna extract, Bendazol, Nitroxoline, etc.) where we did not identify the purpose of prescription in the context of the main and concomitant diagnoses in the analyzed MPARs (19 cases). It should be noted that the current CPs, approved by the orders of the Ministry of Health of Ukraine served as a standard of good prescribing practice.

5. One of the most important groups of DRPs was **P2.3** "Inappropriate duplication of the PhT group or active ingredient" since such prescriptions increase the risk of an overdose, hence, the development of toxic reactions and complications of PhT. According to the results of the analysis, we detected 6 cases of medicine duplication in 27 MPARs. In particular, Progesterone medicines (Progesterone + "Utrogestan", Progesterone + Dydrogesterone, Progesterone + "Luteina") were prescribed simultaneously using different routes of administration (intramuscular and oral). This contradicts the current CP.

The second largest group of DRPs (n=95) was **P.8** "Problems of modern native Ukrainian clinical practice for the proper drugs prescription": 1) P8.2 "Absence of drugs in available CPs in a particular clinical case" accounted for more than ½ of DRPs of this group (according to the analyzed MPARs 54 drugs were not found in the current CPs); 2) P8.3 "Absence of drugs in the State Drug Formulary" (14 drugs (39 cases) are absent in edition 7 of the Formulary)); 3) P8.1 "Absence of current CP on certain nosology" (no CP "Subchorionic hematoma" in 2 MPARs).

In our opinion, the particular attention should be devoted to **P.3** "Dosing problems", which included 59 DRPs: 1) P3.1 "Drug dose too low or dosage regime not frequent enough"– 4 drugs (Dydrogesterone, Folic acid, Magnesium sulfate, Tranexamic acid) in 23 cases of 27 MPARs. In particular, Dydrogesterone in 8 analyzed MPARs was prescribed as 1 tablet (10 mg) 2 times per day. However, according to the IMU in case of the threat of miscarriage, it should be used due to the regimen as follows:

40 mg single dose following 10 mg 2-3 times per day. 2) P3.2 "Drug dose too high or dosage regime too frequent" included 3 medicines (Progesterone, Folic acid, and Vitamin E), with excessive dose in 18 cases of 27 MPARs. In particular, Progesterone in 9 analyzed MPARs was prescribed as 2.5% intramuscular solution 1 ml 1 time per day, although according to the IMU for prevention and/or elimination of the threat of miscarriage, it is administered intramuscularly or subcutaneously 0.5-2.5 ml of 1% solution daily until the symptoms vanish completely. Regarding vitamin E, in 6 cases dosage was exceeded to 200 mg twice daily, and according to the IMU, in case of abortion threat, it is administered 1-2 times per day 100 mg during 14 days. 3) P3.4 "Duration of PhT too long" included 7 medicines (Progesterone, Metamizole sodium, Magnesium sulfate, Metoclopramide, Etamsylate, Tranexamicacid and Vitamin E), in a total of 18 cases in 27 MPARs. Precisely, in 1 MPAR Metamizole sodium was administered intramuscularly during 18 days instead of 3 days indicated in IMU. Moreover, it was given with Drotaverine in the same syringe. Magnesium sulfate in 1 case was used for 14 days instead of 5-7. It should be noted that prolonged PhT with Magnesium sulfate may promote fetal skeletal demineralization and the risk of neonatal skeletal abnormalities. Therefore according to the IMU continuous treatment with this medicine cannot exceed 5-7 days.

It should also be emphasized that 1 MPAR included both problems of the exceeded duration of administration and concentration of medicines (Progesterone for 20 days). In another MPAR we detected the following problems: the exceeded duration of administration and duplication of medicines (Progesterone + "Utrogestan" for 13 days). These cases can lead to dangerous consequences since excessive amounts of progesterone cause virilization of the female fetus.

P.7 "Technical DRPs" is represented by 26 positions to which, we included the following: 1) frequency of drug administration not indicated; 2) no route of administration indicated (vaginal or sublingual); 3) the dose/concentration of medicines indicated incorrectly; 4) the route of administration not specified; 5) dosing of medicines not indicated; 6) the concentration of medicines (Procaine) not indicated.

The next stage of our study comprised the processing of domain P.5 "Interactions", precisely P5.1 – "Potential DDIs". According to the conducted analysis, 6 DDIs were detected 12 times in 27 MPARs (Table 3).

Table 3. *Characteristics of DDIs (n=12) detected in 27 MPARs*

DDIs	Interaction result	n=12
Drotaverine + Metamizole sodium	Metamizole sodium solution is incompatible (in one syringe) with any other medicines	4
Papaverine hydrochloride + Metamizole sodium	Metamizole sodium solution is incompatible (in one syringe) with any other medicines	3
Glucose + Magnesium sulfate	Glucose reduces the level of Magnesium sulfate due to increased renal clearance. Insignificant interaction	2
Multivitamin complex + Vitamin E	It is not recommended to prescribe vitamin E with other vitamins since it is possible to overdose fat-soluble vitamins due to the deposition of the latter in the body	1
Novo-Passit + Pitofenone with analgesics + Drotaverine	Valerian, as a compound of Novo-Passit, enhances the effect of spasmolytic agents	1

Novo-Passit + Amoxicillin with an enzyme inhibitor	The use of hypericum grass (compound of Novo-Passit) is not recommended for patients taking antibiotics, because of the increased risk of ADRs	1

The P.1 domain "ADRs" included P1.3 – "Toxic effects" potential for 2 medicines: "Tergynan" (*Ternidazole/Neomycin/Nistatin/Prednisolone*) vaginal tablets and Magnesium sulfate. In particular, "Tergynan", which contains Prednisolone, is not recommended for use during pregnancy as the local immunity decreases under its effect. A long-term injection of Magnesium sulfate promotes fetal skeletal demineralization and development of congenital skeletal abnormalities. It is not recommended to exceed 5-7 days of continuous treatment, because the longer duration of PhT can lead to hypocalcemia of the fetus, which causes neonatal skeletal anomalies due to osteoporosis [4, 14, 15].

Discussion

Based on the results of the research, we formed 11 key messages of PhC directed on the physician. The aim of messages is to eliminate the identified typical system DRPs (Table 4).

Table 4. *Key messages of PhC, directed on the physician aiming to eliminate typical errors*

No	Medicines that caused the detected DRPs	Key messages of PhC, directed on the physician aiming to eliminate typical errors, identified in MPARs
1.	Magnesium sulfate	During pregnancy Magnesium sulfate injections should be used with extreme caution, taking into account its blood concentration, and only if the expected therapeutic effect exceeds the potential risk to the fetus
2.	Magnesium sulfate > 5-7 days	Avoid prolonged PhT with injectable Magnesium sulfate, since the latter promotes fetal skeletal demineralization and development of congenital skeletal abnormalities
3.	Oral Magnesium	Administrate oral Magnesium 1 tablet 4-6 times per day (200-300 mg of magnesium per day)
4.	Folic acid	The recommended prescription of Folic acid at a dose of 0.4 mg per day for 12 weeks positively affects the formation of the neural tube of the fetus under the condition of the threat of termination of pregnancy. Women with a history of folate deficiency in fetal development (neural tube defect), require 4 mg/day of Folic acid
5.	Vitamin E	Prescribe oral vitamin E 200 mg per day; may be taken as mono-drug or as a multivitamin complex compound (not both!)
6.	Etamsylate	Tranexamic acid is preferred to Etamsylate. Its use asa hemostatic agent in the 1st and 2ndtrimesters of pregnancy with the risk of miscarriage allows to quickly prevent the threat of abortion
7.	Progesterone +"Utrogestan", Progesterone +Dydrogesterone, Progesterone +"Luteina"	Progesterone should not be administered simultaneously in different dosage forms, in particular, intramuscular and oral according to the current CP
8.	Dydrogesterone	In case of threat of miscarriage should be used according to the following regimen: 40 mg single dose, then 10 mg 2-3 times per day

9.	Progesterone	Possible risk of developing hypospadias (congenital fetus abnormality characterized by the absence of posterior wall of the urethra in its distal sections) in case of Progestagens use during pregnancy for prevention of habitual miscarriage or threat of miscarriage with the background of luteal deficiency, about which the patient should be informed
10.	Gestagenic medicines	Routine prescription of Gestagens for the threat of pregnancy termination does not increase gestation rates, hence is not justified (level of evidence A)
11.	Spasmolytic agents	The use of spasmolytics has no evidence in prevention of the termination of pregnancy

Since the question of the medicines prescribing during pregnancy remains controversial among specialists, we introduce evidence-based information on indications for the use of Progesterone (level of evidence A): 1) the history of 2 or more spontaneous miscarriages in the 1st trimester (habitual abortion); 2) luteal phase insufficiency detected before pregnancy; 3) cured infertility; 4) pregnancy as a result of assisted reproductive technologies. The use of Progesterone for any other indication has no proven effectiveness.

At the final stage of the study, we processed a model of PhC of pregnant women with a threat of miscarriage, as an information-and-explanatory support directed on medical specialists and pregnant women. It consists of 4 prior and interrelated components (Fig. 6).

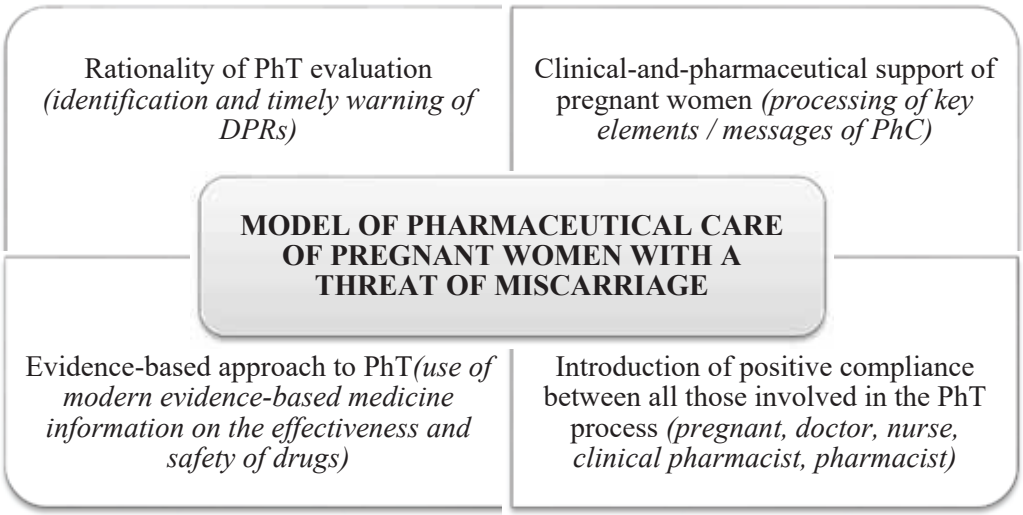

Fig. 6. *Model of the PhC of pregnant women with a threat of miscarriage (original development)*

Thus, PhC model of pregnant women with the threat of miscarriage developed by us includes: 1) evaluation of the rationality of PhT prescriptions, i.e. identification and timely prevention of DRPs; 2) clinical-and-pharmaceutical support of pregnant women, which provides the key messages of PhC directed on the physician, nursing staff, and pregnant women aiming to eliminate typical system DRPs identified during evaluation of PhT schemes; 3) evidence-based approach to PhT is based on the use of modern evidence-based medicine information on the efficacy and safety of drugs; 4) introduction of positive compliance among

all those involved in the process of PhT to ensure the most effective outcome of treatment, preference should be given to ensuring a favorable psycho-emotional climate and social support for a pregnant woman with a threat of miscarriage.

Limitations

The study had several limitations. The major wasthe relatively modest size of the sample. Another drawback is that research was conducted only in one hospital and in one town. Therefore the findings cannot be statistically generalized. Therefore, it is necessary to conduct more research in this area.

Conclusions

1. According to the results of the study, the priority directions for achieving the rationality and safety of PhT for pregnant women with the threat of miscarriage are the following: avoidance of prescription of contraindicated drugs during pregnancy; taking into account the FDA drug safety categories; prescribing of justified medicines (only necessary and appropriate in a specific clinical case, taking into account the gestational age); strict adherence to dosage, frequency and duration of medicines use; careful monitoring of health condition of the pregnant and fetus during and after PhT.

2. The 11 key messages of pharmaceutical care directed on the physician, nursing staff, and pregnant women were formed as the result of the research outcomes. We believe those to be the support in a proper professional decision-making and prevention of typical system DRPs.

3. The model of pharmaceutical care of pregnant women with the threat of miscarriage which consists of 4 prior interrelated components was introduced as an information and explanatory support.

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