



RISK FACTORS OF NON-DEVELOPING PREGNANCY IN THE EARLY STAGES

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ABSTRACT

The article presents results of the study of 52 women with different types of non-developing pregnancy in the early stages (up to 12 weeks). It is well known, that the pregnant woman's age highly affects her reproductive potential. Specific aspects of risk factors of non-developing pregnancy, including age, data of obstetric and gynaecological anamnesis and their impact on the risk of different types of non-developing pregnancy were determined with the aim of substantiating preventive methods.

Thus, it was established, that the most common condition at non-developing pregnancy both in primigravidas and multigravidas is I type anembryonic gestation reaching 46%. Total rate of the death of an embryo is observed in 37% of all cases, wherein in tertigravidas it reaches 50%.

The risk of I type anembryonic gestation increases in primigravidas with age, whereas multigravidas tend to II type anembryonic gestation. Aggravated obstetric-gynaecologic anamnesis is observed in multigravidas more often – in 68% of cases, than in primigravidas. The risk of death of an embryo caused by previous gynaecological disorders is 2 times higher in primigravidas, than in secundigravidas. Previous gynaecological disorders are risk factors of non-developing pregnancy of II type anembryonic gestation only in multigravidas. A high rate of reproduction-significant infections (61%) was revealed: 52% in primigravidas and up to 73% in multigravidas. This indicates the high impact of sexual transmitted infections on the risk of both anembryonic gestation of non-developing pregnancy and death of an embryo. According to the anamnestic data, mixed infections, that highly affect the high frequency of I type anembryonic gestation, were observed in 58% of primigravidas.

Thus, present study confirmed that the causes of non-developing pregnancy include blood progesterone deficiency, luteal-phase defect and incomplete decidual endometrial transformation.

KEYWORDS: recurrent miscarriage, non-developing pregnancy, risk factors, reproductive significant infections, anembryonic gestation, death of the embryo.

INTRODUCTION

Recurrent miscarriage in early stages is one of the most important problems of modern obstetrics. Numerous causes of miscarriage indicate the need in early diagnostic differentiation between risk factors. The risk factor of recurrent miscarriage is especially high in young women, the rate of which reaches 37.1% at the age of up to 18 years [Nazarenko Y, 2006].

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According to the statistical data, the woman's age is one of the significant factors associated with miscarriage. While in the age group of 20-29 years the risk of spontaneous abortion is 10%, in the age group of 45 and older it is as high as 50%. According to the modern literature, the rate of fetal chromosome disorders increases with age [Allison J, Schust D, 2009; Marquard K et al., 2010; Grande M et al., 2012]. Moreover, the prevalence of somatic and gynaecological disorders among fertile women is one of the risk factors of recurrent miscarriage. Previous extragenital diseases were discovered in 53.1% of women

with miscarriage: vascular diseases, renal and gastrointestinal diseases, metabolic disorders [Salov I et al., 2009; Boots C et al., 2014].

Biomedical factors of miscarriage are as follows: genetic, endocrine, immunological (auto-immune and alloimmune), infectious, thrombophilic, anatomic alterations of the uterus: congenital disorders, sex infantilism, uterine hypoplasia, cervical incompetence or uterine synechiae [Linde V et al., 2009; Sidelnikova V, Sukhikh G, 2010; Voropayeva E, 2011].

Non-developing pregnancy is one of the most significant forms of miscarriage. According to different publishing scholars, the rate of non-developing pregnancy in early pregnancy among spontaneous abortions has increased from 10.1-20.0% to 45.0-88.6%; the mean rate is 18.9% [Nesyayeva E, 2005; Radzinskiy V, Orazmuradova A, 2009; Yashchuk A et al., 2013]. According to several authors, the rate of non-developing pregnancy is becoming higher in the age group of 20-30 years; its rate reaches 78% [Radzinskiy V et al., 2015]. Identification and analysis of factors, including age-related and anamnestic ones, that affect the risk of miscarriage, would allow determining the most significant factors. That could become the basis for the development of new means of miscarriage prediction and prevention on the individual basis. It is also important to analyse anamnesis morbi of those women, who have suffered from non-developing pregnancy to ensure more effective recovery of a malfunctioning immune system required to improve antibacterial therapy in the early rehabilitation period [Kagramanova J, 2014].

The aim of the study was to determine the impact of risk factors for different types of non-developing pregnancy in order to substantiate preventive measures.

MATERIAL AND METHODS

Totally 52 women were examined with the diagnosis of non-developing pregnancy in early pregnancy (up to 12 gestational weeks), who were admitted to the gynaecology unit of the University Clinical Hospital No 4.

All patients underwent a comprehensive clinical instrumental and laboratory examination. The diagnosis at hospitalization was established on the basis of small pelvis ultrasound using a 5 Hz transvaginal

probe judging from the mean inner diameter of the gestational sac, presence or absence of the embryo or the absence of fetal heartbeats. The final diagnosis was confirmed morphologically after aspiration of a pathologic gestational sac. Then, all patients received antibacterial and immunotherapy with interferon - alpha 2b suppository rectally.

According to ultrasonic criteria, there are three types of non-developing pregnancy: death of an embryo, anembryonic gestation of both types [Radzinskiy V et al., 2015].

Diagnosis of non-developing pregnancy with I type anembryonic gestation was established in the event of no ultrasonic visualization of the embryo and the mean diameter of the gestational sac over 20 mm [Celen S et al., 2012]. Diagnosis of II type anembryonic gestation was established in the event of a large gestational sac (up to 45-50 mm) and no contour of the embryo or its remains [Savelyeva G et al., 2015]. Death of an embryo was diagnosed in the event of visualization of the gestational sac and the yolk sac at no echo signs of fetal heartbeats.

Statistical analysis was conducted using a special electronic database (of the tracked parameters) with the help of Excel MS Office. The filtration and sorting was performed, the incidence rate was analysed, and etc. Electronic data registration was specially designed to study different potential factors affecting termination of pregnancy.

RESULTS

The distribution of all 52 examined patients by types of non-developing pregnancy was as follows: 24 (46%) – I type anembryonic gestation, 9 (17%) – II type anembryonic gestation, 19 (37%) – death of an embryo. The distribution of patients by types of non-developing pregnancy is presented in figure 1.

While distributing all 52 women, it was revealed, that 23 (44%) of them were primigravidas. The distribution of primigravidas (n=23) by types of non-developing pregnancy was as follows: I type anembryonic gestation – 50%, II type anembryonic gestation – 14%, death of an embryo – 36%. The other 29 (56%) patients were multigravidas.

First diagnosed non-developing pregnancy out of 52 women was registered in 47 patients (90%), 5 (10%) patients had non-developing pregnancy be-

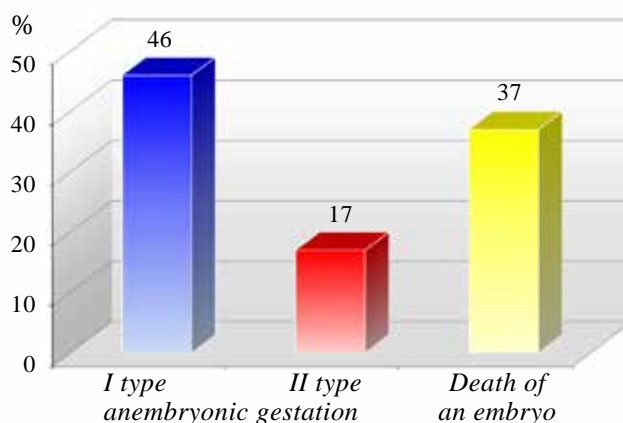


FIGURE 1. Distribution of patients by types of non-developing pregnancy (%)

fore; this was considered recurrent pregnancy loss.

From all admitted patients 15 (29%) were secundigravidas. Distribution by types of non-developing pregnancy: I type anembryonic gestation – 47%, II type anembryonic gestation – 20%, death of an embryo – 33%.

In present cohort 8 (14%) patients were tertigravidas. Distribution by types of non-developing pregnancy in these patients was as follows: in 38% – I type anembryonic gestation, in 12% – II type anembryonic gestation, in 50% – death of an embryo.

From all admitted patients 4 (9%) had the fourth pregnancy. Non-developing pregnancy: I type anembryonic gestation – 50%, II type anembryonic gestation – 25%, death of an embryo – 25%. Only 2 (4%) patients had the fifth pregnancy. Non-developing pregnancy: I type anembryonic gestation – 50%, death of an embryo – 50%. Patients with IV and V pregnancies in the statistical analysis weren't included in the study due to their low number. The distribution of patients by the amount of pregnancies and types of non-developing pregnancy is presented in figure 2.

The highest incidence rate of I type anembryonic gestation among all 52 (100%) women was observed in primigravidas, the lowest – in tertigravidas. The highest incidence rate of II type anembryonic gestation was observed in secundigravidas. However, it is low in comparison with other types of non-developing pregnancy, especially with I type anembryonic gestation. As the histogram shows, the highest death of an embryo rate (50%) was identified in tertigravidas.

The mean age of primigravidas with non-developing pregnancy was 28 ± 5.8 years, from all multi-

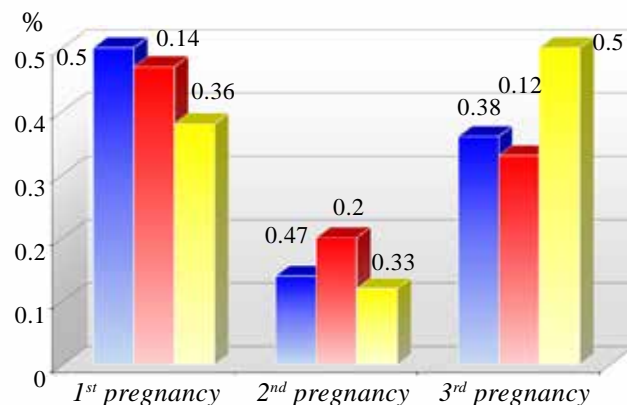


FIGURE 2. Distribution of women by the amount of pregnancies and types of non-developing pregnancy (%), $p < 0.05$
NOTES: I type (■) and II type (■) anembryonic gestation, death of an embryo (■)

gravidas – 31 ± 3.95 years. According to the preliminary analysis, the rate of different types of non-developing pregnancy varied in different groups with age. The small difference in the mean age of primigravidas and multigravidas testifies that the first pregnancy took place rather late. This is one of the factors of non-developing pregnancy.

Two groups of women were identified for further study in order to determine differences in the risk of different types of non-developing pregnancy in the most reproductive category of 38 women out of 52, who were planning for future pregnancy: primigravidas and secundigravidas. These women were chosen, because these two groups represent the highest reproductive categories of women. Therefore, the main results were presented for these two groups.

It was determined that the mean age of primigravidas with non-developing pregnancy of I type anembryonic gestation was 30 ± 6.0 years, with II type anembryonic gestation – 25 ± 0.6 years, with death of an embryo – 27 ± 6.3 years.

The mean age of multigravidas (II pregnancy) with non-developing pregnancy of I type anembryonic gestation (47%) was 29 ± 1.0 years, with II type anembryonic gestation (20%) – 34 ± 2.9 years, with death of an embryo (33%) – 30 ± 2.4 years. The distribution of pregnant women with non-developing pregnancy by age is shown in figure 3.

As figure 3 shows the risk of non-developing pregnancy of I type anembryonic gestation in primigravidas becomes significantly higher with age, whereas multigravidas feature higher risk of II type anembryonic gestation and death of an embryo (Fig. 3). Interestingly, there are no statisti-

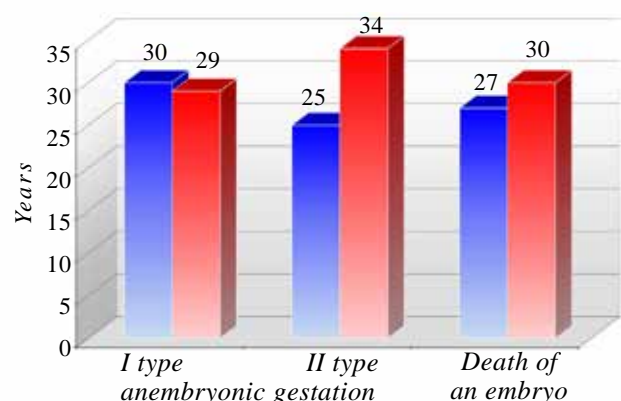


FIGURE 3. Distribution of primigravidas and multigravidas with non-developing pregnancy by mean age ($n=52$), $p<0.05$

NOTES: primigravidas (■), multigravidas (■)

cally significant differences in the age-related rates of I type anembryonic gestation and death of an embryo between these groups.

Hereafter, anamnestic data of the selected groups of patients were analyzed, according to which it was established, that 65% of primigravidas with non-developing pregnancy previously had somatic disorders. Among the other 35% chronic tonsillitis tended to be a prevalent disorder. During II pregnancy 56% of patients previously had urinary disorders (chronic cystitis, chronic pyelonephritis), as well as chronic tonsillitis, atopic dermatitis and anemia.

In order to analyze the data of obstetric and

gynaecological anamnesis and sexually transmitted infections, the obtained results were structured by the incidence rates among patients of I and II groups with identified impact of these factors on the risk of three types of non-developing pregnancy. Gynaecological disorders such as cervical ectropion (33%), menstrual disorder (25%), inflammatory genital disorders (17%), endometrial polyp removal (17%) and adnexal operations (8%) were previously detected in 52% of primigravidas. Analysis of the data of obstetric and gynaecological anamnesis revealed previous pathologies in 87% of multigravidas. Results of the comparative analysis of obstetric and gynaecological anamnesis in women with non-developing pregnancy from both groups are shown in table 1.

Gynaecological disorders were a risk factor of I type anembryonic gestation and death of an embryo in primigravidas ($n=23$) to the same extent (Table 1). There were no cases of II type anembryonic gestation among primigravidas. Gynaecological disorders are a factor of high risk of non-developing pregnancy in secundigravidas (Table 1). Whereby, I type anembryonic gestation is observed in 50% of cases, which is 2 times more often than the death of an embryo and II type anembryonic gestation. The role of gynaecological disorders in the development of different types of non-developing pregnancy in different groups of patients is presented in figure 4.

TABLE 1

Analysis of obstetric-gynaecologic pathologies in women with non-developing pregnancy by groups

Gynaecological disorders and operations in the medical history	Primigravidas $n=23$ (100%)			Multigravidas $n=15$ (100%)			Total $n=38$ (100%)
	Anembryonic gestation		Death of an embryo	Anembryonic gestation		Death of an embryo	
	I type	II type		I type	II type		
Chronic salpingo-oophoritis	8	0	8	8	0	0	12
Chronic endometritis	0	0	0	4	0	4	4
Cervical ectropion	9	0	25	22	13	13	40
Ovarian dysfunction	8	0	17	0	8	0	16
Endometrial polyp removal	17	0	0	4	0	0	12
Adnexal operation	8	0	0	8	0	0	8
Aggravated course of the previous pregnancy and childbirth	0	0	0	0	0	4	2
Post-caesarean uterine scar	0	0	0	4	4	4	6
Total	50%	0	50%	50%	25%	25%	100%

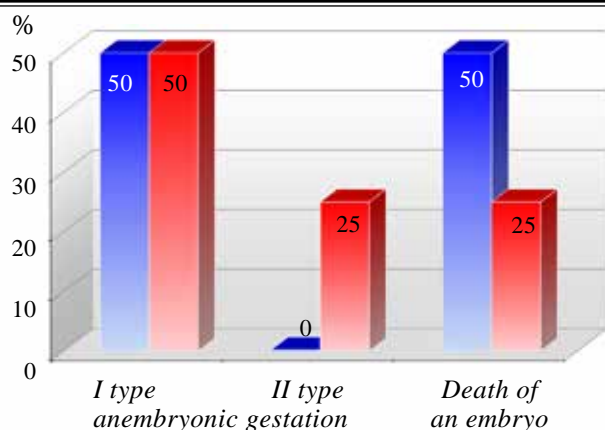


FIGURE 4. Role of gynaecological disorders in different types of non-developing pregnancy
NOTES: Primigravidas (■), multigravidas (■)

Previous gynaecological disorders affect the risk of non-developing pregnancy of I type anembryonic gestation in primigravidas and secundigravidas to a comparable extent (Fig. 4). The risk of the death of an embryo caused by previous gynaecological disorders is 2 times higher in primigravidas than in secundigravidas. Previous gynaecological disorders are a risk factor of non-developing pregnancy of II type anembryonic gestation only in multigravidas.

Reproduction-significant infections were analyzed in the identified groups of patients, and a high total rate of such infections (61%) was revealed: 52% in primigravidas and up to 73% in multigravidas. This is a risk factor of non-developing pregnancy.

The primary spectrum of reproduction-significant infections in primigravidas and multigravidas

with non-developing pregnancy is shown in table 2.

Reproduction-significant infections are a factor of high risk of non-developing pregnancy in both groups (Table 2). The pregnancy outcome secondary to the infection leads to I type anembryonic gestation in 48% of cases; this is 1.7 times more often than the death of an embryo and 2 times more often than II type anembryonic gestation. There were no differences between non-developing pregnancy of II type anembryonic gestation and the death of an embryo in primigravidas. Mixed infections were noted in the medical history of 58% primigravidas. They also highly affect the risk of I type anembryonic gestation.

Reproduction-significant infections contributed to death of an embryo in 47% of multigravidas. Comparative analysis of non-developing pregnancy types, secondary to reproduction-significant infections in women in groups is shown in figure 5.

Therefore, reproduction-significant infections are a risk factor of I type anembryonic gestation in the group of primigravidas and death of an embryo in multigravidas.

It is known, that the causes of non-developing pregnancy include blood progesterone deficiency, luteal-phase defect and incomplete decidual endometrial transformation. Prescription of hormonal drugs results in comprehensive pregnancy-associated endometrial alterations and prolonged pregnancy.

However, according to the published morphological study results, non-developing pregnancy may occur not only in the event of incomplete

TABLE 2

Primary spectrum of reproduction-significant infections in women with non-developing pregnancy by groups

Primary spectrum of reproduction-significant infections in past medical history	Primigravidas (%)			Multigravidas (%)		
	Anembryonic gestation		Death of an embryo	Anembryonic gestation		Death of an embryo
	I type	II type		I type	II type	
Mycoplasma hominis, Ureaplasma urealyticum	14	5	10	11	0	11
Gardnerella vaginalis	5	10	0	5	0	5
Herpes simplex virus of type 1 and 2	14	5	5	11	5	5
Human papilloma virus	5	5	5	0	5	5
Cytomegalovirus	0	0	5	0	0	0
C. albicans	10	0	5	0	5	16
Ch. trachomatis	0	0	0	5	5	5
Total (percentage by types of non-developing pregnancy)	48	24	28	32	21	47

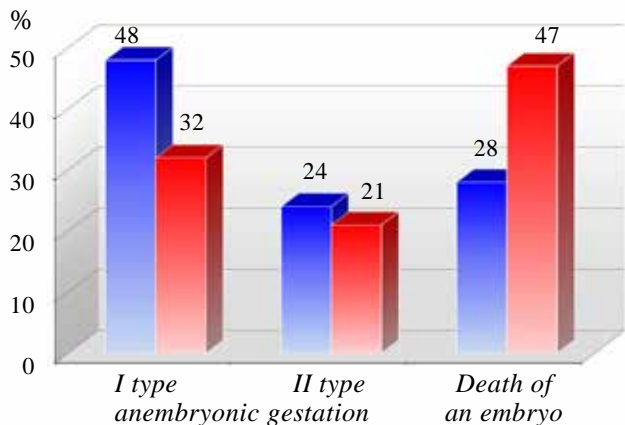


FIGURE 5. Role of infections in the development of different types of non-developing pregnancy in groups
NOTES: Primigravidas (■), multigravidas (■)

pregnancy-associated transformation of the endometrial stroma, but also in the event of complete endometrial transformation regardless of pregnancy-saving hormone therapy [Tral T, 2014]. Hormonal drugs do not play a key role in forming endometrial glandular system. Pregnancy-associated endometrium is a subject to involutinal-dystrophic alterations, necrobiotic processes and inflammatory reactions. That is why additional intake of hormonal drugs helps to prolong pregnancy. In each individual case, it means later diagnosis of non-developing pregnancy, longer gestational being of the sac in the uterine cavity, development of endometritis and coagulation alterations.

Objective signs of aggravated pregnancy such as presence/absence of bloody issue were assessed, which was the reason for 33 (63.4%) patients to visit a gynaecologist; 17 (33%) patients took recommended doses of progesterone to prolong the pregnancy.

The number of patients taking progesterone in both groups (primigravidas and multigravidas) was approximately twice as low as the number of patients not undergoing hormone therapy (Table 3). In both groups, non-developing pregnancy was twice as often observed in the patients not taking progesterone as in the patients undergoing hormone therapy.

TABLE 3

Distribution of primigravidas and multigravidas by gestagen intake

Group of pregnant women	Patients with		Total (n=38)
	hormone therapy	no hormone therapy	
Primigravidas	30%	70%	100%
Multigravidas	33%	67%	100%

Progesterone was prescribed to primigravidas due to aggravated gynaecological anamnesis. Upon appearance of blood issue, 70% of primigravidas without taking progesterone were hospitalized, where small pelvis ultrasound of such patients confirmed the diagnosis of non-developing pregnancy. The gestational sac remained inside for 3-4 weeks from the time of fetal death until the time of diagnosis.

According to the survey, hormonal drugs were prescribed to multigravidas with non-developing pregnancy on outpatient basis due to aggravated obstetric-gynaecologic anamnesis. Progesterone maintenance therapy without a control ultrasonic examination to confirm progressive pregnancy also resulted in late diagnosis of non-developing pregnancy and long gestational being of sac in the uterine cavity.

Thus, the rate of non-developing pregnancy was two times higher in patients not taking progesterone in both groups.

The comparative analysis of pregnancy outcomes in the presence/absence of hormone therapy is given in figure 6.

In both groups on the background of high rate of anembryonic gestation, primigravidas not undergoing hormone therapy are especially a subject to I type anembryonic gestation, whereas patients taking hormonal drugs more often feature death of an embryo. However, the cumulative risk of different types of non-developing pregnancy did not depend on hormone therapy. It is interesting to note, that if we consider the patients not taking hormonal drugs the control group to determine the impact of

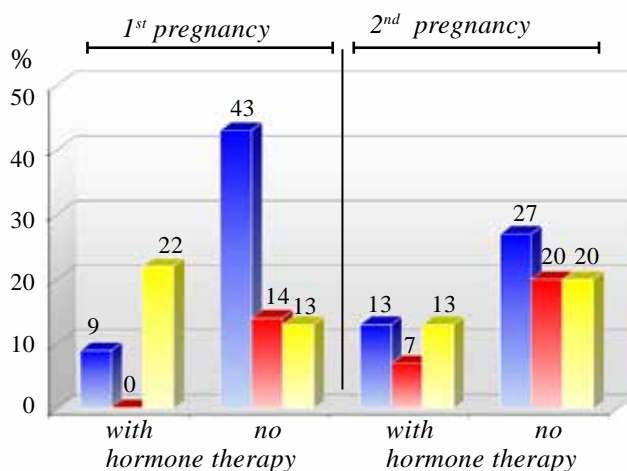


FIGURE 6. The comparative analysis of a result of pregnancy depending on hormonal therapy
NOTES: I (■) and II (■) type anembryonic gestation, death of an embryo (■)

progesterone on pregnancy prolongation, the calculation results show, that hormone intake decreases the risk of non-developing pregnancy approximately 2.1 times.

The cumulative risk of anembryonic gestation of both types in secundigravidas is higher than the risk of death of an embryo. If we consider the secundigravidas not taking hormonal drugs the control group, the risk of non-developing pregnancy decreases approximately 2 times. At the same time the rate of anembryonic gestation (anembryonic gestation of I and II types) and death of an embryo did not differ both in secundigravidas and among primigravidas.

DISCUSSION

According to the results of performed comprehensive examination of patients with different types of non-developing pregnancy, such risk factors as age, obstetric-gynaecologic anamnesis, reproduction-significant infections and endocrine disorders were determined. This substantiates the following preventive principles:

- Timely planning for pregnancy is a measure of preventing non-developing pregnancy.
- One of the measures of preventing high rates of non-developing pregnancy, endometritis and coagulation disorders is the timely ultrasonic examination of pregnant at term (7-8 weeks from the last menstrual period).
- Previous reproduction-significant infections highly affect the risk of non-developing pregnancy of all three types, trigger faulty anlage of the chorion and extraembryonic organs in the event of anembryonic gestation or death of an embryo, which proves the prevention of sexually transmitted infections.
- Obstetric-gynaecologic anamnesis is a risk factor of non-developing pregnancy of II type anembryonic gestation only in multigravidas, whereas in primigravidas previous gynaecological disorders increase the risk of death of an embryo.
- Present study confirmed that the causes of non-developing pregnancy include blood progesterone deficiency, luteal-phase defect and incomplete decidual endometrial transformation. It is reasonable to prescribe hormonal drugs for prolonging pregnancy only after small pelvis ultra-

sound and a follow-up examination in 7-10 days for the visualization of the embryo. This helps to avoid late diagnosis of non-developing pregnancy. Progesterone intake at anembryonic gestation of I and II types does not prolong pregnancy; such an intake prolongs only the duration of the gestational sac's being in the uterine cavity. The study results showed that intake of hormonal drugs is not a key to achievement of favourable pregnancy outcome.

CONCLUSION

Thus, according to the conducted study of women with different types non-developing pregnancy, it was established that I type anembryonic gestation is the most common condition among both primigravidas and multigravidas; the incidence rate reaches 46%. Total rate of death of an embryo is 37%, and in tertigravidas it reaches 50%.

The pregnant woman's age highly affects her reproductive potential. The risk of non-developing pregnancy of I type anembryonic gestation in primigravidas becomes significantly higher with age, whereas multigravidas feature higher risk of II type anembryonic gestation. Timely planning of pregnancy helps to prevent non-developing pregnancy.

Aggravated obstetric-gynaecologic anamnesis is observed in multigravidas more often (68%) than in primigravidas. The risk of death of an embryo caused by previous gynaecological disorders in primigravidas is 2 times higher than in secundigravidas. Previous gynaecological disorders are a risk factor of non-developing pregnancy of II type anembryonic gestation only in multigravidas.

The high rate (62%) of reproduction-significant infections was established: 72% of primigravidas featured anembryonic gestation, 28% – death of an embryo, whereas only 53% of multigravidas feature anembryonic gestation – almost as many as multigravidas with death of an embryo. Mixed infections were detected in 58% of primigravidas, which highly affect the risk of I type anembryonic gestation in primigravidas.

Hormone intake by multigravidas does not effectively prolong pregnancy, also on the background of high total rate of I type anembryonic gestation and in connection with concurrence of several risk factors.

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