Epidemiology of critical states during pregnancy after assisted reproductive technologies

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Abstract

Aim: The aim of this research was to have a thorough study of predictors of critical states during pregnancy after assisted reproductive technologies.

Materials and methods: A retrospective study of 303 patients with “near-miss,” out of which 37 are pregnancy cases after ART (the main group) and 265 are spontaneous pregnancy cases (the control group).

Results: Pregnancy after ART constituted 12.3% of all critical states. In the main group (10.8%), severe ovarian hyperstimulation prevailed over all possible reasons for critical states within the period of up to 22 weeks of gestation, whereas bleeding predominated in the control group (57.1%). When pregnancy terms exceeded 22 weeks, the leading reason for “near-miss” in the main group was preeclampsia (59.5%) with underlying thrombophilia (29.7%) and gestation pancreatic diabetes (32.4%); bleeding was the main factor in the control group (36.6%).

Conclusion: Women after assisted reproductive technologies constitute a high-risk group for critical obstetric states not only in the nearest time period but also long after ART.

Introduction

In 2009, Reproductive Health Department of WHO proposed to introduce a systematic analysis of “near-miss” cases induced by severe obstetric complications and to use the information obtained to control the quality of medical services responsible for maternity protection [1]. This approach to the study of maternal death rates has been applied for over 20 years by now [2–4], and it has provided more information on the subject than the analysis of maternal losses. In Russia, the analysis of similar data has been popular since 2010; however, until now the research and the papers on this topic have been sporadic. The authors used terms such as “near-miss” [3] and “nearly deceased” [5] to characterize severe obstetric complications. The interest for audit in aborted maternal deaths for the past two decades has been instigated by great advancement in decreasing maternal death rates. To go further, we need another sphere for analysis, and such data can be pooled from systematic data processing of all “near-miss” cases [4].

Modern tendencies of reducing maternal death rates call forth the necessity to analyze the terminal states connected with pregnancy. Maternal death rate is not only a reliable criterion for the effectiveness of scientific achievements, but also an indicator of reproductive health, which demonstrates the multi-factor character of the overall situation. Among these factors are economics, ecology, social-hygienic and medical-organizational factors [6–8]. The analysis of maternal losses can undoubtedly help in establishing their causes, as well as faults in medical services themselves; it can also help to identify the factors that could have been changed while organizing perinatal assistance. At the present stage, however, maternal death rate is not the only indicator to provide information of this scope. The prevalence of severe obstetric complications is many times greater than maternal losses themselves [9], which proves the advantageousness of a systematic study of “near-miss” cases. This can be done by processing a larger material for a fuller statistical analysis [6].

Presently, the study of critical states and their causes reveals that a significant number of fatal outcomes are connected with the faults of obstetric services and their organization. In the first place, the quality of obstetric–gynecologic services in rural areas is very low [6]. Many papers have been published both at home and abroad on the issue of maternal deaths caused by numerous factors [9]. The defects of diagnostics and treatment that affected the lives of patients (“nearly deceased” cases) are equally well researched. The authors shed light on a whole range of defects, from poor diagnostics to “obstetrician’s aggression” [9–11].

Presently, the study of death cases and the cases of patients who were helped out of critical states (“near-miss” cases) focuses on the development of terminal states during pregnancy and helps to calculate the allowable costs of monitoring patients and their intensive treatment.

Relative compatibility of maternal deaths and similar “near-miss” cases with different outcomes allows a consistent analysis of obstetric catastrophes and their chronology; it also provides reliable information about medical errors made. A profound
comparative analysis gives an insight into what causes death or conditions survival [12,13].

Today, risk factors of possible pregnancy complications include preeclampsia during previous pregnancies, age, first pregnancy, multiple pregnancies, genetic factors, endocrine system pathology, social aspects, occupational hazards, pernicious habits, unsatisfactory environmental setting, insufficient or imbalanced nutrition, complicated obstetric and gynecological history, genital inflammatory diseases, typically with urinary tract involvement, and cardiovascular diseases.

Assisted reproductive technologies are by themselves risk factors of gestation complications with a high probability of ovarian hyperstimulation syndrome, pregnancy termination, extraterine pregnancy, preeclampsia, multiple pregnancies, preterm labor, including super early miscarriages, perinatal losses and thromboembolic complications.

Ovarian hyperstimulation syndrome is characterized by a wide spectrum of clinical and laboratory manifestations: from smaller biochemical changes to a massive transfer of the liquid part of blood from intravascular to ‘the third dimension,’ which leads to hypovolemia, hemocoagulation, electrolyte imbalance, hypercoagulability and other complications [14]. Research published on the issue reveals that the frequency of ovarian hyperstimulation syndrome varies from 0.5% to 33% with different schemes of ovulation stimulation and does not reveal a downward trend. Severe forms of the syndrome that require hospitalization have been diagnosed in 0.2–10% of all cases [15].

The most commonly occurring of all possible complications during pregnancy (64.5%) after IVF is preeclampsia, that is, disorders in major organs and systems in a female body. After IVF, the risk of thrombosis and thrombolytic complications increases significantly, especially for patients with hereditary and acquired thrombophilia.

In recent years, due to the development of molecular genetics, there appeared a possibility to diagnose genetic polymorphisms associated with the risk of thrombosis (factor V Leiden mutation, prothrombin mutation, etc.), which provided an explanation for unaccountable cases of severe complications in gestation. The characteristic feature of polymorph variants of these genes is that they may not manifest themselves in any possible manner for quite a long time. Pathological signs usually appear when other conditions come into play, one of these being pregnancy, especially after in vitro fertilization [14,16].

The intensity of hypercoagulation states in different forms of thrombophilia, as well as the frequency and severity of thrombotic episodes depend on the degree of hemostatic imbalances and accompanying (background) states, on pathological processes and influences.

Long-term hormonal preparation of patients for assisted reproductive technologies is an additional trigger for thrombotic complications. Hormonal strain directly leads to the activation of the hemostatic system [14].

Pathologic clotting or uncontrolled growth of the thrombus with underlying hormone load in the case of thrombophilia leads to circulatory embarrassment in the vitals or to the consumption of procoagulants with the development of ischemia [17].

From the modern point of view, thrombophilia is considered an etiopathogenic factor in a wide variety of diseases and syndromes; it quite often combines with other systemic syndromes, including SIRS, metabolic syndrome, DIC syndrome, oxidative stress, endotheliopathy, fetal loss syndrome, preeclampsia, thrombophilic complications of hormonal contraception, hormonal replacement therapy, etc. [18]. It has been proven that the basis for pregnancy complications is formed by desequencing invasion stages of the trophoblast and insufficient transformation of spiral arteries which leads to decreased blood supply to the growing placenta, hypoxia, parasecretion of angiogenic factors, spontaneous miscarriages, intrauterine growth restriction and fetal death, placenta detachment, and preeclampsia [19].

A great role in the pathogenesis of such pregnancy complications as placental deficiency, intrauterine growth retardation syndrome and preeclampsia is played by thrombophilia, an imbalance in the products of growth factors responsible for both vessel walls and placenta angiogenesis and therefore, for the proper formation and development of the latter. The pathologic invasion of the thromboblast into spiral arteries induces the development of different pregnancy complications, leads to ischemia in the placenta and preeclampsia, placental deficiency and intrauterine growth retardation syndrome (IUGR). Chorion detachment and fetal loss at the early stages of pregnancy account for 20–25% of all pregnancies [19].

Therefore, the necessity to single out “near-miss” groups of women after assisted reproductive technologies with reference to multi-factor predictors of critical situations is vital in the study of epidemiology and its special features; it is also important for the clinical presentations in this group of patients.

The aim of this research is to study the predictors of critical states during pregnancy after assisted reproductive technologies.

Materials and methods

A retrospective comparative study of patients who suffered critical states during pregnancy was conducted. The object of the research was general totality of all “near-miss” cases in Ural Federal Region. The unit of observation statistics was a female resident of Ural Federal Region (a constituent territory of Russian Federation) who nearly died of direct or indirect causes in complicated gestation course, difficult delivery and puerperal period, according to explanatory notes for all “near-miss” cases.

The research studied patients who, in the course of gestation, suffered severe preeclampsia, preeclampsia, bleeding (over 1500 ml) and extragenital pathologies (the criteria considered for patient treatment included vasoactive drugs used, hysterecomy, blood transfusion, artificial ventilation ≥1 h, hemodialysis and cardiopulmonary resuscitation).

The selection criterion for the patients was WHO classification of real and possible cases of maternal mortality, which was developed by Pattinson RC, Say L, Souza JP in 2009 [20].

The method of continuous sampling enabled us to form a group of 302 patients who had suffered critical states during pregnancy; 265 women had spontaneous pregnancies, and 37 were studied after assisted reproductive technologies. The percentage of “near-miss” patients who became pregnant after assisted reproductive technologies was 12.3%. It is noteworthy that childbirth through assisted reproductive technologies in RF in 2014 constituted 0.98% only.

Two groups were formed consequently: the main group (n = 37), a continuous sampling of women who had suffered critical states during pregnancy induced by assisted reproductive technologies, and the control group (n = 96), a random sampling of women who had suffered critical states during pregnancy that developed in its natural cycle.

The methods of assisted reproductive technologies used in vitro fertilization in 62.2% of all cases, and every third married couple (28.6%) resorted to IVF and ICSI; 5.41% used the donor program and 2.7% used insemination and cryotechnologies.

The research was approved by Ethics Committee of FSBI ‘‘Ural Research Institute of Maternity and Childhood Protection’’ of Public Health Ministry of Russia.

The statistical treatment of the data was performed on the platform of Microsoft Excel 2010; M was defined as the
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arithmetic mean, standard sampling deviation, an error of the arithmetic mean. The comparison of average values was made on the basis of Student’s t-test for unbiased samplings with adjustments for differences in dispersion. The correlation between indicators was defined through correlation analysis, with Pearson correlation coefficient and Germanness defined on Chaddock scale. The difference in average values was taken as statistically reliable if the value did not exceed 0.05.

Results

The average age of women in the main group was 32.6 ± 4.89, whereas in the control group it was 30.7 ± 5.8, which defined the compatibility for the groups.

For pregnancy terms over 22 weeks in both groups, obstetric catastrophes were the main reason for “near-miss” cases in relation to the term of gestation. For pregnancy terms less than 22 weeks, the primary reason for “near-miss” cases in the group of women after assisted reproductive technologies was ovarian hyperstimulation syndrome (10.8%). Bleeding (57.14%) and extragenital pathology (33.3%) were dominant in the group of women with spontaneous pregnancy, which seriously differed one from the other (p<0.05).

When the pregnancy term exceeded 22 weeks, such complications as severe preeclampsia were twice as frequent (59.46%) among women after assisted reproductive technologies, which significantly differed (p<0.05) from the group with spontaneous pregnancy (27.55%). Extragénital pathology was a more frequent reason (p<0.05) for critical states (Table 1) in the group of women with spontaneous pregnancy (32.29%).

Hypercoagulation disorders, responsible for placental deficiency (PD), were registered in more than a half of all cases (59.46%), 14.5% of which were diagnosed as genetic hyperhomocysteinemia (PD), were registered in more than a half of all cases (53.5%), 14.5% of which were diagnosed as genetic hyperhomocysteinemia (MTHFR-C677T), 11.6% as a mutation in the gene of plasminogen activator inhibitor, 5.5% as a mutation in prothrombin (F2-20210), 4.6% as a mutation in ITGB3 gene (platelet membrane receptor), 1.2% as Leiden mutation (F5). A combination of antiphospholipid syndrome with genetic forms of thrombophilia was found in 27% of all cases (Figure 1).

It is interesting to note that social factors include unemployment (12.5% of women were unemployed). The number of officially married women in the control group is notably lower (p<0.05; 70.83% in the control group versus 94.59% in the main group). The groups are compatible in all the other social factors including urban status, individual property in ownership, desired pregnancy, pernicious habits and occupational hazards.

From the point of view of parity, the groups notably differed (p<0.05) by the majority of primagravidas (29.7%) in the main group and multigravidas (29.2%) in the control group (Table 2).

In obstetric–gynecologic history, the leading positions were occupied by inflammatory diseases of pelvic organs (43.24%) in the main group, which notably differed this group (p<0.05) from the control group (16.67%).

The surgical history of pelvic organs in the main group occupied the second place (40.54%) and was registered twice more often (p<0.05) than in the control group (7.29%), which is conditioned by a high rate of inflammatory diseases of pelvic organs.

Within the structure of extragenital diseases, gestation pancreatic diabetes was notably more frequent (p<0.05) in the main group (32.4%) than in the control group (6.25%). This can be explained by a higher hormone load on patients during assisted reproductive technologies (Table 3).

In the main group, extragenital pathology was more often detected before pregnancy (p<0.05, 89.19%), which is connected with thorough medical examination prior to assisted reproductive technologies. The quality of the examination, however, is to be improved, since 37.8% of all diseases were detected during pregnancy. The absence of any pregnancy checkup was noted in the control group, since extragenital pathology was only detected during pregnancy in every third patient (27.08%).

The women were mainly admitted to hospital in a satisfactory state; however, in the control group, 17.7% of the pregnant women were out of case at the time of hospitalization (Table 4).

In both groups, delivery times corresponded to 34 weeks of gestation. The usual mode of delivery was cesarean operation in both groups (81.08% and 83.33%). However, in the control group, operative delivery was more often performed on an emergency basis (p<0.05, 73.96% as compared to 51.35% in the main group), whereas in the main group, the operation was routine (29.73% as compared to 9.38% in the control group). Planned

Table 1. Structure of near-miss causes.

| Causes                          | n = 37 | Abs. | M ± m | n = 265 | Abs. | M ± m |
|---------------------------------|-------|------|-------|---------|------|-------|
| **Up to 22 weeks and incl.**    |       |      |       |         |      |       |
| Bleeding                       | 4     | 10.81 ± 5.1 | 42   | 15.85 ± 6.0 |
| Extragénital pathology         | –     | –    | 14    | 33.3 ± 7.27 |
| Sepsis                         | –     | –    | 2     | 4.76 ± 3.29 |
| Other                          | 4     | 10.81 ± 5.1 | 3    | 1.13 ± 1.74 |
| **After 22 weeks**             |       |      |       |         |      |       |
| Bleeding during pregnancy and delivery | 34   | 91.89 ± 5.1 | 223  | 84.15 ± 6.0 |
| Sepsis                         | –     | –    | 6     | 2.26 ± 2.15 |
| Preeclampsia and eclampsia     | 22    | 59.46 ± 8.07* | 73   | 27.55 ± 7.31* |
| Amniotic fluid embolism        | –     | –    | 1     | 0.36 ± 1.01 |
| Uterus rupture                 | –     | –    | 10    | 3.77 ± 3.13 |
| Extragénital pathology         | 1     | 2.70 ± 2.67* | 31   | 32.29 ± 7.69* |

*p<0.05.

Figure 1. Frequency of different forms of thrombophilia in patients after IVF.

Table 2. Parity in women with near-miss.

| Factors                          | Main group, n = 37 | Control group, n = 96 |
|---------------------------------|--------------------|-----------------------|
| First                           | 11                 | 11                    |
| Second                          | 11                 | 22                    |
| Third                           | 8                  | 23                    |
| Fourth                          | 5                  | 14                    |
| Fifth and more                  | 1                  | 28                    |

*p<0.05.
In a timing period, more distant from ART, the leading cause of critical states during pregnancy was preeclampsia, which occurred twice more often (59.46%); this result is significantly different from the result of women with critical states during spontaneous pregnancy ($p<0.05$, 27.55%). The predictor for severe preeclampsia was hypercoagulation disorders in 53.5% of all cases with underlying thrombophilia of different types. Our data conform to the other works published on the issue that state a higher risk of severe preeclampsia and hypertension complications for women pregnant after ART [20–22].

In the structure of extragenital pathology leading to a critical state, gestation pancreatic diabetes was predominant and more frequent among women pregnant after ART than among women with critical states with spontaneous pregnancies (32.4% as compared to 6.25%; $p<0.05$). This can be explained by a higher hormone load during assisted reproductive technologies, which is conducive to carbohydrate exchange imbalance.

### Discussion

Any pregnancy that happened as a result of assisted reproductive technologies is a high-risk pregnancy involving maternal and perinatal complications. This is connected with infertility factor in women's medical history, high doses of hormones used to stimulate ovulation, and initial risk factors.

The totality of these adverse conditions can lead to critical states, which threaten a woman's life. Such states can develop either immediately after ART, or within a more distant time period, for example, during a pregnancy.

In the structure of all critical states, pregnancy after ART accounts for 12.3% of all cases. It is noteworthy that the number of women who became pregnant after ART in the overall population does not exceed 1%. Therefore, the risk of critical states development in pregnant women after ART is 10 times higher than after spontaneous conception.

As concerns the development of obstetric catastrophes when pregnancy terms do not exceed 22 weeks, a severe syndrome of ovarian hyperstimulation plays a major role in 10.8% of all pregnancy cases after ART, whereas obstetric bleeding (57.14%) and extragenital pathologies (33.3%) have a greater role in spontaneous conception cases, which significantly differentiates the groups ($p<0.05$).

### Table 3. Frequency of extragenital diseases in women with near-miss.

| Factors                        | Main group, Abs. | Control group, Abs. | Main group, M±m | Control group, M±m |
|-------------------------------|------------------|---------------------|------------------|---------------------|
| Cardiovascular system         | 15               | 26                  | 40.54 ± 8.07     | 27.08 ± 7.31       |
| Respiratory organs            | 2                | 2                   | 5.41 ± 3.72      | 2.08 ± 2.35        |
| Urinary system                | 6                | 13                  | 16.22 ± 6.06     | 13.54 ± 5.63       |
| Obesity                       | 2                | 5                   | 5.41 ± 3.72      | 5.21 ± 3.65        |
| Thrombophilia                 | 11               | 5                   | 29.73 ± 7.51*    | 5.21 ± 3.65*       |
| Gestation pancreatic diabetes | 12               | 6                   | 32.43 ± 7.70*    | 6.25 ± 3.98*       |

* $p<0.05$.

### Table 4. Frequency of complications and risk factors of a given pregnancy with near-miss.

| Factors                        | Main group, Abs. | Control group, Abs. | Main group, M±m | Control group, M±m |
|-------------------------------|------------------|---------------------|------------------|---------------------|
| Severe preeclampsia           | 20               | 17                  | 54.05 ± 8.19*    | 17.71 ± 6.28*       |
| Eclampsia                     | 1                | 6                   | 2.70 ± 2.67      | 6.25 ± 3.98         |
| HELLP syndrome                | 2                | 10                  | 5.41 ± 3.72      | 11.46 ± 5.24        |
| Placental presentation        | 1                | 16                  | 2.70 ± 2.67*     | 16.67 ± 6.13*       |
| Premature detachment of placenta | 1             | 3                   | 37.84 ± 7.97*    | 3.13 ± 2.86*        |
| Multiple pregnancy            | 14               | 9                   | 21.62 ± 6.77     | 9.38 ± 4.79         |
| IUGR                           | 8                | 9                   | 37.84 ± 7.97*    | 3.13 ± 2.86*        |

* $p<0.05$.

Pregnant women after ART are a high-risk group for critical states classified as ‘near-miss’ in both the nearest and a more distant time period after ART. The structure of such maternal critical states is different from the structure of critical states when the pregnancy is spontaneous. Among pregnant women after ART with the pregnancy term not exceeding 22 weeks, the only cause of ‘near-miss’ is ovarian hyperstimulation syndrome. When the pregnancy term exceeds 22 weeks, the main causes are severe preeclampsia and hypertension complications with underlying extragenital pathology linked with hypercoagulation and carbohydrate exchange imbalance.

### Conclusion

The authors declare the absence of any conflicting interests.
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