

Assessment of risk factors and interventions affecting the prognosis in triplet gestations

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INTRODUCTION

The effectiveness of infertility treatment procedures has increased significantly over the past two decades. As a consequence of the aging maternal population, and "side effect" of increasing use of ovulation-induction agents and assisted reproductive techniques, the frequency of twin and higher order multiple pregnancies have increased several times.

The majority of triplet pregnancies end in preterm birth before 37 weeks of pregnancy. The rate of early (28 to 31.9 weeks) and very early (<28 weeks) premature births is high. It results in significantly worse perinatal mortality and morbidity indicators compared to singleton pregnancies.

Over the last decades, the average length of triplet pregnancies, so the rate of early preterm birth did not change significantly, despite the improvement in pregnancy care and the extension of obstetrical tools. As a result of development in perinatology and neonatology, however, the life expectancy of the newborn triplets has improved significantly. Nevertheless, among the triplets survived the neonatal period, the frequency of brain injury causing permanent mental and/or physical disability is 15 to 20 times higher compared to singleton pregnancies, and 3.5 to 4-fold compared to twins. Major problem in triplet pregnancy is that some of serious maternal complications and diseases are more prevalent than in singleton pregnancies.

The ideal solution would be to reduce the number of iatrogenic triplet pregnancies with careful administration of ovulation-induction agents and limiting the number of transferred embryos during assisted reproductive treatment.

A new option is the multifetal pregnancy reduction, which reduces the incidence of maternal complications and improves the perinatal outcomes in higher order multifetal pregnancies. Such an intervention becomes common practice if its effectiveness is supported by biological indicators, and, on the other hand, other factors (religious, ethical, social and financial considerations) also contribute to acceptance. The reduction, however, is not acceptable to all for ethical reasons.

For these reasons, after diagnosis of triplet gestation, detailed information should be provided to pregnant women on risks associated with triplet gestations, on maternal and fetal risks of non-reduced triplet pregnancies, on the chances of newborn triplets, on the option of multifetal pregnancy reduction, which helps to make prudent decision on wearing the pregnancy further without reduction or to reduce. Such data are not currently available in Hungary.

Some risk factors are known at the first trimester visit (maternal age, parity, mode of conception, weight, height etc). Taking of those factors into account during counseling, personalized risk assessment is possible, which may facilitate the patient's decision. It has not yet been an attempt in the Hungarian triplet population to identify these risk factors and to determine their predictive values.

Other options are the use of interventions preventing early preterm birth with aim to increase the duration of pregnancy: prophylactic cerclage surgery and prolonged bed rest. Performing prophylactic cerclage surgery in triplet gestation is

controversial. The long-term bed rest may reduce the uterine activity through a reduction in physical activity, but this beneficial effect, however, is not justified.

Besides anemia, thrombocytopenia is one of the most common hematological abnormalities in pregnancy. The most common clinical entity that involves thrombocytopenia during pregnancy is gestational thrombocytopenia, which accounts for >75% of cases. The second most common cause is pregnancy-induced hypertension. Idiopathic thrombocytopenic purpura (ITP) and a large spectrum of other diseases can also cause thrombocytopenia during pregnancy.

Thrombocytopenias associated with pregnancy have so far mainly been studied in singleton pregnancies. There is little information on the incidence and causes of thrombocytopenia in multiple pregnancies.

AIMS

1. What are the characteristic maternal features of Hungarian triplet-population? What are the rates of maternal complications during pregnancy and postpartum period in triplet gestation? What are the rates of fetal malformations, especially congenital heart anomalies? What are the perinatal and neonatal mortality rates in triplet pregnancy? What is the frequency of neonatal complications in triplets? Is there any change in the values of these indicators over the last two decades?
2. Are different the rates of maternal complications and perinatal mortality indicators in triplet and twin pregnancies?
 - 3.1. Should we consider older (≥ 35 years) maternal age as a risk factor in triplet pregnancy based on the frequency of maternal complications, the perinatal outcomes as well as the rate of neonatal complications?
 - 3.2. Should we consider multiparity as a risk factor in triplet pregnancy based on the frequency of maternal complications, the perinatal outcomes as well as the rate of neonatal complications?
 - 3.3. Should we consider conception with in vitro fertilization as a risk factor in triplet pregnancy based on the frequency of maternal complications, the perinatal outcomes as well as the rate of neonatal complications?
4. How frequent is the maternal thrombocytopenia in triplet gestation and what are the causes of it? What are the risks of thrombocytopenia? Is there any change in the platelet count in triplet pregnancy with gestational age?
 - 5.1. Is there any increase in the duration of triplet gestations, any improvement in perinatal and neonatal mortality and morbidity data after prophylactic cerclage surgery performed in the second trimester in asymptomatic triplet pregnancy without prior ultrasound examination of cervical length, based only on the fact of triplet gestation?
 - 5.2. Does the hospitalization of asymptomatic patients with triplet gestation before 28 weeks of pregnancy results in better perinatal mortality and morbidity data compared to patients admitted to hospital after 28 weeks of pregnancy?

PATIENTS AND METHODS

The study population consisted of all patients with triplet gestation who delivered at the I. Department of Obstetrics and Gynecology between July 1, 1990 and December 31, 2011. The inclusion criterion was documentation of living fetuses during 18 weeks routine ultrasound examination. Patients undergoing multifetal pregnancy reductions were excluded.

Other study group consisted of twin gestations delivered at our Department in a 15-month period (in 2004-2005) in the second half of the study period. The inclusion criterion in this study group was also the documentation of living fetuses during 18 weeks routine ultrasound examination. Patients undergoing multifetal pregnancy reductions were also excluded.

The long, 21.5-year study period can not be considered uniform in many aspects: in 1990-2000, the assisted reproductive techniques were less prevalent, and until 1997, the perinatal period began after 28 weeks of pregnancy according to the laws in force. The data of this period were collected retrospectively by reviewing the patient's medical charts and other documents.

In the period of 2001-2011, the assisted reproductive techniques have become more accessible with the increase in the number of fertility centers. The laws in force determined the beginning of the perinatal period at 24th weeks of pregnancy. Data were collected prospectively during this period in a structured, planned form.

In spite of the long study period, the principles of prenatal care were the same in the study group, and the basic methods of neonatal care (ventilation, surfactant treatment) were available from the beginning of the study. They determine the maternal outcome and the perinatal mortality data in short term. The neonatal morbidity data were also examined, however, it should be noted that the attitude of the neonatal care undergone significant change.

In the dissertation the demographic and obstetric medical history data (maternal age at delivery, previous births, mode of conception), the frequency of maternal complications (hypertension, gestational diabetes, urinary tract infections, hematological abnormalities, intrahepatic cholestasis, skin lesions), the rate of preterm labor and premature rupture of membranes, the frequency of interventions used in order to improve the prognosis (cerclage surgery, steroid prophylaxis), the data associated with the hospitalization, perinatal data (gestational age at delivery, rate of preterm, early premature and very-early premature births, birth weight, rate of low birth weight, very-low birth weight and very-very-low birth weight infants, mode of delivery, Apgar scores, perinatal mortality rates, rate of major malformations), postpartum complications (bleeding, fever, hematologic abnormalities) and interventions used to treat them (transfusion, surgery), the rates of neonatal morbidity (intraventricular hemorrhage, transient tachypnea, respiratory distress syndrome, pneumothorax, pneumonia/sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus Botalli, jaundice, anemia immediately after birth) and the frequency of use of oxygen therapy and/or ventilation were analyzed.

The frequencies were expressed as a percentage. The value of each attribute was expressed in the form of mean \pm standard deviation (SD). In case of high standard deviation I used the median and the range of the values. Continuous variables were compared with the unpaired Student's t-test, while categorical data were analyzed with χ^2 -test with Yates' correction or Fisher's exact test as appropriate. The two-sided P value of <0.05 was considered statistically significant.

Comparing the risk or odds of some features were used relative risk (RR) or odds ratio (OR) with 95% confidence interval (CI). The trend of changes in platelet counts was examined with linear regression and was characterized by Pearson's correlation coefficient. Data processing and statistical tests were performed with Microsoft Excel 2007 (Microsoft Corp., Redmond, Wa.) software.

RESULTS

1. The maternal and fetal prognosis of triplet pregnancies and their changes over the last two decades

During the study period, 183 patients meeting the inclusion criteria delivered triplets. Eight patients (4.4%) delivered preivable fetuses at 20-23 weeks of pregnancy, 175 cases (95.6%) resulted in delivery. The average maternal age at delivery was 30.4 ± 4.0 years, the proportion of pregnant women ≥ 35 years was 16.6%, and the rate of nulliparous patients was 79.4%. 16.6% of the triplet pregnancies were conceived spontaneously, while 81.7% were a result of infertility treatment.

Pregnancy-induced hypertension occurred in 16.6% of cases (preeclampsia 8.0%, transient hypertension of pregnancy 6.9% and HELLP [Hemolysis, Elevated Liver enzymes, Low Platelet count] syndrome 1.7%). Triplet pregnancies were complicated with gestational diabetes in 22.9% of cases. During the triplet gestation thrombocytopenia was observed in 28.0%, anemia in 17.1%, intrahepatic cholestasis of pregnancy in 9.1%. No maternal death occurred.

The average duration of pregnancy was 32.1 ± 3.2 weeks. The very early premature (<28 weeks) birth rate was 10.9%, the early premature (28 to 31.9 weeks) birth rate was 31.4%. The one-minute Apgar score was 8.1 ± 0.9 , a five-minute Apgar score was 9.2 ± 0.7 .

The mean birth weight of the live born triplets was 1644 ± 511 g. 28.2% of the fetuses was born with very-low (1000-1499 g) birth weight. In 2001-2011, the average birth weight was lower (1728 ± 475 vs. 1611 ± 521 g, $P=0.018$), and the rate of very-very-low (500-999 g) or very-low (1000-1499 g) birth weight infants was significantly higher (6.1% vs. 13.1%, $P=0.033$, and 1.6% vs. 30.8%, $P=0.047$).

The late intrauterine mortality was 19.0%. Early neonatal mortality was 46.6%, late neonatal mortality was 11.7%, while the overall neonatal mortality rate was 58.3%. The perinatal mortality rate 64.8% and 46.6% was purified perinatal mortality.

Major malformations were observed in 9.5 %, (1-1 diaphragmatic hernia, 21-trisomy with atrioventricular septal defect, omphalocele, univentricular heart and isolated transposition of great arteries). The frequency of cardiac malformations calculated on pregnancy was 1.7% (3/175).

In postpartum period anemia was observed in 46.3%, thrombocytopenia in 38.3%, significant bleeding (in excess of 500 ml or more) in 9.7%, fever occurred in 10.9%, transfusions were required in 12.0%, hysterectomy and/or hypogastric artery ligation in four cases (2.3%), Curettage and uterine lavage was performed in six cases (3.4%).

After birth, 65.9% of the newborns required ventilation or prolonged O₂ therapy. Intracranial hemorrhage was diagnosed in 9.5% of newborns, respiratory distress syndrome in 19.1%, transient tachypnea in 5.2%, pneumonia/sepsis in 63.7%, and neonatal jaundice in 37.9%, respectively. The proportion of newborns requiring long-term ventilation or O₂ therapy increased significantly in 2001-2011. Respiratory distress syndrome, sepsis/pneumonia, jaundice and anemia were observed more frequently. The incidence of other neonatal diseases did not change significantly.

2. Comparison of the maternal and fetal prognosis of triplet and twin pregnancies

Of the 183 triplet pregnancies 8 (4.4%) ended in midtrimester (20-23 weeks) abortion, while 175 cases (96.6%) ended in delivery. Of the 206 twin pregnancies 9 cases (4.4%) ended in midtrimester abortion, 197 cases (95.6%) ended in delivery. The rate of midtrimester abortions did not differ between the two groups (RR 1.0, 95% CI 0.39-2.54).

Comparing the triplet and twin pregnancies ended in delivery, there was no significant difference between the two groups in mean maternal age (30.4±4.0 vs. 30.6±5.2 years). There was no significant difference between the two groups in the rate of most maternal complications, although most complications occurred more frequently among triplets. Transient gestational hypertension occurred more frequently among triplet pregnancies (6.9% vs. 1.5%, P=0.02), although the incidence of pregnancy-induced hypertension was not different in the two groups. Gestational diabetes (22.9% vs. 12.2%, P=0.010), thrombocytopenia (28.0% vs. 13.7%, P=0.001) and preterm labor (54.3% vs. 35.0%, P<0.001) were observed more frequently in triplet pregnancies.

The rates of maternal complications and interventions in postpartum period were not different in the two groups, however puerperal fever (10.9% vs. 4.1%, P=0.020) and thrombocytopenia (38.3% vs. 23.9%, P=0.004) were observed more frequently in the triplet group.

The average duration of triplet pregnancies was shorter (32.3±3.2 vs. 33.8±3.7 weeks, p<0.001), while very-early and early premature birth rate did not differ significantly in the two groups. The cesarean rate was higher among triplet

pregnancies (96.6% vs. 81.2%, $P<0.001$), and the one- and five-minute Apgar scores were lower as well (8.1 ± 0.9 vs. 8.4 ± 0.9 , $P<0.001$, and 9.2 ± 0.8 vs. 9.4 ± 0.8 , $P<0.001$).

The average birth weight was higher in the twin group (1644 ± 506 vs. 2031 ± 697 g, $P<0.001$). The rate of very-very-low birth weight infants did not differ in the two groups, however, the frequency of very-low birth weight infants was higher in the triplet group (28.2% vs. 15.5%, $P<0.001$). The perinatal mortality rates did not differ in triplet and twin group, except early neonatal mortality which was found higher in triplet group (46.6‰ vs. 13.2‰, $P=0.009$).

3. Analysis of risk factors known in first trimester in triplet pregnancies

3.1. Maternal age as a risk factor in triplet pregnancy

Of 175 patients with triplet gestation, 29 were 35 years of age or older (35-39 years) at delivery (16.6%), whereas 146 younger than 35 years (18-34 years) (83.4%). The rates of maternal complications during pregnancy were similar in the two groups.

There was no difference between the two groups in the mean gestational age at delivery (32.6 ± 2.9 vs. 32.3 ± 3.3 weeks). The rates of very early and early premature births did not differ significantly in the two groups. The intrauterine death rates were similar in the two groups. The average birth weight of live born infants was higher in the group of patients over 35 years of age (1771 ± 515 vs. 1619 ± 507 g, $P=0.012$). The rates of very-very-low birth weight and very-low birth weight infants were also lower in this group, but the differences were not statistically significant. The newborns of patients over 35 years of age had higher one-minute and five-minute Apgar scores (8.3 ± 0.8 vs. 8.0 ± 0.9 , $P=0.058$, and 9.4 ± 0.7 vs. 9.2 ± 0.7 , $P=0.064$). The perinatal mortality rates and the frequency of postpartum maternal complications showed no significant difference in the two groups.

The infants of patients over 35 years of age required less ventilation (54.8% vs. 68.2%, $P=0.039$). The frequency of neonatal complications was similar in the two groups.

3.2. Parity as a risk factor in triplet pregnancy

Of 175 patients with triplet pregnancy, 36 (20.6%) had a history of one or more births, 139 pregnancies (79.4%) had not given birth previously. The rates of maternal complications during pregnancy did not differ in the two groups, except pregnancy-induced hypertension which was lower in the group of multiparous patients (2.8% vs. 20.9%, $P=0.011$).

The mean gestational age at delivery was significantly higher in the group of multiparous patients (33.2 ± 2.9 vs. 31.9 ± 3.2 weeks, $P=0.026$). Both very early and early premature birth rates were lower in the multiparous group, but the differences were not significant. The average birth weight of the infants in the group of multiparous patients was significantly higher than that in the group of nulliparous

patients (1862±512 vs. 1587±495 g, $P<0.001$). The rates of very-very-low and very-low birth weight infants were lower in the group of multiparous patients, but differences were not statistically significant. The one-minute Apgar score was higher in the group of multiparous patients (8.3±0.8 vs. 8.0±1.0, $P=0.016$), whereas the five minute Apgar score did not differ in the two groups.

The perinatal mortality rates and the frequency of postpartum maternal complications showed no significant difference in the two groups.

The infants of multiparous patients required less ventilation (50.6% vs. 70.0%, $P<0.001$), especially SIMV (Synchronized Intermittent Mandatory Ventilation). The rates of most neonatal complications were similar in the two groups, except sepsis/pneumonia which occurred more frequently among newborns of nulliparous patients (50.6% vs. 67.3%, $P=0.005$).

3.3. Mode of conception as a risk factor in triplet gestation

Of 175 triplet pregnancies 100 (57.1%) resulted from in vitro fertilization, 72 (41.1%) were conceived in vivo (spontaneously, after ovulation-induction and/or insemination). The mean maternal age was significantly higher in pregnancies resulted from in vitro fertilization (31.5±3.4 vs. 29.0±4.5 years, $P<0.001$). The rates of serious maternal complications during pregnancy did not differ in the two groups.

The mean gestational age at delivery did not differ in the two groups (32.2±3.2 vs. 32.1±3.3 weeks) and the rates of very early and early premature births were also similar in the two groups. There was no significant difference in mean birth weight of the live born infants (1661±505 g vs. 1613±510 g), and in the rates of very-very-low birth weight and very-low birth weight infants. The one-minute and five-minute Apgar scores characterizing fetal condition after birth did not differ in the two groups.

Perinatal mortality rates showed no significant difference in the two groups, however, the corrected perinatal mortality was significantly higher among pregnancies resulted from in vitro fertilization (67.6% vs. 14.4%, $P=0.009$). The frequency of postpartum maternal complications showed no significant difference in the two groups.

The need for ventilation of newborns was similar in the two groups (65.2% vs. 68.3%). The incidence of respiratory distress syndrome (14.6% vs. 26.2%, $P=0.005$) and anemia (7.7% and 17.1%, $P=0.006$) were higher among infants conceived spontaneously, however the frequencies of most neonatal complications were similar in the two groups.

4. Incidence and causes of maternal thrombocytopenia as a risk factor in triplet gestation

Thrombocytopenia was observed during the triplet gestation in 49 cases (28.0%), and after delivery in another 18 cases (10.3%), so the overall occurrence of thrombocytopenia in relation to triplet pregnancy was 38.3%. Thrombocytopenia was

not observed before 25 weeks of pregnancy. On average, thrombocytopenia was diagnosed at 31.4 ± 2.7 weeks of gestation. Thrombocytopenia observed during triplet pregnancy was mild, moderate and severe in 75.5% (37/49), 18.4% (9/49), and 6.1% (3/49) of the cases, respectively. The lowest platelet count was $57000/\mu\text{l}$. The vast majority of thrombocytopenias occurring after delivery were mild (94.4%, 17/18), the platelet count fell under $70000/\mu\text{l}$ in a one single case.

During pregnancy, thrombocytopenia was associated with transient gestational hypertension (3 cases), preeclampsia (4 cases) and HELLP syndrome (3 cases) in 20.4% of cases (10/49). Platelet count fell below $150000/\mu\text{l}$ after intrauterine fetal death in one case, and associated with chronic hypertension in another case, while gestational thrombocytopenia was diagnosed in 73.5% of the cases (36/49). SLE, antiphospholipid syndrome and ITP were not detected.

Two of three cases of severe thrombocytopenia was considered as gestational thrombocytopenia. In the third case the diagnosis was HELLP syndrome. In cases of moderate thrombocytopenia (9 cases), one case was caused by HELLP syndrome, one by preeclampsia, one by gestational hypertension, six cases were considered as gestational thrombocytopenia. The cause of severe thrombocytopenia presenting after delivery was serious atonic bleeding requiring hysterectomy.

We compared the group of thrombocytopenic women (49 cases) and the group of patients with normal platelet count during the entire pregnancy (126 cases). There was no statistically significant difference between the two groups in maternal characteristics. The mean gestational age at delivery was significantly higher in the thrombocytopenic group (34.0 ± 2.2 vs. 31.6 ± 3.3 weeks, $P < 0.001$), and the mean birth weight was also higher (1947 ± 407 vs. 1526 ± 498 g, $P < 0.001$). The proportion of pregnancies completed after 32 weeks was higher in the thrombocytopenic group (85.7% vs. 50.0%, $P < 0.001$) and the rate of infants with birth weight > 1500 g was also higher (84.1% vs. 50.0%, $P < 0.001$). The perinatal mortality rate was lower in the thrombocytopenic group (13.6‰ vs. 84.9‰, $P < 0.001$).

Severe hemorrhage after delivery occurred more frequently in the thrombocytopenic group (20.4% vs. 5.6%, $P = 0.007$), and these patients also required more blood transfusions (20.4% vs. 9.7%, $P = 0.040$).

On the basis of 640 available observations on platelet counts, we determined the mean platelet count for each gestational week between 16 and 36 weeks of pregnancy. The mean platelet count showed a strong negative correlation with gestational age ($r = -0.947$, $P < 0.001$), declined continuously after 22 weeks, and 36 weeks approached the limit of thrombocytopenia ($150000/\mu\text{l}$) (Figure 1).

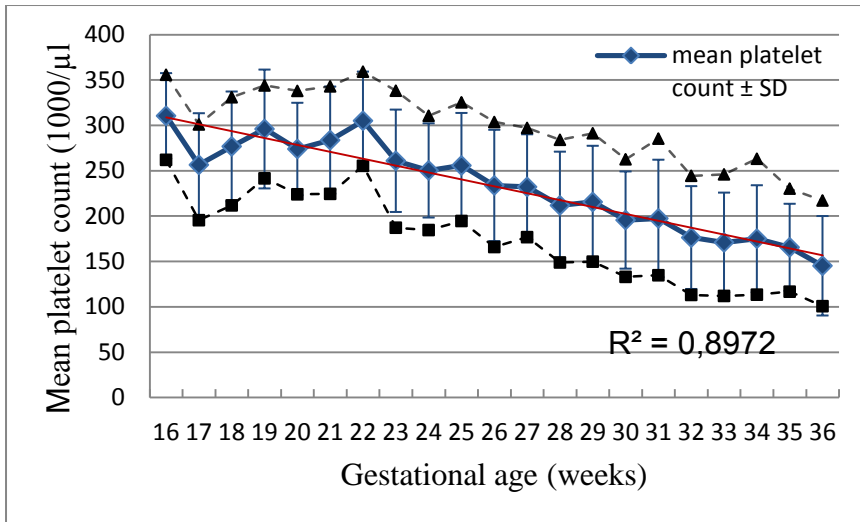


Figure 1 Changes in the mean platelet count in triplet gestation and the 10-90 percentile range ($r=-0.947$, $y=430.394-7.5988*x$, $P<0.001$)

5. Investigation of interventions with aim to improve the prognosis of triplet gestation

5.1. The effect of prophylactic cerclage surgery on the outcome of triplet pregnancies

Of the study population of 175 triplets, prophylactic cerclage surgery at 18-23 weeks of pregnancy was performed in 19 cases (10.9%), whereas 156 patients (89.1%) completed the pregnancy without cerclage surgery. There was no midtrimester abortion after cerclage surgery.

The incidence of maternal complications did not differ in the two groups, and there was no significant difference in the postpartum complications.

In the triplet pregnancies with or without cerclage surgery, there was no significant difference in the duration of pregnancy (31.5 ± 3.5 vs. 32.2 ± 3.2 weeks of pregnancy), in the rates of very-early and early premature births. There was no significant difference between the two groups in mean birth weight (1575 ± 486 vs. 1653 ± 514 g), in the rate of very-very-low and very-low birth weight neonates. The one-minute Apgar scores were lower after cerclage surgery (7.8 ± 1.0 vs. 8.1 ± 0.9 , $P=0.027$), the five-minute Apgar scores did not differ in the two groups (9.1 ± 0.7 vs. 9.2 ± 0.7).

The late neonatal mortality was higher (53.6% vs. 6.5%, $P=0.019$; RR 8.20, 95% CI 1.69-39.64) after cerclage surgery, other perinatal characteristics, however, showed no significant difference.

The incidence of neonatal complications did not differ significantly in the two groups. However, mechanical ventilation in neonates was needed less after cerclage surgery (38.9% vs. 65.8%, $P=0.002$; RR 0.59, 95% CI 0.39-0.90).

5.2. The impact of early hospitalization on the outcome of triplet pregnancies

Of the study population of 175 triplets, 99 patients (56.6%) were hospitalized before 28 weeks of pregnancy. Among them, 57 patients (32.6%) were asymptomatic, and were admitted for observation. 76 patients (45.6%) were hospitalized at or after 28 weeks of pregnancy, partly asymptomatic, in part because of complaints.

The group of patients hospitalized before 28 weeks for observation, and the group of patients admitted at or after 28 weeks of pregnancy did not differ in mean maternal age at delivery (30.3 ± 4.3 vs. 30.0 ± 3.8 years), and in the rate of older (≥ 35 years) or multiparous women. The rate of maternal complications did not differ in the two groups in most of cases, however, gestational diabetes (19/57, 33.3% vs. 11/76, 14.57%, $P=0.018$; RR 2.30, 95% CI 1.19-4.45) were more common among asymptomatic patients hospitalized before 28 weeks. There was no significant difference between the two groups in the incidence of postpartum complications.

All of 28 asymptomatic pregnant women hospitalized before 28 weeks of pregnancy delivered after 28 weeks. The duration of pregnancy (33.0 ± 2.3 vs. 33.1 ± 2.3 weeks), the rate of very-very-early and very-early preterm births, the mean birth weight (1764 ± 428 vs. 1793 ± 429 g) and the rate of very-very-low and very-low birth weight neonates did not differ in the two groups. The one-minute and five-minute Apgar scores were not significantly different in the two groups. There was no difference in the perinatal indicators of asymptomatic patients admitted before 28 weeks of pregnancy, or hospitalized later. Ventilation or oxygen therapy was required in similar proportions of the two groups, and the rates of neonatal complications were similar.

CONCLUSIONS

1. 16.6% of the triplet pregnancies conceived spontaneously, 81.7% as a result of infertility treatment. The rate of triplets conceived with ovulation induction decreased. The frequency of maternal complications is high: pregnancy-induced hypertension 16.6% (preeclampsia 8.0%, transient hypertension of pregnancy 6.9% and HELLP syndrome 1.7%), gestational diabetes 22.9%, cholestasis 9.1%, premature labor 54.3%, premature rupture of membranes 33.7%. The mean duration of triplet pregnancies is 32.1 ± 3.2 weeks. The rates of very-early and early premature births are high (10.9% and 31.4%). The mean birth weight of live born triplets is 1644 ± 511 g.

The rates of very-very-low and very-low birth weight newborns are very high (11.1% and 28.2%). The latter increases, the mean birth weight decreases. The late fetal mortality in triplet pregnancy is 19.0‰, the neonatal mortality 53.3‰ and the perinatal mortality 64.8‰, respectively. Prenatally detected severe heart defects were identified in 1.75% of patients with triplet pregnancy, so triplet pregnancy per se is an indication for fetal echocardiography. After delivery, significant hemorrhage occurred in 9.7%, 12.0% required blood transfusion, and 2.3% abdominal surgery. 65.9% of triplet neonates required ventilation after birth, and this rate increases. Intraventricular hemorrhage occurred in 9.5%, jaundice in 37.9%, respiratory distress syndrome in 19.1%, sepsis/pneumonia in 63.7%, and the frequency of the latter three complications increases.

2. The risk of maternal complications during pregnancy and in the postpartum period is not higher in triplet pregnancy than in twin gestation, however, the hospitalization is longer, and it begins at earlier gestational age. Triplet pregnancies are completed at earlier gestational age, the average birth weight is lower, the one-minute and five-minute Apgar scores are lower, the rate of very-low birth weight infants is higher, and the early neonatal mortality rate is significantly higher. The newborns' condition after the birth is significantly worse in triplet pregnancy, which - taking into account the right of self-determination of pregnant patients, the individual social circumstances and the financial burden borne by the society – can establish the indication of reduction to twin pregnancy.

3.1. Based on the rate of maternal complications, the perinatal data and mortality rates, the frequency of postpartum maternal complications and neonatal morbidity, older (\geq 35 years) maternal age reduces the risk, so it is not considered a risk factor.

3.2. Based on the rate of maternal complications, the perinatal data and mortality rates, the frequency of postpartum maternal complications and neonatal morbidity, multiparity reduces the risk, so it is not considered a risk factor. Nulliparity increases the risk.

3.3. Based on the rate of maternal complications, the perinatal data and mortality rates, the frequency of postpartum maternal complications and neonatal morbidity, conception with in vitro fertilization do not substantially affect the prognosis of triplet pregnancies; therefore can not be considered a risk factor.

4. Thrombocytopenia occurs more frequently in triplet gestations than in the general pregnant population, and the rate of moderate and severe forms is higher. The distribution of causes is comparable to that of the general pregnant population, and does not depend on the severity of thrombocytopenia. In cases of thrombocytopenia, the risk of massive postpartum hemorrhage and the need for blood transfusion is higher, but the risk of other complications is not associated with thrombocytopenia. The average platelet count in triplet pregnancies is closely related to gestational age, it decreases with increasing gestational age.

5.1. The prophylactic cerclage surgery performed in the second trimester of triplet pregnancy does not increase the duration of the pregnancy, does not improve the

perinatal mortality and neonatal morbidity rates, so that intervention is not recommended for routine use.

5.2. Based on the rates of maternal complications, perinatal mortality and neonatal complications, early (<28 weeks of pregnancy) hospitalization of asymptomatic pregnant patients with triplet gestation does not improve the prognosis of triplet pregnancies. The early admission and long-term hospitalization of asymptomatic pregnant patients with triplet pregnancy therefore is not recommended.

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