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ORIGINAL PAPER

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Retrospective Study of the Correlation Between Twin Pregnancies and Perinatal Outcome in Association to the Impact of Preterm Birth

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ABSTRACT

Background: Twin pregnancies make up 2% to 4% of all births. Incidence of spontaneous twin pregnancies varies around the world, with percentages ranging from 8/1000 to >17/1000 births. The variation in twin pregnancy rates is thought to be due to dizygotic pregnancies, since monozygotic pregnancies have a consistent incidence of 3.5/1000 to 4/1000 births. The incidence of twin pregnancies after the widespread use of assisted reproduction has increased significantly. **Objective:** The purpose of the present study is to investigate factors, who contribute to improve the perinatal outcome in twin pregnancies. Support will be provided by the results of twin pregnancies by the Department of Obstetrics and Gynaecology of Demokrition University of Thrace (Alexandroupolis, Greece) in the last fifteen years. **Methods:** From the above Department, data were collected on the number of twin pregnancies, maternal age, gestational age, mode of delivery (spontaneous delivery or caesarean section), birth weight and rate of twin pregnancies with assisted reproduction. **Results:** The results showed the increasing trend of twin pregnancies and births. A total of 304 twin pregnancies were identified (rate 2.75%). The rate of assisted reproduction was 34.83% in our sample, while the rate of caesarean deliveries was 95.5%, showing a large increase

in recent years. In ten cases, normal delivery was successfully performed. The gestational age in twin pregnancies that ended with normal delivery was 37.37 + 3 weeks and the fetuses were both cephalic presentations. The main reason for admission of newborns to the NICU Department was prematurity. **Conclusion:** The constantly improving education of perinatologists and understanding of the pathophysiology may lead to individualization of their treatment, and improvement of their prognosis based on recent scientific data from other international centers. **Keywords:** Twin pregnancies, modus of terminating births, perinatal outcome.

1. .BACKGROUND

Twin pregnancies make up 2% to 4% of all births. In fact, the incidence of spontaneous twin pregnancies varies around the world, with percentages ranging from 8/1000 to >17/1000 births. Globally, the rate of twin pregnancy is 12.0 per 1000 births during the last years (1, 2). The variation in twin pregnancy rates is thought to be due to dizygotic pregnancies, since monozygotic pregnancies have a consistent incidence of 3.5/1000 to 4/1000 births (1, 2). The incidence of twin pregnancies after the widespread use of assisted reproduction has increased significant-

ly. The rate of twin pregnancies using "in vitro fertilization (IVF)" or "microinsemination (ICSI)" is 20% to 40%, while using insemination and intrauterine insemination with controlled ovarian hyperstimulation (IUI-COH) with ovulation induction is 10% to 15%. Most twins resulting from assisted reproduction are dizygotic (3-6). The incidence of dizygotic twins after assisted reproduction can be significantly reduced by using the embryo selection method and the selective transfer of an embryo. However, the incidence of monozygotic twin pregnancies after assisted reproduction remains higher compared to spontaneous monozygotic twin pregnancies. In fact, the incidence of monozygotic twin pregnancies after assisted reproduction is 0.9%. Due to the rise in artificial insemination over the past 20 years, there has been an increase in twin and multiple pregnancies, raising concerns about an associated rise in long-term morbidity. Both monozygotic and monochorionic twins following IVF appear to be at elevated risk in relation to blastocyst transfer and maternal age (under 35 years) (6-8).

Another factor that keeps twin pregnancy rates high after assisted reproduction is parents preferences. It has been found that up to 60% of couples prefer twin pregnancies .

In particular, specifically the age of the woman, the period of infertility and attempt to conceive trying to achieve pregnancy, the desire to avoid many IVFs and the transfer of fresh embryos lead couples to choose to conceive twins. Multiple pregnancies lead to higher rates of prematurity and low birth weight (LBW) neonates. The incidence of twin/multiple pregnancies is increasing due to advanced maternal age and the increase in assisted reproduction. Does chorionicity matter in terms of twin outcome ? Approximately 3.1 percent of live newborns are from twin pregnancies and varies between different countries (3). This variety is attributed to the change in the frequency of dizygotes (DZ) while monozygotes (MZ) are stable. For the Caucasian race, most twins are dizygotic (70%) and 30% MZ. (in the absence of the use of assisted reproductive technology). Chorionicity refers to the type of placenta (monochorionic, dichorionic placentas).Dichorionic placentas may be united or separate, however their examination shows the absence of anastomoses between the 2 placentas (8-12).

2. OBJECTIVE

The goal of this retrospective study was to investigate the fetal outcome in twin pregnancies in the Department of Obstetrics and Gynecology of the Democritus University of Thrace and to compare these results with similar data from other international centers.

3. MATERIAL AND METHODS

In a 15-year retrospective study (2007-2022) of the records of deliveries performed at the University Obstetrics-Gynecology Clinic Alexandroupoli of the Democritus University of Thrace during the above period and data were collected regarding; the number of twin pregnancies, the age of the mother, the gestational age at delivery, the length of the cervix, the parity of the partici-

pating pregnant women, the modus of delivery, the birth weight, perinatal condition of newborns, the length of hospitalization time in the NICU, the percentage of twin pregnancies with assisted reproduction, the percentage of twin pregnancies with spontaneous conception, the percentage of twins among all deliveries, chorionicity , birth complications.

The retrospective study concerns twin pregnancies in order to investigate the following parameters:

- The frequency of twin pregnancies;
- The percentage of spontaneous conception or after assisted reproduction methods;
- Method of obstetric outcome;
- Determining the weeks of obstetric treatment of the reported pregnancies;
- Assessment of perinatal morbidity.

Ethical approval for this prospective study was confirmed by the ethics committee of the University Hospital in Alexandroupolis, Democritus University of Thrace, (Alexandroupolis, Greece; reference no. 8/33/25/6/2020). All patients provided written informed consent gave their written consent for their participation in the present study.

Statistical analysis

A retrospective study was conducted to analyze the final outcome of twin neonates. The data were analyzed with SPSS software. Relative (%) and absolute frequencies were presented for qualitative variables, while quantitative variables were presented using mean \pm standard deviation. Chi-square test (χ^2) was used for the univariate analysis of qualitative variables. Differences were considered as statistically significant at a p-value < 0.05 . SPSS 23 for Windows was used for the analysis.

4. RESULTS

In our study, we utilized data from 304 twin neonates The mean age of the mothers was 33,28 years old (min=23, max=43, SD \pm 3,36). The mean weight of the neonates was 1154,28mg (min=530, max=1500, SD \pm 253,3). 54,9%(n=167) of the pregnant women were having their second childbirth, whilst 28,3%(n=86), 14,1%(n=43) and 2,6%(n=8), their first, third and fourth childbirth, respectively. 54,9%(n=167) of conception's method were In Vitro Fertilization (IVF) and the remaining 45,1%(n=137)

	N	%	
Conception Method	IVF	167	54,9
	Normal procedure	137	45,1
Number of child-births of employment	I	86	28,3
	II	167	54,9
	III	43	14,1
	IV	8	2,6
Age(years,mean, SD)	33,28 \pm 3,36		
Weight(mg,mean, SD)	1154,28 \pm 253,3		
Chorionicity	Monochorionic	27	8,9
	Dichorionic	277	91,1

Table 1. Characteristics of the research sample

Medical Condition	N	%
Diabetes of pregnancy	15	37,8
Healthy	110	36,2
Thyroid medical condition	56	18,4
Diabetes of youth	16	5,3
Systemic Lupus Erythematosus	6	2
Rheumatoid Arthritis	1	0,3

Table 2. Medical conditions of the mothers

followed the normal procedure. Almost all the fetuses (91,1%, n=277) were dichorionic (Table 1).

More than 1/3 of the mothers (37,8%, n=115) were diagnosed with diabetes during pregnancy. A similar percentage (36,2%, n=110) didn't have any health problems. Of the remainder 18,4%(n=56) had thyroid problems, 5,3%(n=16) had juvenile diabetes, 2%(n=6) had Systemic Lupus Erythematosus (SLE) and 0,3%(n=1) had Rheumatoid Arthritis (Table 2). We attempted to examine the factors affecting the perinatal outcome among women in our study. Similar percentage of monochorionic and dichorionic neonates (25,4% and 25,9% respectively) eventually died, but we didn't find that chorionicity has a statistically significant correlation with perinatal outcome. Similar results were found when we tried to examine the effect of corticosteroids use to the neonates. More than ¾ (77%) of the neonates in which we administered corticosteroids had a normal growth, but again we didn't find that corticosteroids use has a statistically significant correlation with perinatal outcome. As a second analysis of the previous question, we attempted to examine the effect of corticosteroids the number of corticosteroids doses on the neonates. In our study we administered 1 or 2 doses of corticosteroids. Almost the same percentages in the 2 groups, 73,5% for 1 dose and 83,6% for 2 doses, had normal growth.

Finally, we attempted to examine the effect of pregnancy's duration to the final outcome of neonates. It is well known in literature that preterm babies born in 29 weeks and earlier have higher morbidity and mortality rates than babies born after 30 weeks of gestation. In our study these data are verified. We separated our samples into 2 categories according to the week they were born. We found that gestational age 30 weeks and above is significantly associated with normal growth as final outcome. The results from the univariate analysis can be found in Table 3.

5. DISCUSSION

Twin pregnancies are associated with a 2 to 3.5 times increased risk of pregnancy pathology compared to singleton pregnancies. The incidence of these complications ranges from 12.9 % to 37 % mainly after 20 weeks of gestation. Increased production of chorioplacental lactogen (HPL) causes insulin resistance, while weight gain during pregnancy, body mass index and maternal

age can lead to the onset of gestational diabetes. Also, the large increase in size of the uterus can lead to obstructive uropathy and UTIs, preterm delivery, placental abruption and premature rupture of membranes (PROM) as well as postpartum bleeding (13-16)

Women carrying multiples are 6 times more likely to deliver preterm and 13 times more likely to deliver before 32 weeks compared to singleton pregnancies. However, twins delivered before 32 weeks have twice the risk of

Variable	Perinatal outcome			
	Death (%)	Normal Growth (%)	Transfer (%)	P-Value
chorionicity				
Monochorionic	7 (25,9)	20 (74,1)	0	0.7
Dichorionic	70 (25,4)	204 (73,6)	3 (1)	
Corticosteroid use				
Yes	35 (31,8)	74 (67,3)		0.175
No	42 (22)	150 (77)	1 (0,9) 2 (1)	
Number of corticosteroid doses				
1 Dose	30 (24,8)	89 (73,5)	2 (1,7)	0.116
2 Doses	10 (16,4)	61 (83,6)	0	
Gestational age				
29 weeks and earlier	56 (35,2)	101 (63,5)	2 (1,3)	<0.001
30 weeks and above	21 (14,6)	123 (84,7)	1 (0,7)	

Table 3. Univariate analysis of the sample

cerebral hemorrhage, osteomalacia, and consequently stroke. of paralysis compared to babies from singleton pregnancies (17-22).

Preterm births affect 15 million newborns annually, with rates of 5% in European, 10% in American, and 18% in African countries. The leading cause of newborn fatalities and the main justification for neonatal hospitalization on a global scale is preterm delivery. Approximately 70 % and 36 % of neonatal and infant deaths are due to prematurity, respectively. Regardless of etiology, spontaneous preterm labor is the result of early cervical changes in length and dilation (23, 24).

Because obstetrician-gynecologists usually see pregnant women during the dynamic process of preterm labor, it is difficult to determine whether the cervix was actually incompetent or if some other process contributed to the changes in the cervix. This results in the diagnosis of cervical insufficiency. Uterus to be retroactively placed when a second-trimester miscarriage or premature birth has now taken place

Taking the above into consideration it is understandable that it is difficult to determine the true incidence of cervical insufficiency with studies suggesting that the true incidence is in the range of 1%. The presence of reduced cervical length during second trimester ultrasound assessment is associated with an increased risk of preterm delivery but is not sufficient to make a diagnosis

of cervical insufficiency (26-31).

In cases of twin pregnancies, the predictive value of measuring the length of the cervix is lower compared to singleton pregnancies. In singleton pregnancies, the increase in the risk of preterm birth is observed at around 15 mm, while in twins at around 25 mm. Although the limitations are larger than in singleton pregnancies due to uterine hypertension, the cervix should still be evaluated in twin pregnancies. Therefore, between weeks 18 and 22 of pregnancy is when the cervix should be measured.

Cervical length in twin pregnancies less than 25 mm at 24 weeks' gestation is associated with a 6.9-fold increase in the likelihood of delivery before 37 weeks compared with cervical length greater than or equal to 25 mm (OR 6.9; 95% CI 2.0, 24.2) Also, a cervical length of less than 25 mm has been found to increase the probability of delivery before 28 weeks' gestation from 3.5% to 25.8% and before 37 weeks' gestation from 41.2% to 75.5%. Analysis of twenty-one studies that measured of cervical length in women carrying twins concluded that a cervical length of less than 20 mm at a gestational age between 20 weeks and 24 weeks of gestation increases the risk of delivery before 32 weeks of gestation from 6.8% to 42.4% and the risk of delivery before 34 weeks of gestation from 15.3 % to 61.9 % (33-36).

Furthermore, serial measurements of cervical length using transvaginal ultrasound have begun to be suggested as a better predictor of preterm labor in women carrying twins. In fact, in a study where they measured the cervical length consecutively in 4 periods [18 and 21 + 6 / 7 weeks (period 1), 22 and 24 + 6 / 7 (period 2), 25 and 27 + 6 / 7 (period 3) and 28 and 32 weeks (period 4)] found that there was a statistically significant association between cervical length below the tenth percentile in each of the 4 periods and an increased risk of delivery before 32 weeks' gestation.

Specifically, during the 1st period the relative risk was increased by 7.2 times (RR = 7.2 (3.1 – 16.5), during the 2nd period by 15.3 times (RR = 15.3 (6.4 – 36.7), during the 3rd period by 10.3 times (RR = 10.3 (4.4 – 24.3) and in the 4th period by 23.1 times (RR = 23.1 (8.3 – 64.1) (33-36). Moreover, the benefit of consecutive measurements in the prognosis of preterm birth was demonstrated by the fact that compared to a single measurement, consecutive measurements in the 4 periods was associated with an increased rate of positive prognosis of preterm birth before 32 weeks of gestation from 28% (in one measurement) to 69% (in consecutive measurements).

And the positive predictive value increased from 5.21 (in one measurement) to 14.54 (in consecutive measurements), while the negative predictive value decreased from 0.76 (in one measurement) to 0.32 (in consecutive measurements) (33-36).

Funneling of the internal cervical os could also be used as an additional tool for predicting preterm labor in twin pregnancies. The sensitivity of internal cervical os at 22 weeks' gestation in predicting delivery before 32 weeks' and 35 weeks' gestation has been found to be 54% and 33%, respectively (33-36).

The specificity of cervical dilation at 22 weeks of gestation in predicting delivery before 32 weeks and 35 weeks of gestation is 89% and 91%, respectively. Furthermore, the sensitivity of finding a cervical length less than or equal to 30mm at 22 weeks of gestation for predicting preterm labor before 32 weeks and 35 weeks of gestation are 46% and 27%, respectively. The specificity of finding a cervical length less than or equal to 30 mm at 22 weeks of gestation for predicting preterm labor before 32 weeks and 35 weeks of gestation are 89% and 90%, respectively

The presence of funneling at 27 weeks of gestation had an increased sensitivity for predicting preterm birth before 32 weeks and 35 weeks of gestation (86% and 54%, respectively) with a specificity similar to that at 22 weeks of gestation (78% and 82%, respectively). Furthermore, the sensitivity of finding a cervical length less than or equal to 25 mm at 27 weeks of gestation for predicting preterm delivery before 32 weeks and 35 weeks of gestation is 100% and 54%, respectively 80. The specificity of finding a cervical length of uterine size less than or equal to 25 mm at 27 weeks of gestation for predicting preterm delivery before 32 weeks and 35 weeks of gestation is 84% and 87%, respectively (33-36).

In twin pregnancies, the risk of prematurity is significantly higher when the cervix appears shorter than 20 mm between 15 and 24 weeks of gestation, while in triplet pregnancies, a cervical length <25 mm between 15 and 24 weeks of gestation is associated with the occurrence of preterm birth below 32 weeks at a rate of 51%. In a study involving 464 twin pregnancies with ultrasound measurement of their cervix at 23 weeks (22-24 weeks) it was found that the risk of prematurity before 33 weeks was inversely related to the cervical length at this gestational age (33-36).

Specifically, the risk increases gradually from 2.5% when the length is 60 mm, to 5 % at a length of 40 mm, to 12 % at a length of 25 mm, to 17 % at a length of 20 mm and to 80 % at a length of 8 mm. In another multicenter prospective study with a sample of 383 twin pregnancies, it was found that the risk of preterm delivery before 28 weeks was 2.3% (1.5% for dichorionic twin pregnancies and 9.1% for monochorionic pregnancies), while before the risk of prematurity before 35 weeks of gestation reached 18.5% (17.1% for twin pregnancies and 29.5% for singleton pregnancies). The positive predictive value was 5 % for cervical length less than or equal to 20 mm, 7–8 % for length less than or equal to 25 mm, 16–17 % for length less than 30 mm and 34–48 % for length less than 35 mm (33-36).

The negative predictive value ranged from 1.2% at 28 weeks to 18.6% at 35 weeks. Therefore, based on the available studies on twin pregnancies, the ultrasound assessment of the cervical length around the 23rd week of pregnancy appears to be a useful diagnostic tool in the prediction of premature birth, with the limit of the critical length for a "short-dangerous" cervix being is set at 20–25 mm depending on the results of each study.

In fact, it has been estimated that approximately 58% of twins will be born before 37 weeks while 12% will be born before 34 weeks of gestation. Although births un-

der 32 weeks of gestation are constitute only 1% to 2%, essentially these births are due responsible for 50% of long-term neurological problems as well as for and 60% of neonatal mortality. For this reason, the goal should be the early prediction and delay of preterm labor so that the final termination of labor is done occurs after 32 weeks of pregnancy (33-36).

Also, severe neonatal morbidity has been shown to occur at birth weights of less than 1500 grams. In particular, it is estimated that 10% of live neonates born below 1500 grams will develop mental retardation, vision problems, or behavioral issues. This implies that when preterm delivery occurs below 32 to 34 weeks of gestation, most obstetricians and gynecologists use aggressive treatment to prevent preterm delivery.

The administration of a cortisone regimen may have contributed positively to the excellent perinatal outcome, although the usefulness of cortisone in twin pregnancies has not yet been clarified, which was confirmed in our study (Table 3).

According to our study results we found no significant correlation between cortisone use, the number of cortisone doses administered and chorionicity and perinatal outcome (P-Value 0.7, p 0.175, p 0.116) but a significant positive association was found with pregnancies earlier than 29 weeks and later than 30 weeks (P-Value < 0.0001) (Table 3).

Twin pregnancies are responsible for 10% of perinatal mortality and 60% of abnormal fetal positions.

In recent years, an increase in the frequency of twin pregnancies after spontaneous conception has been observed in developed countries, a fact that is mainly due to the decision to have children at a more advanced age 6% against 2.3% 4 years ago. In addition, an increase in the incidence of twin pregnancies worldwide was found during the last decade as a result of the increased demand for assisted reproduction methods. Twin pregnancies are characterized by a greater morbidity and perinatal mortality, as well as a greater maternal morbidity and mortality attributable primarily to the greatest danger of bleeding. There is an increase in the relative risk of stillbirth as well as an increased risk of adverse events during childbirth (37-38).

Neonatal mortality rates for twins compared to singleton pregnancies is 4.3/1000 versus 3.8/1000 for neonates weighing 2501-3000g, and 7.4/1000 versus 2.2/1000 for neonates weighing >3000g. This study also found twice the mortality during childbirth. In the same study it was further discovered that the above mortality for twins weighing >2500g is 1.221/1000 compared to a corresponding 0.34/1000 for singleton pregnancies (37-38).

The risk of perinatal death of twins has decreased over the past three decades, but a smaller reduction is observed in the most mature neonates (34-37 weeks) compared to the least mature ones. A higher perinatal mortality was also observed in twin neonates with a birth weight >2500g compared to equivalent weight neonates of singleton pregnancies (39-42).

Also important factors that influence the Obstetrician towards the choice of elective CS are the often found

relatively advanced (>35 years) age of the participants, as well as the fact that the majority are first-borns. In cases of premature labor or severe intrauterine growth retardation, most recommend performing CS in pregnancies <32 weeks or when the birth weight is <1500g (42-45).

Regarding the method of conception, twin pregnancies after IVF, ICSI show a higher frequency of premature deliveries, births of newborns with low birth weight, and other complications. The risk of stillbirth increases after the completion of the 37th week of pregnancy and is 6-9 times greater in dichorionic twins and even more in monochorionic twins therefore, performing an elective CS at the 37th week for dichorionic twins and the 36th week for monochorionics is considered a reasonable option. The International society for twin studies and the SOGC recommend delivery before the completion of the 38th week of pregnancy and the suggest planning of a selective low transverse Caesarean section at the 38th week as a logical option. Absolute indications for performing CS are monoamniotic twins due to a high risk of prolapse of the umbilical cord, conjoined twins situation where the presentation of the first twin is not cephalic, and other absolute indications (42-45).

When the presentation of the 1st of the fetuses is in breech, a CS is recommended due to wedging and inability to descend the protruding parts through the pelvic canal, especially when the presentation of the 2nd is cephalic. Although this scenario very rare, it is associated with high perinatal mortality

Traditionally, when the presentation of the first is cephalic and there are no other complications, a vaginal delivery can be attempted. However, there is a lack of well-designed prospective studies. Even when the presentation is cephalic, the approach to vaginal delivery remains debatable due to the obstetric complications that may appear after the delivery of the 1st fetus (placental abruption, umbilical cord prolapse, fetal bradycardia). In this case, increased incidence of post-operative maternal infection should also be taken into account, emergency CS for the birth of the 2nd fetus becomes necessary (46-50).

According to the same study, the main cause of neonatal death in relation to vaginal delivery of the 2nd fetus is fetal asphyxia-acidosis. This condition can also cause cerebral palsy. It should also be noted that the majority of younger Obstetricians due to lack of sufficient training-experience may struggle to manage the increased requirements of Midwifery especially when the presentation of the second twin is not cephalic. According to the findings of Cerulo et al who applied a liberal policy regarding the choice CS when the presentation of the 2nd was not cephalic, an incidence of 84% of CS was recorded. There were similar rates of neonatal morbidity and mortality between the 2 twins. The decision on the method of delivery in twin pregnancies is increasingly challenging for the modern Obstetrician due to the large number of twin pregnancies resulting from the frequent use of assisted reproduction methods. The incidence of stillbirths and perinatal morbidity and mortality are greater in twin pregnancies. Several studies have shown

that vaginal delivery of the second fetus is associated with increased perinatal morbidity and mortality, suggesting that elective CS in all twin pregnancies may significantly protect the second fetus (51-56).

6. CONCLUSION

In twin pregnancies according to our results the chorionicity and antenatal corticosteroid use, as well as the the number of administered corticosteroid doses did not significantly improve the perinatal outcome. However, a significant association was found between the perinatal outcome and the pregnancy week in which the labor was performed. Satisfactory results were found in cases where labor occurred later than 30th week. Furthermore multicentric future studies are necessary to confirm our findings and to investigate more factors to improve the perinatal outcome.

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- **Authors contribution:** MG designed the study and MK collected the data. All authors analyzed the data and gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved..
- **Conflict of interest:** The authors declare no conflict of interest.
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