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Multicentric Multiple Pregnancy Study I - Epidemiology

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Abstract

Objective: The aims of the study are to determine multiple pregnancy ratios in our country, the relationship between multiple pregnancies and assisted reproduction tecniques (ART), birth and pregnancy characteristics of multiples and maternal and fetal complications related to multiple pregnancies.

Methods: A questionnaire was sent to 20 research and education hospital for asking singleton and multiple birth numbers, abortion, vaginal and cesarean delivery ratios in multiple pregnancies and the number of pregnancies achieved with ART between 2003 and 2004. Furthermore, it was also asked maternal age, pregnancy and delivery numbers, age of pregnancy at delivery, mode of delivery, newborn's weigth, sex and mortality ratios, also maternal mortality and morbidity parameters with a more detailed form.

Results: Number of births was 70.091 in centers joined to the study (n:15), 1.86% of them was twins and 0.07% of them was triplets. The ratio of abortion in multiples could not determined, whereas mode of conception could be determined in 37% of cases. 76% of twins and 90% of triplets was achieved with ART. The gestational age at birth and birth weigth in twins were 34.41±3.28 and 2171.69±674.30g, respectively, whereas they were 31.30±3.64 and 1442.70±544.68g in triplets, respectively. Furthermore, 61% of twins and 98% of triplets was born with a birth weigth under 2500 g. The lost of at least one baby in antenatal period or birth was found in 15.52% of twins and in 19.82 % of triplets Cesarean ratio was 63% in twins and 83% in triplets. In one in every two multiple pregnancies, at least one morbidity factor such as preeclampsia, gestational diabetes, preterm delivery or PROM was found.

Conclusion: ART may be responsible in 75% of multiple pregnancies. Abortion rates related to the multiple pregnancies was not known generally. Increased number of preterm delivery and its consequences such as fetal morbidity and mortality, increased cesarean ratios and increased number of maternal complications are all important problems in multiple pergnancies. To avoid creating multiple pregnancies in ART clinics seems the simpliest solution of the problem.

Keywords: Multiple pregnancy, questionnaire, epidemiology.

Çok merkezli çoğul gebelik çalışması 1 - Epidemiyoloji

Amaç: Çalışmanın amacı ülkemizdeki çoğul gebelik oranlarını, Yardımla Üreme Teknikleri (YÜT) ile ilişkisini, çoğul gebeliklere ait gebelik ve doğum özellikleri ile maternal ve fetal komplikasyon oranlarını ortaya koymaktır.

Yöntem: Yirmi değişik Kadın Hastalıkları ve Doğum Merkezine gönderilen anket formlarının yardımı ile 2003-2004 yıllarındaki tekil, çoğul, abortus, sezaryen ve vaginal doğum oranları ile YÜT sonucu oluşan gebelik sayıları sorulmuştur. Ayrıca daha ayrıntılı bir anket formu ile, çoğul gebeliklerde anne yaşı, gebelik ve doğum sayıları, doğum haftası ve şekli, yenidoğan ağırlığı, cinsiyeti ve mortalitesi, ayrıca maternal morbidite-mortalite parametreleri sorgulanmıştır.

Bulgular: Çalışmaya katılan merkezlerdeki (n:15) doğum sayısı 70.091 olup bunların %1.86'sını ikizler, %0.07'sini üçüzler oluşturmuştur. Çoğul gebeliklerdeki abortus oranları belirlenemezken, gebeliğin oluşma şekli (spontan-YÜT) %37 olguda saptanabilmiştir. İkizlerin %76'sı, üçüzlerin %90'ı YÜT ile gebe kalmışlardır. İkizlerde doğum haftası 34.41±3.28, yenidoğan ağırlığı 2171.69±674.30g bulunurken, bunlar üçüzlerde sırası ile 31.30±3.64 hafta ve 1442.70±544.68g bulunmuştur. İkizlerin %61'i, üçüzlerin %98'i 2500g ve altında doğmuştur. İkizlerin %15.52'sinde, üçüzlerin %19.82'sinde gebelikte en az bir fetusun antenatal dönemde veya doğum-

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da kaybedilmiş olduğu belirlenmiştir. Sezaryen oranı ikizlerde %63, üçüzlerde %83 olarak belirlenmiştir. Her iki çoğul gebeden birinde preeklampsi, gestasyonel diyabet, erken doğum veya membran rüptürü gibi en az bir tip morbidite kriterine rastlanmıştır.

Sonuç: Çoğul gebeliklerin %75'inden YÜT kullanımı sorumlu olabilir. Bunlara bağlı abortusların sayısı genelde bilinmemektedir. Çoğul gebeliklerde erken doğum ve bunun yol açtığı fetal morbidite-mortalite ile sezaryen oranlarındaki artış, ayrıca maternal morbidite yadsınamayacak düzeydedir. YÜT kullanımında çoğul gebelikten kaçınılması çözüme katkıda bulunabilecek en basit önlem gibi görünmektedir.

Anahtar Sözcükler: Çoğul gebelik, anket, epidemiyoloji.

Introduction

In the last 20 years, incidence of multiple pregnancies increased dramatically in developed and developing countries due to increasing use of ART and technological developments in this area. Generally, societies accept multiple births as a normal and "nice" event and they expect a good and normal prognosis for both baby and the mother due to media's presentation of this pregnancy complication. On the contrary, physicians who provide health care to these pregnant patients accept multiple pregnancies as a pregnancy complication and these women are required close follow -up. Indeed, beside increased medical complications in mothers, the possibility of complications such as prematurity related to preterm delivery, low birth weight, twin to twin transfusion syndrome in monozygotic twins and risk of congenital anomalies and chromosomal defects increases morbidity and mortality in fetus and newborn.[1-8]

Although it is mentioned that the rate of multiple pregnancies increased in our country in recents years, rate of multiple pregnancies, the factors influence multiple pregnancy rates, maternal and fetal morbidity and mortality related to these pregnancies has not been studied extensively before. Of course increasing number of ART centers and increased use of ART in our country make contribution to this increase in multiple pregnancies. On the other hand, in recent years increasing number of patients profit from infertility treatments due to paying expenses of these treatments by social security institutions. But, multiple pregnancies and related complications due to these infertility treatments are not considered. The need for newborn intensive care units increases because of increased number of preterm birth and low birth weight infants due to multiple pregnancies and preterm babies who do not find a place in these units create a serious area of problem medically, socially and ethically. If we consider that preterm births are still not preventable, we will understand better the contribution of multiple births to the problem.

The aim of this multicentric cross sectional study is providing the rate of multiple pregnancies in our country, the relationship with ART, abortion rates, delivery characteristics and maternal and fetal complications of multiple births.

Methods

This study performed between 2003-2004 with sending questionnaire to the Obstetrics Departments of 20 University and Education and Research Hospitals in different regions of Turkey. In the first section of questionare, it was asked singleton, twin and triplet and quadruplet births, also cesarean and vaginal delivery rates in multiples and ART pregnancy numbers. In the second section of questionare, with a detailed form beside above informations, it was investigated type of conception such as spontaneous, ovulation induction (OI) and intrauterine insemination (IUI), in vitro fertilization (IVF) and intra cytoplazmic sperm injection (ICSI). Furthermore, mother's age, the number of pregnancy and births, weeks of birth and mode of

delivery, newborn wieght, sex and mortality, maternal mortality-morbidity parameters such as preeclampsia, diabetes, preterm premature rupture of membranes (PPROM) and preterm labor were asked.

Results

15 centers answered the questionnaire. 9 of these centers were university hospitals, six of them were education and research hospitals. 15 of centers answered first section of questionnaire, whereas 10 of them completed both sections.

Total number of births in participated 15 centers was 70.091 between 2003-2004. Among these, 68.726 were singleton, 1310 were twins, 53 were triplets and two were quadruplets. According to these numbers, twin's, triplet's and quadruplet's prevalance was 18.6/1000, 0.75/1000, 0.03/1000, respectively. Twins constituted 96 % of multiples. Regarding cesarean rates, triplets were followed by twins and singletons (Table 1).

In the section of abortion rates, only four centers answered and only one of them was considered. In the section of type of conception, 11 centers provided information and information about singletons in this section was found inadequate. It was concluded that information about type of conception provided better in multiples.

Total birth number was 43.258, number of twins and triplets were 818 (1.89 %) and 42 (0.09%), respectively in 10 centers given detailed information. In this group, cesarean ratios were 39.6 %, 73.4 %, 73.8 % in singletons, twins and triplets, respectively. Cesarean ratio was higher in university hospitals than education and research hospitals in singleton pregnancies (%35.7 and % 47.7), whereas they were similar in twins (%74.8 and % 71.6).

Table 1. Cesarean and vaginal delivery rates in singleton, twin and triplet gestations.

	Singleton	Twin	Triplet
Cesarean	34864 (50.72%)	819 (62.50%)	44 (83.00%)
Vaginal delivery	33862 (49.28%)	491 (%37.50%)	9 (17.00%)
All	68726 (98.50%)	1310 (% 1.86%)	53 (0.075%)

Table 2. Demographic data in multiple pregnancies.

	Twin (n:792)	Triplet (n:37)	All (n:829)
Age (Mean±SD)	27.91±5.36	28.77±4.28	27.98±5.32
Number of pregnancies (Mean±SD)	2.40±1.90	2.20±2.41	2.37±1.93
Number of births (Mean±SD)	1.10±1.66	0.97±2.19	1.07±1.70

Table 3. Type of fertilization in twin and triplet gestations.

	Spontaneous	OI-IUI	IVF-ICSI	All
Twin (%)	64 (24.15%)	84 (31.70%)	117 (44.15%)	265
Triplet (%)	4 (10.00%)	11 (27.50%)	25 (62.50%)	40
All (%)	68 (22.29%)	95 (31.14%)	142 (46.55%)	305

OI: *Ovulation induction,* ***IUI:*** *Intra uterine insemination,* ***IVF:*** *In vitro fertilization,* ***ICSI:*** *Intra cytoplasmic sperm injection*

Table 4. Gestational age at birth, mean birth weigth and sex.

	Twin (n:792)	Triplet (n:37)
Gestational age at birth (mean ± SD) (weeks)	34.41±3.28	31.30±3.64
Birth weigth (g) (mean± SD)	2171.69±674.30	1442.70±544.68
Male	808 (52.67%)*	62 (55.85%)
Female	721 (47.00%)*	48 (43.24%)
Sex unknown	5 (0.30%)	1 (0.09%)

**: p<0.01*

Table 5. Birth weigth in twin and triplets (n: 829)

Weigth of the newborn	Twin (n:2x792: 1584)	Triplet (n:3x37:111)	Multiple (n:1695)
≤ 2500 g	979 (61.80%)	109 (98.20%)	1088 (64.19%)
≤ 2000 g	584 (36.87%)	85 (76.58%)	679 (39.47%)
≤ 1500 g	251 (15.84%)	63 (56.75%)	314 (18.52%)
≤ 1000 g	100 (6.31%)	21 (18.92%)	121 (7.14%)
≤ 500 g	26 (1.46%)	5 (4.50%)	31 (1.83%)

Table 6. Gestational age at birth (n: 575).

Gestational age at birth	Twin (n:552)	Triplet (n:23)	Multiple (n:575)
≤ 37 hafta	474 (85.87%)	23 (100%)	497 (86.43%)
≤ 34 hafta	242 (43.84%)	20 (86.95%)	262 (45.56%)
≤ 28 hafta	39 (7.06%)	5 (21.74%)	44 (7.56%)
≤ 24 hafta	14 (2.54%)	1 (4.35%)	15 (2.61%)

Table 7. Mortality rate in twin gestations.

	Twin (n:451)
Both fetuses	35 (7.76%)
One fetus	35 (7.76%)
At least one fetus	70 (15.52%)

Demographic data of 829 multiple pregnancies, consist of 792 twins and 37 triplets, which detailed information could be obtained was shown in Table 2. The mean age of the investigating group was 27.9, mean number of pregnancies was 2.4 and mean number of birth was 1.1.

If we look at the type of conception in multiples, ART pregnancies were major part of 265 twins and 40 triplets (Table 3). 24% of twins and only 10% of triplets occurred spontaneously. The mode of conception was obtained only in 37 % of the cases.

Tablo 8. Reasons and rates of maternal morbidity.

	Preeclampsia	Preterm	PPROM	Gestational Diabetes	HELLP	All
Twin (n:210)	44 (20.95%)	29 (13.81%)	23 (10.95%)	8 (3.91%)	3 (1.43%)	107 (50.95%)
Triplet (n:34)	8 (23.52%)	9 (26.47%)	6 (17.64%)	2 (5.88%)	1 (2.94%)	26 (76.47%)

The mean gestational week on delivery was found 34.41±3.28 in twins, and 30±3.64 in triplets. The mean birth weight in twins and triplets was 2171.69±674.30g and 1442.70± 544.68g, respectively. It was observed that male sex was higher than girls in all groups ($p<0.01$) (Table 4).

The mean birth weight distribution of 829 multiples was shown in Table 5. The cases only one newborn's birth weigh below 2500g constituted 10.80 % of twins (n: 171), whereas both newborns below 2500g constituted 28.60 % of cases (n: 453) and at least one newborn below 2500g was 39.40 %. It was found that 61 % of twins were below 2500g and in triplets this ratio was 98 %. Furthermore, the chance of being below 2000g, 1000g and 500g at birth in triplets was found two, three and three times higher than twins, respectively.

The distribution of the mean gestational week on delivery of 575 multiples was shown in Table 6. If we look at preterm birth ratios, 86 % of twins were born before 37th weeks of gestation. Furthermore, 44 % of twins, 87 % of triplets were born at and before 34th weeks of gestation. The probability of birth before 34th, 28th and 24th weeks of gestation in triplets was found two, three and two times higher than twins, respectively.

The fetal mortality rate (death before or at birth) of 451 twins was 7.76 % (n: 35) in both twins. The rate of mortality in one of the twins was also found same (7.76%) (Table 7).

It was observed that all of the triplets were born at or before 37th weeks of gestation and 94.59 % of newborns were born below a birth weigth of 2500g. Fetal mortality in triplets was 10.81 % in one newborn, 5.4 % in two of the newborns, and 16.21% in all three newborns, whereas total mortality rate was found as 19.82%.

In terms of maternal morbidity and mortality, 107 of 210 twins (50.9%) had at least one morbidity factor, however maternal mortality was reported in none of them. 26 of 34 triplets had at least one maternal morbidity factor (76.4%), with any maternal mortality (Table 8).

Discussion

Whereas advances in technology and social developments causes increase in multiple pregnancies, management and complication of these pregnancies is one of the biggest problem related to pregnancy in all societies. The multiple birth ratios in our study were found 1.94 %. The twins in all births were 1.86 %. This ratio was reported as 0.98 % before in another study based on maternity hospital data.[9] The accepted ratios from different parts of world are between 1-3 %.[1,3,5]

Although multiple births issue is accepted as a nice event in society, in recent years increasing number of multiples and special problems related to these pregnancies causes increase in worries about this issue. Over the past two decades, an epidemic of multiple births has taken place in the developed world due to the widespread use assisted reproductive technology. Looking at the epidemiologic studies in the literature, it was observed that monozygotic (MZ) twinning ratios remained constant in years and begin to rise after increasing use of ART. It was postulated that micromanupilation technique used in IVF may increase MZ twins probability.[1,6]

Preterm birth and prematurity is the most important factor that determine neonatal morbidity and mortality in multiples.[8,10] In a controlled study from our country, preterm birth incidence was found higher in twin pregnancies obtained with ART, when compared with spontaneous twin pregnancies (47% versus 55 %).[11]

56% of ART pregnancies consist of twins and 12.8 % of them consist of triplets and higher order pregnancies. The contribution of ART to

multiple pregnancies was reported as 50-80%.[10] Güney et al.[11] excluding ICSI cases and higher order multiples in their study and reported that 33 % of twin pregnancies occurred after IVF. Yıldırım et al.[9] reported that ART takes places in the etiology of twinning in 16 % of cases. In our study, we observed that only a small part of twins and triplets occured spontaneously (22%), ART was used in more than ? of multiples. The difference between ratios may be due to the study design (retrospective, questionnaire etc.) or defects in interrogation. The tendecy of families to preserve and not to report ART history in our country may affect the rations in the literature.

Multiple pregnancies both after ART and occured spontaneously, bring maternal and fetal risks.[12-18] Chorionicity in twin pregnancies is extremely important in terms of complications. Fetal risks increase in monochorionic pregnancies.[13] IUGR, preterm delivery, TTTS are all best examples.[12] In Yıldırım et al.[9] study from our country, perinatal mortality and neonatal morbidity was found higher in monochorionic pregnancies. On the other hand, higher incidence of monozygotic conceptions in ART pregnancies may be a protecting factor from other general complications.[19] Yıldırım et al.[9] reported monochorionic twinning as 15%, whereas Güney et al.[11] in their series of 104 cases of spontaneous twins, determined monozygocity as 20%, and reported that this ratio decreased to 3% in IVF pregnancies. However, in the same study, premature rupture of membranes and preterm delivery were found more often in IVF pregnancies. One of the limitations of our study is that no data exist related to chorionicity. Because of absence of a question about this issue in the questionare and also defects in the registration systems, obscured to reach reliable data about multiple pregnancies.

Whatever they occured, one of the most important complication related to multiple pregnancies is prematurity. Multiple pregnancies are responsible in 25% of all preterm births.[12] In a study, preterm delivery ratio below 37th week in twin pregnancies was reported between 42 % and 68%.[14] In our study, we determined most of the twin and triplet pregnancies ended before 37th weeks of gestation.

Moise et al.[20] observed that low birth weight occured 60-70% of twin pregnancies. Güney et al.[11] reported that 51-65% of twins were born below 2500 g, 10-15% of them were born below 1500 g. In our study, these ratios were determined as 61% and 16%, respectively. Yıldırım et al.[9] reported that mean birth weigth in dichorionic and monochorionic twins was between 2037 and 2053 g, whereas Güney et al.[11] reported this between 2090 and 2210 g in spontaneous and IVF pregnancies. In our study, mean twin birth weigth was 2171 g.

In all delivery weeks, preterm delivery may cause complications such as respiratory distress syndrome, necrotizing enterocolitis and intraventricular haemorrhage. Most of the twin pregnancies were born between 34 and 37 weeks of gestation, in late preterm period, because of obstetric complications and preterm labor. Although mortality and morbidity in late preterm period was lower when compared to births before 34th weeks of gestation, low birth weight and prematurity related complications still exist and should be considered.[17,18] In our study, mean delivery week in twins was 34.4 and similar to other studies.[9,11]

Perinatal mortality rate was reported as 7.7% in the study of Güney et al.,[11] 7.8% in the study of Karlık et al.[21] and 8.9% in the study of Yıldırım et al.[9] In our study, this ratio was found as 15 %, higher than other studies, due to including all fetuses after 20 weeks and also maternal complications.

Preterm delivery rate was even higher in triplets and higher order pregnancies. 42% of babies in this group were delivered before 32th weeks of gestation, 14% of them were delivered

before 28th weeks of gestation. 73% of them need neonatal intensive care unit.[17] If we considered insufficient number of neonatal care units in our country, it is obvious that preterm births due to multiple pregnancies and insufficient number of ventilators and places in neonatal intensive care units bring ethical, moral and legal problems together. In our study, the fetal mortality and low birth weight ratio was found high and agreed with literature.[22]

Female sex was reported higher than boys in multiple pregnancies.[11,21] We found a contrary data in our study. It could be explained by male dominance due to increased ART pregnancies and time difference between studies.

Maternal complications such as preeclampsia, hypertension, gestational diabetes, ablatio and placenta previa, preterm birth increase in multiple pregnancies.[10,12,14] Yıldırım et al.[9] determined the rate of maternal morbidity as 16%. In our study this ratio (if preterm delivery is not considered) was found 26% for preeclampsia and gestational diabetes. Besides these, maternal complications such as premature rupture of membranes and preterm labor were also found high and agreed with literature.[10,13,15,17]

In our study, 2/3 of twins and almost all triplets were delivered by cesarean. The contribution of multiple pregnancies to increase cesarean rates in our country is obvious. Güney et al.[11] reported the incidence of cesarean in spontaneous twins as 67% and in IVF twins as 84%. Decreasing multiple pregnancies should be in preventive strategies for decreasing cesarean rates.

Conclusion

As a result; multiple pregnancies besides higher perinatal mortality ve morbidity cause increase in maternal morbiditity and mortality. As a restricted public survey study, in this study, it was found that the main reason of increased rates of multiples which the incidence was 1.94% in all deliveries was ART. Both preterm delivery and prematurity risks related to multiple pregnancies and increased pregnancy risks of ART, management of infertility patients makes it special. When these couples are informed about treatments, complications of multiple pregnancies should be mentioned. Preventive measures such as single embryo transfer, restricted use of gonadotrophins, using cryopreservation tecnique can be used for obtaining singleton pregnancies.

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