

Multiple pregnancy and preterm labor

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ABSTRACT

Objective: Multiple gestations are high risk pregnancies, which may be complicated by pre-maturity, low birth weight infants, pre-eclampsia, anemia, postpartum hemorrhage, intrauterine growth restriction, neonatal morbidity and high perinatal, neonatal and infant mortality. This study was carried out to determine the incidence and effect of multiple pregnancies on pre-term labor in tertiary care hospitals.

Methods: Retrospective case record analysis of 375 cases of multiple pregnancies that were reported at Armed Forces Hospital and King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, between January 2000 and December 2001. The data was analyzed to determine the incidence of multiple pregnancies and its effect on pre-term delivery.

Results: The over whole incidence of twins was 14/1000 births. Premature labor in multiple pregnancies was 7 times greater than singletons (42% versus 6.4%). Almost half of multiple pregnancy cases were delivered by cesarean section (49% versus 14%). Pregnancy was induced in 34% of cases. Cervical cerclage was applied

in only 8% of cases and betamemetics were administered to only 11% of cases. Fetal distress in labor, abnormal presentation and previous uterine scar were the main indications for cesarean section. Fifty percent had no antenatal complications, gestational diabetes complicated 16%, and anemia was reported in 22% of cases.

Conclusion: Preterm delivery remains the most serious complication of multiple pregnancies. Multiple gestation children may suffer long term sequel of prenatal complications, including cerebral palsy and hearing disabilities. Every effort should be made to reduce the risk of multiple gestation and pre-term labor through proper control and close monitoring of fertility drugs, limiting number of embryo transfer to maximum of 3 or only 2, improving the socioeconomic status of expectant mothers, reduce cigarette smoking, relieve maternal stress, restriction of maternal activity, frequent contact with health care personnel and treatment of any obstetric or medical disorders.

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In the United States of America (USA) in 1995 while multiple birth constituted 2.6% of all births, it accounted for 20% of all low birth weight infants, 13% of all pre-term deliveries and 14% of all neonatal deaths.¹ The world wide increase in the rate of multiple pregnancies over the last 2 decades was related to the use of fertility drugs for ovulation induction and in vitro fertilizations (IVF)² and a shift towards bearing children at older maternal age >30 years.³ Pre-term delivery, toxemia of pregnancy and anemia remain the most important complications of multiple pregnancies.⁴ The

incidence of pre-term delivery is significantly elevated in multiple pregnancies and consequently, the incidence of low/very low birth weight infants and perinatal mortality.⁵ Almost half of deliveries occurred prematurely (<37-weeks' gestation). This increase adds substantially to medical costs.² The increase in the number of multiple births was associated with 3-4 fold increases in the risk of cerebral palsy for babies from multiple births. Babies weighing <1500gm at birth have a 60 fold increase in the rate of cerebral palsy compared with babies weighing 2500 gm or more.⁶

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Methods. A retrospective case record analysis of all multiple pregnancies and deliveries at Armed Forces Hospital (AFH) and King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia, during the period of January 2000 through to December 2001 was carried out. The data collected was analyzed to determine the incidence of multiple pregnancy, maternal age, parity, pregnancy complications, postpartum complications, mode of delivery, indications for cesarean section, sex ratio, and effect of multiple pregnancies of preterm deliveries. The AFH and KKUH are tertiary care hospitals conducting around 8000 and 5000 deliveries per year. The hospital population is relatively constant. In view of this consistency and, to make data meaningful it was felt necessary to add the data together. Antenatal clinics are held daily. Unbooked mothers account for 10% of hospital population. The routine antenatal admission for bed rest, use of tocolytics, administration of corticosteroids, and application of cervical cerclage is not a routine practice in either unit for multiple pregnancies. Twins with scarred uterus and multiple pregnancy of higher order are delivered by cesarean section. In labor, fetal heart and uterine contractions are monitored continuously. A portable ultrasound scan machine is available in the delivery room to determine fetal position and presentation.

The aim of this study was to determine the overall incidence of multiple pregnancy and its effect on prematurity and perinatal mortality as compared to singleton. Chi-square was used for statistical analysis. *P* value <0.05 was considered significant.

Results. During the study period, there were 375 cases of multiple pregnancy reported. This gave an overall incidence of twins of 14/1000 births, and that of triplets of 0.72/1000 births. **Table 1** shows analysis of obstetrics population in the 2 units. A total of 24993 mothers were delivered and 1450 (5.8%) instrumental deliveries were carried out. Cesarean section was performed in 3548 (14.2%) cases. A perinatal mortality rate of 13 per thousand was reported. The incidence of twins was 1:73 at AFH as compared to 1:68 at KKUH. There were 11 sets of triplets at AFH and 7 sets of triplets at KKUH. **Table 2** shows the maternal characteristics. Pre-mature labor occurred in 42% of multiple pregnancies. Cervical cerclage was applied in 8% of cases and 11% required tocolytics. Pregnancy was induced in 34% of cases. Forty-nine were delivered by cesarean section as compared to 14% of general obstetrics population. **Table 3** shows the indications for cesarean section. Abnormal presentation of first twin or both was the leading indication in 25% of cases. Previous cesarean section (16%) and fetal distress (18%) were the

Table 1 - Obstetrics population (Armed Forces Hospital and King Khalid University Hospital 2000-2001).

Variables	AFH	KKUH	Total
Total n of deliveries	15818	9175	24993
Total n of instrumental deliveries	675	755	1450
(%)	4.3	8.2	5.8
Total n of cesarean sections	2326	1222	3548
(%)	14.7	13.3	14.2
Total stillbirths	123	98	221
Stillbirth rate	7.8	10.7	8.8
Total neonatal deaths	74	29	103
Neonatal death rate	4.7	3.2	4.1
Perinatal mortality rate	12.4	13.8	13
Maternal deaths	1	0	1
Twins	218	135	353
Incidence	1:73	1:68	1:71
Per thousand	13.8	15	14
Triplets	11	7	18
Incidence per thousand	0.7	0.76	0.72
Quadruplets	0	3	3
Sextuplets	0	1	1
AFH - Armed Forces Hospital KKUH - King Khalid University Hospital			

Table 2 - Maternal characteristics.

Characteristics	AFH	KKUH	Total
Maternal age (\pm SD)	30.8 \pm 0.42	30.1 \pm 0.47	30.4 \pm 0.44
Parity (\pm SD)	2.8 \pm 0.25	2.4 \pm 0.20	2.6 \pm 0.22
Mean gestational age at delivery (weeks) (\pm SD)	34.6 \pm 0.30	35.8 \pm 0.35	34.7 \pm 0.32
Mean birth weight (grams)	2175 \pm 650	2235 \pm 740	2210 \pm 450
Booked (%)	203 (88.6)	143 (98)	346 (92)
Premature labor	93 (41)	66 (45)	159 (42)
Cervical cerclage	19 (8.3)	11 (7.35)	30 (8)
Tocolytics	15 (6.5)	26 (17.8)	41 (11)
Corticosteroids	68 (30)	35 (24)	103 (27)
Spontaneous labor	175 (77)	97 (66)	273 (73)
Induced labor	32 (14)	12 (8)	44 (12)
Spontaneous pregnancy	143 (62)	106 (73)	249 (66)
Induced pregnancy	86 (38)	40 (27)	126 (34)
Vaginal delivery	116 (51)	75 (51)	291 (51)
Cesarean section	113 (49)	71 (49)	184 (49)
Cesarean section second twin	6 (3)	6 (4)	12 (3.2)
Males	231 (50)	145 (47)	376 (48)
Females	238 (50)	162 (153)	400 (52)
AFH - Armed Forces Hospital KKUH - King Khalid University Hospital			

Table 3 - Indication for cesarean section.

Indication	AFH (n=113)	KKUH (n=71)	Total (n=184)
Breech Twin I	14	20	34 (18)
Previous cesarean	18	11	29 (16)
Second twins	6	6	12 (6.5)
Fetal distress	25	8	33 (18)
Cord prolapse	3	6	9 (4.9)
Abnormal presentation	5	8	13 (7)
Failure to progress	9	3	12 (6.5)
Twin-Twin transfusion	3	0	3 (1.6)
IVF pregnancy	8	0	8 (4.3)
Ante-partum hemorrhage	7	0	7 (3.8)
Herpes gestationalis	1	1	2 (1)
One twin IUFD	0	3	3 (1.6)
Intrauterine growth restriction	7	1	8 (4.3)
Multiple pregnancy of higher order	7	3	10 (5)
Pre-eclampsia	4	1	5 (2.5)

AFH - Armed Forces Hospital
 KKUH- King Khalid University Hospital
 IVF - in vitro fertilization, IUFD - Intra-uterine fetal death

Table 4 - Antenatal complications.

Complication	AFH	KKUH	Total
None	120	68	188 (50)
SROM	25	18	43 (11)
Diabetes	40	20	60 (16)
Hypertension	8	19	27 (7)
Hypothyroidism	1	4	5 (1.3)
One IUFD	3	6	9 (2.4)
Antepartum hemorrhage	10	3	13 (3.5)
Deep vein thrombosis	0	1	1 (0.2)
Placenta Praevia	4	0	4 (1)
Twin-twin transfusion	3	0	3 (0.8)
Anemia	53	30	83 (22)

AFH - Armed Forces Hospital
 KKUH- King Khalid University Hospital
 SROM - spontaneous rupture of membrane
 IUFD - Intra-uterine fetal death

second and third main indication. Failure to progress (6.5%) and multiple pregnancy of higher order (5%) were the fourth and fifth leading indication. **Table 4** shows the antenatal complications in multiple pregnancies. Half of the cases had no complications. Anemia complicated 22% of cases and impaired glucose tolerance was reported in 16%. Hypertension and ante-partum hemorrhage occurred in 7% and 3.5% of cases. **Table 5** shows the post-partum complications. Post-partum hemorrhage was the main one. **Table 6** shows the causes of intrauterine fetal and perinatal mortality in multiple pregnancies. The perinatal mortality of 48 per thousand was reported. **Table 7** shows the incidence of preterm labor in multiple pregnancies, which was approximately 7 times that of singleton. **Table 8** shows the perinatal mortality for multiple pregnancies, which was 6 times that of singletons. (40 versus 6.7 per thousand) ($P<0.001$)

Discussion. Multiple pregnancies are a serious complication of assisted reproductive techniques. Fifteen percent of twins and 60% of triplets and higher order births are the result of sub-fertility treatment in Great Britain.⁷ The incidence of twin births at AFH rose by 46% between 1981 and 2001 (9.5/1000-14.1/1000).⁸ This rise in incidence was similar to that reported from KKUH (10/1000-15/1000).⁹ Multiple birth rates increase with increasing maternal age at first pregnancy (>30 years).³ There is a worldwide shift towards bearing children at an older age. In the USA, 33% of all mothers giving birth in 1994 aged over 30-years as compared to 16% in 1984.³ The increase of the rate of multiple births in our society was related to the use of sub-fertility treatment and increase in maternal age at first pregnancy. The rate of teenage mothers has shown a steady decline from 18.6% in 1979 to 5% in the year 2000.¹⁰ Prophylaxis is always better than treatment. However, the prevention of naturally occurring multiple pregnancies is not possible. Reducing the number of medically induced multiple pregnancies is the most effective prevention of neonatal morbidity related to infertility treatments. Thirty-four percent of multiple pregnancies were induced in both institutions. Multiple pregnancies are regarded as a serious complication of assisted reproductive treatment cycles. Since the goal of infertility therapy is a healthy child, multiple gestations put that goal at risk. Prevention by using lower dosage gonadotrophin regimens remains the most important mean of decreasing multiple gestation rates. If there are more than 3 mature follicles, the cycle should be converted to an IVF cycle, or it should be canceled and intercourse should be avoided. In IVF cycles, the risk of multiple pregnancies is significantly increased when 3 embryos are transferred instead of

Table 5 - Postpartum complications.

Complication	AFH	KKUH	Total
Hypertension	0	3	3
Post-partum hemorrhage	3	2	5
Postpartum pyrexia	0	2	2
Cervical tear	2	0	2
AFH -Armed Forces Hospital KKUH - King Khalid University Hospital			

Table 6 - Causes of intrauterine fetal death.

Cause of death	AFH	KKUH	Total
Unknown	7	2	9
Degenerative placenta	0	3	3
Cord accident	0	1	1
Chorioamnionitis	0	1	1
Twin-twin transfusion syndrome	1	0	1
Total	8	7	15
AFH -Armed Forces Hospital KKUH - King Khalid University Hospital			

Table 7 - Pre-mature labor in singleton and multiple pregnancy (AFH and KKUH 2000-2001).

Pregnancy	n	Pre-term	%
Multiple pregnancies	375	159	(42)
Singleton	24618	1573	(6.4)
<i>P</i> <0.001			

Table 8 - Pregnancy outcome in multiple pregnancy and singletons.

Pregnancy	n	Perinatal deaths	Perinatal mortality rate
Multiple pregnancies	778	31	40
Singleton	24619	165	6.7
<i>P</i> <0.001			

2.¹¹ The number of embryos transferred can be limited to 2 embryos without jeopardizing the pregnancy rate in most circumstances.¹² Assisted reproductive technology pregnancies remain to have poorer than usual outcome.¹¹ Compared to singleton births, fetal neonatal and perinatal mortality rates are 3-6 times higher in twins and 5-15 times higher in multiple births of higher order. The increase in the number of multiple births was associated with 3-4 fold increases in the risk of cerebral palsy for babies from multiple births.⁶ Cerebral palsy rates among survivals are 6 times higher in twins and 20 times higher in triplets.¹² Babies weighing <1500gm at birth have a 60 fold increase in the rate of cerebral palsy compared with babies weighing 2500 gm or more.⁶ Multiple gestations are high-risk pregnancies, which may be complicated by pre-maturity, low birth weight, pre-eclampsia, anemia, post-partum hemorrhage, intra-uterine growth restriction, neonatal morbidity and high neonatal and infant mortality. Multiple gestation children may suffer long term sequel of prenatal complications, including cerebral palsy and hearing disabilities. Toxemia of pregnancy was reported in (23.1%) of cases and anemia in (46.2%).¹³

In an attempt to prevent the risk of premature birth in triplets and high order in multiple pregnancies, multifetal pregnancy reduction (MPR) is carried out. Unfortunately (MPR) had a limited effect as the proportion of pre-term deliveries and the prevalence of low birth weight in reduced pregnancies remained at the same level found in spontaneous twin or singleton pregnancy. The procedure itself is associated with the increased risk of miscarriage (7.6% for triplets, 13% for quadruplets, 17% for quintuplets and 21% for sextuplets or more),⁹ premature rupture of the membrane and adverse psychological effects.¹⁴ Embryo reduction should be used as a last resort.¹⁵ More than 50% of patients with 3 or more gestational sacs had spontaneous reduction before 12 weeks. The surviving fetuses weighed less and were born earlier than unreduced pregnancies with the same initial number of fetuses.¹⁶ The diagnoses of pre-term labor is perhaps one of the most difficult tasks facing obstetricians today due to the lack of understanding of the causes and patho-physiology of pre-term labor, and treatment modalities are aiming at symptoms rather than cause. Between 25-75% of pregnant woman suspected of having, premature labor will go on to deliver at term without intervention.¹⁷ Neither oral nor intravenous betamimetics prophylaxis has shown effective in routinely preventing pre-term labor. Its use in active labor is associated with an increased risk of pulmonary edema. Systematic corticosteroids between 28 and 34 weeks in triplet pregnancies will help in reducing the risk of hyaline membrane disease in infants of these pregnancies.¹⁸

Corticosteroids were administered in only 27% of cases of multiple pregnancies. Cervical cerclage is indicated in selected cases. Cervical cerclage was applied in only 8% of cases. Bed rest is ineffective but will reduce the risk of developing hypertension and low birth weight. Reducing physical activity and standing at work in patients who have multiple gestations can prevent pre-maturity.¹⁹ These data support the therapeutic interventions aimed at delayed delivery of subsequent fetuses.²⁰ There is little evidence regarding the best mode of delivery for women with multiple pregnancies. All triplets in both institutions are delivered by cesarean section. In selected cases, vaginal delivery of triplet gestations can be accomplished without increased maternal or neonatal morbidity and mortality.²¹ Thirty to forty percent of all naturally conceived twins are monozygotic. Two thirds of these are mono-chorionic. Twenty-five percent of all twins are mono-chorionic di-amniotic. The perinatal mortality of monochorionic is 5 times greater than di-chorionic ones and the morbidity is 8 times greater. The increase in morbidity is due to pre-maturity, cerebral lesions, congenital malformation, and twin-to-twin transfusion syndrome, which occurs in 10-30% of mono-chorionic twins.²² The use of ultrasound in the first trimester allows us to diagnose number of multiples, chronicity, amnionicity, presence/absence of nuchal translucency, early growth discordance, and severe malformation. In the second and third trimester, cervical assessment, early grading and treatment of twin-to-twin transfusion syndrome, diagnosis of malformation and growth disturbance, Doppler velocimetry, position of multiples, and decision of the optimal route of delivery.²³ A twin birth weight discordance of >40% before 32 weeks' gestation has clearly been demonstrated to be a risk factor for pre-term birth.²⁴ A trans-vaginal ultrasonic measurement of the cervix >35mm at 18-24 weeks in twin gestation can identify patients at low risk for delivery before 34 weeks.²⁵ A shorter cervix measured before and not after 30 weeks' gestation was a stronger predictor of pre-term delivery.²⁶ When maternal weight gains of 40-45 pounds were achieved, good outcome for both twins weighing >2500g were reported. A weight gain of <0.85 pounds/week before 24 weeks was significantly associated with poor intrauterine growth and higher morbidity among twins regardless of subsequent rate of gain.²⁷

In conclusion, preterm delivery remains the most serious complication of multiple pregnancies. Multiple gestation children may suffer long term sequel of prenatal complications, including cerebral palsy and hearing disabilities. Every effort should be made to reduce the risk of multiple gestation and pre-term labor through proper control of and close monitoring of fertility drugs, limiting number of

embryo transfer to a maximum of 3 or only 2, improve the socioeconomic status of maternal mothers, reduce cigarette smoking, relieve maternal stress, restriction of maternal activity, frequent contact with health care personnel and treatment of any obstetric or medical disorders.

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