A comparison of pregnancy outcome between high-order multiple and twin pregnancies: matched-pair retrospective study

H Lam, PC Ho

Objective. To compare the pregnancy outcome between high-order multiple and twin pregnancies.
Design. Matched-pair retrospective analysis.
Setting. University teaching hospital, Hong Kong.
Patients. Patient records from 38 high-order multiple pregnancies that were delivered over a period of 15 years, and those from matched twin pregnancies.
Main outcome measures. Obstetric and perinatal outcomes.
Results. The incidence of high-order multiple pregnancies increased over the study period in association with the more frequent practice of ovulation induction and other assisted reproductive techniques. High-order multiple pregnancies were associated with a higher incidence of maternal complications and a significantly higher perinatal mortality rate than were twin pregnancies.
Conclusion. Efforts should be made to prevent multiple pregnancies by carefully monitoring ovulation treatment and by limiting the number of embryos transferred.

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Key words: Comparative study; Fertilization in vitro; Ovulation induction; Pregnancy, multiple; Pregnancy outcome

Introduction

The incidence of multiple pregnancies, including high-order multiple pregnancies (HMPs), has been increasing recently due to the more frequent use of ovulation-inducing agents and assisted reproduction techniques. The natural incidence of a pregnancy of high multifoetal order usually follows Hellin's law, which is represented as (frequency of twins)$^{n-1}$, in which 'n' is number of foetuses. The natural incidence of triplet pregnancies has been reported to range from 1 per 6400 to 1 per 9520 pregnancies and that of quadruplet pregnancies, to range from 1 per 537 to 1 per 600 000.[1] It is thus important to assess the maternal and neonatal risks of high multifoetal gestation. A retrospective study was performed at the Queen Mary Hospital to quantify the complications of HMPs and to determine whether they were associated with a significantly greater risk of adverse outcome compared with twin pregnancies.

Department of Obstetrics and Gynaecology, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
H Lam, FHKAM (Obstetrics and Gynaecology)
PC Ho, MD, FRCOG

Correspondence to: Dr H Lam

Methods

Matching criteria

A matched-pair analysis was conducted to compare maternal and neonatal outcomes of HMPs (ie triplet and higher-order pregnancies) with those of twin pregnancies. All HMPs delivered in the Department of Obstetrics and Gynaecology at the Queen Mary Hospital from January 1981 to December 1995 were identified from a computerised perinatal database. Thirty-eight cases were found and all records were reviewed. Patients from the records were then paired with those from records of twin pregnancies that had been delivered in the same department. The following criteria were used for patient matching: maternal age (within 5 years); race (Chinese/non-Chinese); educational level (no education, primary school level, secondary school level, tertiary level, or above); previous delivery (yes/no); household income (<HK$10 000, HK$10 000 to <HK$40 000, or >HK$40 000); and smoking (yes/no). Each HMP was matched with a twin pregnancy as closely as possible timewise. All twins were also delivered within a period of 5 years of each other.

Pregnancy outcomes

The pregnancy outcomes included preterm labour,

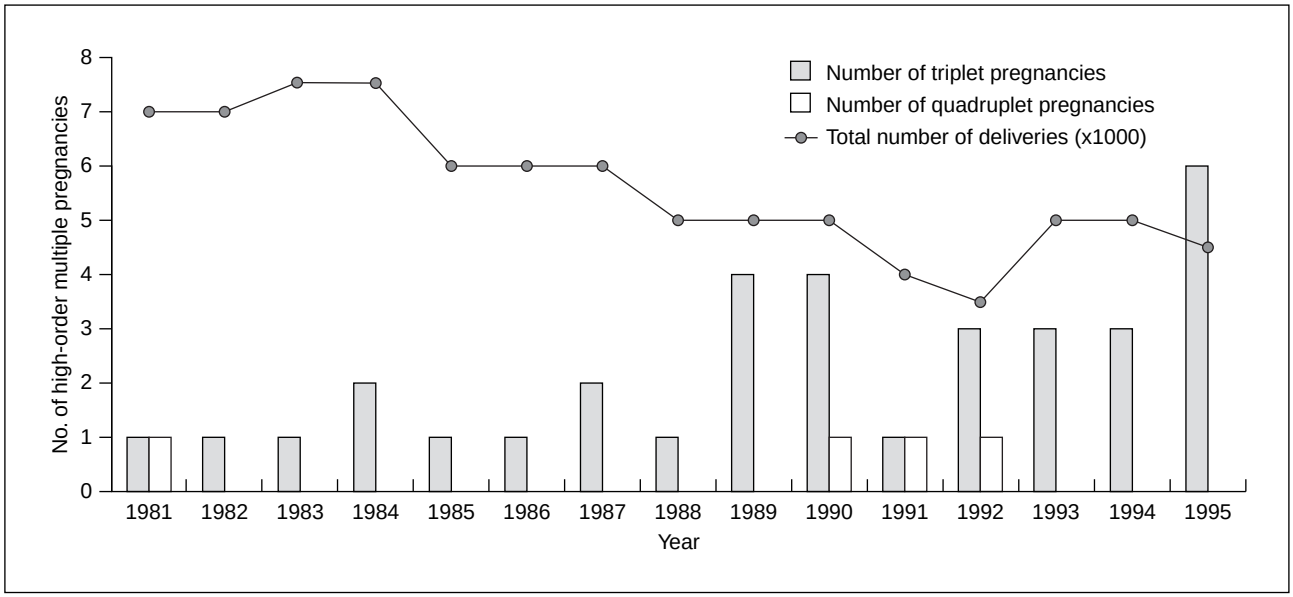

Fig. The annual incidence of high-order multiple pregnancies at the Queen Mary Hospital (1981-1995)

gestational hypertension, anaemia, discordant growth, intrauterine growth retardation, and gestational diabetes mellitus. Preterm labour was defined as uterine activity that caused progressive cervical change at less than 37 weeks' gestation. Gestational hypertension was defined as an elevation of blood pressure above 130/90 mm Hg on two consecutive readings, 4 hours apart, with or without proteinuria, but with a normal blood pressure returning before 20 weeks of gestation. Anaemia was defined as a haemoglobin level of less than 100 g/L. Discordant growth was defined as a difference in birthweight of more than 500 g or 10% (with reference to the largest foetus in the same pregnancy). Intrauterine growth retardation was defined as a birthweight of less than the 10th percentile of the corresponding weight for that particular gestational age. Gestational diabetes mellitus was defined according to the World Health Organization definition. After giving oral glucose 75 g to the mother, the fasting blood glucose level was recorded; a level of 8 μmol/L or more, or a 2-hour blood glucose level of 11 μmol/L or more was classified as gestational diabetes mellitus. A fasting blood glucose level of 6 to 8 μmol/L, and/or a 2-hour blood glucose level of 8 to 11 μmol/L was classified as impaired glucose tolerance.

The incidence of HMPs within the 15-year period was calculated and causes of the pregnancies were recorded. The antenatal complications and the perinatal outcomes of the delivery of triplets and quadruplets were compared with those of the delivery of twins. In the statistical analysis, the Chi squared test or Fisher's exact test was used to compare discontinuous variables. For continuous variables such as birthweight and gestational age, the Mann-Whitney *U* test was used. A two-tailed probability level of P=0.05 or less was interpreted as being statistically significant. Multiple regression analysis was used to identify the relationship between birthweight, duration of neonatal hospital stay, gestational age, and the order of the multiple pregnancy.

Results

Between January 1981 and December 1995, there were 83 198 deliveries, 678 sets of twins, 34 sets of triplets, and four pairs of quadruplets. The incidence of multiple pregnancy was 1 per 123 deliveries for twins, 1 per 2447 deliveries for triplets, and 1 per 20 800 deliveries for quadruplets. All sets of quadruplets were conceived by using assisted reproduction techniques. The incidence of multiple pregnancies during the study period is shown in the Figure. The practice of assisted reproduction began at the Queen Mary Hospital in 1986. The incidence of multiple pregnancies has since increased (Table 1) and the causes of HMPs are

Table 1. Incidence of multiple pregnancies

Year	Twins	Triplets (expected*)	Quadruplets (expected*)
1981-1985	1/147	1/8420 (1/21 609)	1/42 099 (1/3 176 500)
1986-1991	1/110	1/2257 (1/12 100)	1/14 670 (1/1 331 000)
1992-1995	1/107	1/1146 (1/11 449)	1/18 336 (1/1 225 000)

* Expected incidence of high-order multiple pregnancies calculated using Hellin's law

Table 2. Causes of high-order multiple pregnancies

Cause	Pregnancies No. (%)
Spontaneous	9 (24)
Induction of ovulation	
clomiphene citrate	4 (10)
gonadotrophins	11 (29)
Subtotal	15 (39)
Assisted reproduction	
in vitro fertilisation	10 (26)
gamete intrafallopian transfer	3 (8)
pronuclear stage tubal transfer	1 (3)
Subtotal	14 (37)
Total	38

shown in Table 2. Of the matched twin pregnancies, 34 (89%) occurred spontaneously, one was induced by using clomiphene citrate, and one by using gonadotrophin. In addition, two were conceived by using in vitro fertilisation. There were no significant differences in terms of maternal age, parity, and race because of the matching criteria used. The mean matching age was 31 years (range, 23-38 years).

The antenatal complications in the high-order multifoetal and twin pregnancies are shown in Table 3. Ninety-five percent of the triplet and quadruplet pregnancies and 51% of the twin pregnancies had one or more antenatal complications. Preterm labour and intrauterine growth retardation were the two most common complications in HMPs. Most of the other complications also occurred more frequently in triplet and quadruplet pregnancies than in twin pregnancies.

Preterm labour

Almost 95% of HMPs were delivered before term, because of preterm labour, maternal factors (eg abdominal distension or gestational hypertension), or foetal reasons (eg discordant growth, intrauterine growth retardation, or foetal distress). Thirty-one percent of HMPs were delivered before 34 weeks' gestation.

Missed abortion

Missed abortions occurred in two triplet pregnancies and involved three foetuses. In one triplet pregnancy, there was a missed abortion of one of the foetal sacs at 15 weeks' gestation. The other two foetuses were delivered vaginally at term; the birthweights were 2.5 kg and 2.7 kg. In another triplet pregnancy, which was spontaneously conceived, there were missed abortions of two fetal sacs at 6 and 8 weeks' gestation respectively. The remaining foetus had intrauterine growth retardation. The patient went into preterm labour at 30 weeks' gestation and had a cord prolapse following the spontaneous rupture of the membranes. The baby was delivered by lower-segment caesarean section and weighed 1 kg. There were no missed abortions in any of the twin pregnancies.

Intrauterine death

Two intrauterine deaths occurred in one triplet pregnancy that was complicated by intrauterine growth retardation of all three foetuses. The deaths were at 28 and 30 weeks' gestation and the weights at delivery were 268 g and 538 g, respectively. The live foetus was delivered by lower-segment caesarean section at 32 weeks' gestation because of suspected foetal distress, as shown by an absence of end-diastolic flow during a Doppler ultrasonographic study of the umbilical artery. A male infant weighing 1.185 kg—small for gestational age—was delivered. The stillbirth rate for HMPs was thus 17 per 1000 total high-order multiple births. There were no intrauterine deaths among the twin pregnancies.

Modes of delivery

Thirty-six (95%) of the 38 HMPs were delivered by lower-segment caesarean section; the indication for caesarean section was HMP. Two HMPs were delivered vaginally; one was a triplet pregnancy in 1981. The patient had preterm labour with membrane rupture at 26 weeks' gestation. The three babies were delivered vaginally and with cephalic presentation. They were

Table 3. Maternal and foetal complications of high-order multiple and twin pregnancies

Antenatal complications	Triplets and quadruplets, n=38 No. (%)	Twins, n=38 No. (%)	P value
Antenatal anaemia	7 (18)	3 (8)	ns
Preterm labour	15 (39)	5 (13)	<0.05
Gestational diabetes or impaired glucose tolerance	10 (26)	4 (10)	ns
Gestational hypertension	9 (24)	4 (10)	ns
Discordant growth	9 (24)	5 (13)	ns
Intrauterine growth retardation	20 (53)	9 (24)	<0.05
Missed abortion	2 (5)	0	ns
Intrauterine death	1 (3)	0	ns
Post-partum anaemia	2 (5)	4 (10)	ns

ns not significant

Table 4. Neonatal outcome in high-order multiple and twin pregnancies

Outcome	Triplets and quadruplets, n=38	Twins, n=38	P value
Gestational age at delivery (wk) [mean (SD)]	32.9 (2.5)	36.5 (2.7)	<0.05
Birthweight (kg) [mean (SD)]	1.70 (0.72)	2.3.0 (0.68)	<0.05*
Duration of hospital stay (d) [mean (SD)]	26.0 (46.2)	11.0 (5.0)	<0.05†
Mean 1-minute Apgar score	6	7	ns
Mean 5-minute Apgar score	8	9	ns
Perinatal death	13	2	<0.05
Sex of babies	49% female	54% female	ns
Congenital abnormality	3	4	ns

* Gestational age: regression coefficient, R=156; SE(R)=8.46; P<0.05. High-order multiple pregnancy: regression coefficient, R=54; SE(R)=59.4; P>0.05

† Gestational age: regression coefficient, R=-1.7; SE(R)=0.39; P<0.05. High-order multiple pregnancy; regression coefficient, R=-7.4; SE(R)=2.5; P<0.05

all severely asphyxiated and the birthweights ranged from 760 to 840 g; early neonatal death occurred in all three babies. In twin pregnancies, only 34% (13 of 38) babies were delivered by lower-segment caesarean section.

The neonatal outcomes are shown in Table 4. There was a significantly lower gestational age at delivery in the HMPs compared with the twin pregnancies. High-order multiple pregnancies also had a significantly lower mean birthweight. However, using multiple regression analysis, birthweight (as the dependent variable) was found to be significantly related with gestational age. The perinatal mortality was 11.3% (113/1000) in high-order multiple deliveries and 2.6% (26/1000) in twin deliveries (P<0.05). The duration of hospital stay was longer for HMPs than it was for twin pregnancies (P<0.05). Using multiple regression analysis, hospital stay (as the dependent variable) was found to be significantly related to the gestational age and the type of multiple pregnancy.

Discussion

As shown in other reports,[2] there was an increasing incidence of HMPs during the review period. The incidence of triplet pregnancies in 1986 was three times the expected incidence, as calculated from Hellin's law. In 1990, the incidence had increased to nine times than that expected. This increase correlated with the greater use of assisted reproduction techniques and the more liberal use of human menopausal gonadotrophins to treat subfertility. Only 21% of the triplet and quadruplet pregnancies occurred spontaneously.

Most HMPs were associated with a higher risk of maternal and neonatal complications. Thus, measures should be taken to reduce the incidence of HMPs—for example, when using clomiphene citrate as an oral ovulation-inducing agent, one should begin with the lowest dosage. The dosage of clomiphene citrate should be increased only if there is no evidence of ovulation. For most of the patients in the HMP group, however, ovulation was induced by using human menopausal gonadotrophins. Careful biochemical and ultrasonographic monitoring of follicle development is also necessary. When there are more than two mature follicles, the ovulation induction cycle should be abandoned to reduce the chance of HMPs. Similarly, the number of fertilised oocytes and embryos replaced should be limited to three in all assisted reproduction procedures. Since the development of embryo cryopreservation, there has no longer been any justification for replacing more than three fertilised oocytes or embryos.

This study shows that the incidence of maternal complications is greater for HMPs. This trend has also been shown in other studies, where the incidence ranges from 19% to 46%[3-5]—the incidence in this study was 23%. Severe gestational hypertension, for example, occurred more often among the HMPs. Anaemia has been reported to occur in approximately 35% of triplet pregnancies.[1] The high incidence of anaemia is due to the increased nutritional demand on the mother, because of the greater number of foetuses. At the Queen Mary Hospital, folate and iron supplements are given to all patients who have a multiple pregnancy and in whom the degree of anaemia is mild (haemoglobin level, >90 g/L).

Intrauterine growth retardation occurred more often in HMPs than in twin pregnancies. The difference is due to the higher chance of placental insufficiency as the number of foetuses increase. Growth retardation might also be related to other antenatal complications such as gestational hypertension, which occurred more frequently in HMPs and which tended to be more severe. Intrauterine growth retardation occurred in 53% of HMPs and discordant growth occurred in 24%; both figures were higher than those found for twin pregnancies. The mean birthweights decreased as the number of foetuses in a pregnancy increased. Because of the high incidence of intrauterine growth retar-

dation,[6] it is important to monitor foetal growth with serial ultrasound examinations.

Preterm delivery is the most important factor in predicting the neonatal outcome in multiple pregnancies, and the length of gestation is inversely proportional to the number of foetuses present. The incidence of preterm delivery in twin pregnancies approaches 50% in some studies[7] and that of triplets ranges from 64% to 88%.[8] In this study, preterm deliveries occurred in 95% of HMPs (20 of 21 deliveries), while preterm labour occurred in 39% (15 of 38 pregnancies). The mean gestational age at delivery was 32.9 weeks in this study, which is comparable to that reported in other series.[9,10] Various methods have been used to try to prevent prematurity, but none have been proven to be effective. These methods include the use of oral progesterone throughout pregnancy or prophylactic cervical cerclage. Bedrest has not been shown to prolong gestation in twin pregnancies; however, bedrest may increase the mean birthweight at delivery,[11] probably owing to an improvement in the uteroplacental circulation. Similar studies have not been conducted for HMPs.

The perinatal mortality rate in HMPs was 113 per 1000 in this study, which is lower than the figures from earlier reports. All the neonatal deaths occurred in babies born before 28 weeks' gestation. The perinatal mortality rate quoted in other studies ranges from 133 per 1000 to 312 per 1000.[1,9,12,13] The lower mortality rate in this study is probably related to the advancements in neonatal intensive care. One study has also shown a lower perinatal mortality rate, of 50 to 60 per 1000.[8]

Caesarean section was the most common method of delivery in this study. Two pregnancies, in which missed abortion occurred in one or two foetal sacs in early pregnancy, were subsequently delivered vaginally. One of the vaginal deliveries was the preterm delivery of a triplet at 26 weeks' gestation. Vaginal delivery has been described by many authors but differences in perinatal mortality have been described between the first and third foetus.[3,9] Birth order is one of the most important factors for neonatal outcome; however, this is not the case for pregnancies delivered by caesarean section.

In summary, efforts should be made to prevent multiple pregnancies by careful monitoring of ovulation treatment and by limiting the number of embryos transferred after in vitro fertilisation. This study has shown that triplet and quadruplet pregnancies were complicated by a higher incidence of preterm labour and delivery, growth retardation, discordancy, and antenatal anaemia. The mean birthweight was lower for HMPs than it was for twin pregnancies.

There has recently been an increasing trend towards the selective reduction in multiple pregnancies of higher order.[14] The argument is that the perinatal mortality and morbidity are lower for twins. However, reduction is not without complications, which include early or late abortion, or preterm labour,[15-17] An important feature is to explain to any prospective parents that pregnancies of higher order carry a higher incidence of antenatal complications and a very high incidence of neonatal morbidity, which may mean prolonged and expensive hospitalisation for the neonates.

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