Perinatal mortality rate in multiple pregnancies: a 20-year retrospective study from a tertiary obstetric unit in Hong Kong

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ABSTRACT

Introduction: Multiple pregnancies have become more common, but their perinatal mortality rate remains higher than the rate among singleton pregnancies. This retrospective study investigated the prevalence and causes of perinatal mortality among multiple pregnancies in Hong Kong.

Methods: All multiple pregnancies in a university tertiary obstetric unit between 2000 and 2019 were reviewed, and the medical records of cases complicated by stillbirth and neonatal death were identified. The causes of perinatal mortality were determined based on clinical assessment and laboratory results, then compared between the first (2000-2009) and second (2010-2019) decades.

Results: The prevalence of multiple pregnancies increased from 1.41% in the first decade to 1.91% in the second decade (P<0.001). Compared with the first decade, the second decade had a lower stillbirth rate (14.72 vs 7.68 [both per 1000 births]; P=0.026), late neonatal death rate (4.78 vs 1.16 [both per 1000 livebirths]; P=0.030), and total mortality rate (25.32 vs 13.82 [both per 1000 births]; P=0.006). The decline in stillbirth rate was related to improvements in antenatal care and treatment. The decline in the late neonatal death rate was related to a reduction in preterm birth before 34 weeks (18.5% vs 15.2%; P=0.006), as well as an improvement in the mortality rate in the subgroup of 31-33 weeks (19.23 vs 0 [both per 1000 livebirths]; P=0.035).

Conclusion: Although the prevalence of multiple pregnancies increased during the study period, the corresponding total perinatal mortality rate improved by 45.4%.

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New knowledge added by this study

- The prevalence of multiple pregnancies increased from 1.41% in 2000-2009 to 1.91% in 2010-2019, but the total perinatal mortality rate decreased by 45.4% (from 25.32 per 1000 births to 13.82 per 1000 births).
- The stillbirth rate decreased from 14.72 per 1000 births to 7.68 per 1000 births because of close antenatal ultrasonographic monitoring, as well as fetal intervention including fetoscopic laser coagulation.
- The late neonatal death rate decreased from 4.78 per 1000 births to 1.16 per 1000 births because of a reduction in the rate of preterm deliveries before 34 weeks of gestation, as well as improvements in intensive neonatal care that increased the survival rate for babies delivered at 31-33 weeks of gestation.

Implications for clinical practice or policy

- Designated regular ultrasonography examinations and antenatal clinical examinations, beginning in the first trimester, are essential for reducing perinatal mortality in multiple pregnancies (particularly when a monochorionic placenta is present).
- Territory-wide monitoring of perinatal mortality is needed to maintain the standard of perinatal care in Hong Kong.

Introduction

The global prevalence of multiple pregnancies has been increasing since the introduction of assisted reproductive technology in 1978.[1] However, the risk of perinatal mortality is four-fold to seven-fold higher in twin pregnancies than in singleton pregnancies; this risk is further increased in triplet and quadruplet pregnancies.[2,3] In particular, multiple pregnancies with a monochorionic (MC) component are at greater risk, compared with multiple pregnancies that lack a MC component.[4,5] Preterm deliveries, selective fetal growth restriction, twin-to-twin transfusion syndrome (TTTS), and congenital anomalies are responsible for the higher rate of

多胎妊娠圍產期死亡率：香港公立醫院產科20年回顧性研究

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引言：多胎妊娠越趨普遍，但其圍產期死亡率仍高於單胎妊娠。這項回顧性研究檢視香港多胎妊娠圍產期死亡率和原因。

方法：本研究檢視2000年至2019年期間香港一所教學醫院產科所有多胎妊娠案例，並審閱死胎和新生兒死亡病例的醫療記錄。透過臨床評估和化驗結果確定圍產期死亡原因，然後把第一個（2000-2009）和第二個（2010-2019）十年的數據進行比較。

結果：多胎妊娠的發生率從第一個十年的1.41%升至第二個十年的1.91%（P<0.001）。與第一個十年相比，第二個十年有較低死胎率（每1000例活產嬰兒：14.72比7.68；P=0.026）、晚期新生兒死亡率（每1000例活產嬰兒：4.78比1.16；P=0.030）和總死亡率（每1000例活產嬰兒：25.32比13.82；P=0.006）。死胎率下降與改善產前護理和治療有關。研究顯示34孕週前早產的比例減少（18.5%比15.2%；P=0.006），以及31-33孕週胎兒死亡情況也有所改善（每1000例活產嬰兒：19.23比0；P=0.035）均有助降低晚期新生兒死亡率。

結論：在研究期間，多胎妊娠的發生率有上升趨勢，但相應的圍產期總死亡率卻改善達45.4%。

perinatal mortality in multiple pregnancies.[2,6-8] In the UK, the Confidential Enquiry into Maternal and Child Health and Perinatal Mortality Surveillance Report for Births showed that the stillbirth (SB) rate for twin pregnancies had decreased from 17.58 per 1000 total births in 2000 to 6.16 per 1000 total births in 2016, whereas the SB rate for singleton pregnancies remained unchanged. Moreover, the neonatal mortality for twin pregnancies decreased from 23.2 to 5.34 per 1000 livebirths for the same period of time.[9,10] These changes can presumably be attributed to the 2011 implementation of national guidelines in the UK[11] concerning structured and more intensive antenatal monitoring; the guidelines emphasise the use of ultrasonography to determine chorioamnionicity and clarify the gestational age prior to delivery in uncomplicated multiple pregnancies.[12]

To our knowledge, no Hong Kong–specific data are available regarding the trends and causes of perinatal mortality in multiple pregnancies. We recently reported the improvement of perinatal mortality in singleton pregnancies at a tertiary centre in Hong Kong between 2000 and 2019.[13] In the present study, we aimed to assess changes in the rates of perinatal mortality in multiple pregnancies, their underlying causes, and trends between 2000 and 2019 in the same obstetric unit, which is a referral centre for complicated multiple pregnancies.

Methods

Study setting

This study comprised a sub-analysis of our retrospective investigation of perinatal mortality in Prince of Wales Hospital, Hong Kong, over a 20-year period from 1 January 2000 to 31 December 2019, with a focus on multiple pregnancies. The hospital serves a population of approximately 1.7 million in the New Territories East region of Hong Kong, with an annual delivery rate of around 6000-7000 (approximately one-sixth of all births in all public hospitals, and one-ninth of all births in Hong Kong). Furthermore, the obstetric unit is a tertiary centre that receives complicated multiple pregnancies referred from other hospitals; it also serves as a maternal fetal medicine training centre accredited by both The Royal College of Obstetricians and Gynaecologists (RCOG; https://www.rcog.org.uk) and The Hong Kong College of Obstetricians and Gynaecologists (HKCOG; www.hkcog.org.hk). The STROBE reporting guideline was followed when writing this manuscript.

Data collection and analysis

Records of all multiple pregnancies delivered at the study hospital were retrieved from the hospital database. Multiple pregnancies were defined as pregnancies in which >1 fetus remained alive in utero by 24 weeks of gestation. Thus, the final pregnancy order was defined according to the number of live fetuses at 24 weeks. For example, if a twin was lost before 24 weeks of gestation because of spontaneous in utero death or fetal reduction, such that only one fetus remained alive at 24 weeks, the pregnancy was considered singleton. In contrast, if a twin was lost at 26 weeks of gestation and the co-twin was delivered at 37 weeks, the pregnancy was considered a twin pregnancy with one in utero fetal death. Because the delivery of a dead fetus might have been deferred until the delivery of its live co-fetus, the definition of the time of in utero fetal death or SB was based on the timing of death, rather than the timing of delivery. Stillbirth was defined as fetal death that occurred at or after 24 weeks of gestation; late SB was defined as fetal death that occurred at or after 28 weeks. Neonatal death (NND) was defined as the death of a livebirth and was subcategorised into early (death within 7 days after birth) and late (death between 8 and 28 days after birth).

Statistical analysis

The SB rate was calculated as the number of SBs divided by the total number of births (SBs and livebirths after 24 weeks). Early, late, and total (early plus late) NND rates were calculated as the number of NNDs in a specific period divided by the total number of livebirths (excluding SBs). The

perinatal mortality rate was calculated as the sum of SBs and early NNDs divided by the total number of births. Continuous variables were compared by independent samples *t* tests or the Mann-Whitney *U* test for parametric and non-parametric data, respectively. For comparisons of risk factors, 95% confidence intervals of the differences or odds ratios were included. Categorical variables were compared by the Chi squared test or Fisher's exact test, as appropriate. The level of significance was set at a two-sided P value of <0.05. Data analysis was performed with SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States).

Results

Multiple pregnancy types, prevalences, and mortalities

During the 20-year study period, there were 2126 multiple pregnancies, including 2077 (97.7%) twin pregnancies, 48 (2.26%) triplet pregnancies, and one (0.05%) quadruplet pregnancy; the quadruplet pregnancy was quadrachorionic quadra-amniotic. Among the twin pregnancies, 1377 (66.3%) were dichorionic-diamniotic, 670 (32.3%) were monochorionic-diamniotic, and 21 (1.0%) were monochorionic-monoamniotic; chorioamnionicity in the remaining nine (0.4%) was unknown. Among the triplet pregnancies, 25 (52.1%) were trichorionic-triamniotic; the remaining 23 (47.9%) triplet pregnancies had ≥1 MC component, including 14 dichorionic-triamniotic, seven monochorionic-triamniotic, one monochorionic-diamniotic, and one dichorionic-diamniotic. Thus, among 4302 total births from multiple pregnancies, 1451 (33.7%) were from 714 pregnancies with a MC component, 2833 (65.9%) [including the quadruplets] were from 1403 pregnancies without a MC component, and 18 (0.4%) were from the nine twin pregnancies of uncertain chorioamnionicity.

The prevalence of multiple pregnancies increased from 1.41% (837 per 59 469 pregnancies) in the first decade to 1.91% (1289 per 67 316 pregnancies) in the second decade (P<0.001). This change was caused by increases in both MC multiple pregnancies (from 309 [0.52%] to 405 [0.60%]) and non-MC multiple pregnancies (from 519 [0.87%] to 884 [1.31%]) between the first and second decades; the increase in non-MC multiple pregnancies was greater. The nine twin pregnancies with unknown chorioamnionicity were all delivered in the first decade.

Overall, there were 45 SBs, 23 early NNDs, and 11 late NNDs during the study period (Table 1). Among the 45 SBs in multiple pregnancies, 21 (46.7%) occurred between 24 and 27 weeks of gestation, whereas 24 (53.3%) occurred thereafter; the late SB rate was 5.71 per 1000 births. Forty-three SBs (10.35 per 1000 births) occurred in twin pregnancies (including five double SBs: four pairs of monochorionic-diamniotic twins and one pair of dichorionic diamniotic twins), whereas two SBs (13.89 per 1000 births) occurred in triplet pregnancies; these SB rates did not significantly differ. Furthermore, there were 28 NNDs (6.81 per 1000 births) in twin pregnancies and six NNDs (42.25 per 1000 births) in triplet pregnancies; the NND rate was significantly higher in triplet pregnancies (P=0.001). Therefore, the total mortality rate (17.09 per 1000 births vs 55.56 per 1000 births; P=0.005) and the perinatal mortality rate (14.93 per 1000 births vs 41.67 per 1000 births; P=0.025) were both higher in triplet pregnancies (Table 1). There were no instances of perinatal mortality in the only case of quadruplet pregnancy or in the nine twin pregnancies of unknown chorioamnionicity.

Among the twin pregnancies, the MC group had significantly higher rates of SB (18.81 per 1000

TABLE 1. Rates of stillbirth, NND, and perinatal mortality in multiple pregnancies, compared between 2000-2009 and 2010-2019, and compared among orders of pregnancy*

All births	Total n=4302	2000-2009 n=1698	2010-2019 n=2604	P value	Twin n=4154	Triplet n=144	Quadruplet n=4	P value†
Stillbirth	45 (10.46)	25 (14.72)	20 (7.68)	0.026	43 (10.35)	2 (13.89)	0	0.663
All births ≥28 weeks	**n=4205**	**n=1657**	**n=2548**		**n=4069**	**n=132**	**n=4**	
Late stillbirth	24 (5.71)	13 (7.85)	11 (4.32)	0.202	23 (5.65)	1 (7.58)	0	0.536
Early NND	23 (5.40)	10 (5.98)	13 (5.03)	0.844	19 (4.62)	4 (28.17)	0	0.006
Late NND	11 (2.58)	8 (4.78)	3 (1.16)	0.030	9 (2.19)	2 (14.08)	0	0.050
Total NND	34 (7.99)	18 (10.76)	16 (6.19)	0.102	28 (6.81)	6 (42.25)	0	0.001
Perinatal mortality	68 (15.81)	35 (20.61)	33 (12.67)	0.041	62 (14.93)	6 (41.67)	0	0.025
Total mortality	79 (18.36)	43 (25.32)	36 (13.82)	0.006	71 (17.09)	8 (55.56)	0	0.005

Abbreviation: NND = neonatal death

* Data are presented as No. (/1000), unless otherwise specified

† Comparisons were between twin and triplet pregnancies because there was only one quadruplet pregnancy

TABLE 2. Rates of stillbirth, NND, and perinatal mortality, compared among twin and triplet pregnancies with and without a monochorionic component*

	Twin			Triplet			Overall			Overall MC			Overall non-MC		
	MC n=1382	Non-MC n=2754	P value	MC n=69	Non-MC n=75	P value	MC n=1451	Non-MC n=2829	P value	2000-2009 n=627	2010-2019 n=824	P value	2000-2009 n=1049	2010-2019 n=1780	P value
Stillbirth	26 (18.81)	17 (6.17)	<0.001	1 (14.49)	1 (13.33)	0.999	27 (18.61)	18 (6.36)	<0.001	12 (19.14)	15 (18.20)	0.896	13 (12.39)	5 (2.81)	0.004
Early NND	8 (5.90)	11 (4.02)	0.556	4 (58.82)	0	0.050	12 (8.43)	11 (3.91)	0.096	2 (3.25)	10 (12.36)	0.116	8 (7.72)	3 (1.69)	0.023
Late NND	6 (4.42)	3 (1.10)	0.068	2 (29.41)	0	0.228	8 (5.62)	3 (1.07)	0.009	6 (9.76)	2 (2.47)	0.083	2 (1.93)	1 (0.56)	0.559
Total NND	14 (10.32)	14 (5.12)	0.089	6 (88.24)	0	0.011	20 (14.04)	14 (4.98)	0.002	8 (13.01)	12 (14.83)	0.950	10 (9.65)	4 (2.25)	0.016
Perinatal mortality	34 (24.60)	28 (10.17)	<0.001	5 (72.46)	1 (13.33)	0.104	39 (26.88)	29 (10.25)	<0.001	14 (22.33)	25 (30.34)	0.350	21 (20.02)	8 (4.49)	<0.001
Total mortality	40 (28.94)	31 (11.26)	<0.001	7 (101.45)	1 (13.33)	0.028	47 (32.39)	32 (11.31)	<0.001	20 (31.90)	27 (32.77)	0.926	23 (21.93)	9 (5.06)	<0.001

Abbreviations: monochorionic = MC; NND = neonatal death

* Data are presented as No. (/1000), unless otherwise specified. There were no SBs or NNDs among the 18 twins of uncertain chorioamnionicity and single quadruplet pregnancy. Data concerning these pregnancies were excluded from the table

births vs 6.17 per 1000 births; P<0.001) compared with the non-MC group, but the early, late and total NND rates did not differ between groups. Overall, the MC twin group had higher rates of total mortality (28.94 per 1000 births vs 11.26 per 1000 births; P<0.001) and perinatal mortality (24.60 per 1000 births vs 10.17 per 1000 births; P<0.001), compared with the non-MC twin group. Among the triplet pregnancies, the MC group also had significantly higher rates of total NND (88.24 per 1000 births vs 0; P=0.011) and total mortality (101.45 per 1000 births vs 13.33 per 1000 births; P=0.028) [Table 2].

Changes in stillbirth and neonatal death rates during the study period

The following rates were significantly lower in the second decade, compared with the first decade: overall SB (14.72 per 1000 births vs 7.68 per 1000 births; P=0.026), late NND (4.78 per 1000 births vs 1.16 per 1000 births; P=0.030), perinatal mortality (20.61 per 1000 births vs 12.67 per 1000 births; P=0.041) and total mortality (25.32 per 1000 births vs 13.82 per 1000 births; P=0.006) [Table 1]. Notably, the rates of early NND and total NND did not significantly differ between decades. In the non-MC group, the following rates were significantly lower in the second decade: overall SB (12.39 per 1000 births vs 2.81 per 1000 births; P=0.004), early NND (7.72 per 1000 births vs 1.69 per 1000 births; P=0.023), and total NND (9.65 per 1000 births vs 2.25 per 1000 births; P=0.016). No differences between decades were observed in the MC group (Table 2).

Details of stillbirths in multiple pregnancies

The maternal characteristics associated with SBs in multiple pregnancies are shown in Supplementary Table 1 of the Appendix. Compared with the livebirth group (excluding cases with NND), mothers in the SB group were significantly younger (30.3 ± 6.6 years vs 32.7 ± 5.3 years; P=0.004) and the proportion of mothers aged ≥35 years was lower (17.5% vs 38.5%; P=0.007). Maternal characteristics were comparable between the two groups in terms of ethnicity, booking status, parity, and body mass index. The prevalences of all medical diseases were also comparable.

Table 3 and the Supplementary Figure a show the respective incidences and distribution of the causes of SB among multiple pregnancies. The most common cause was fetal growth restriction (13; 28.9%), followed by TTTS [7; 15.5%]. Other causes of SB included pre-eclampsia/hypertension (3; 6.7%), congenital and genetic abnormalities (3; 6.7%), chorioamnionitis (3; 6.7%), other maternal medical diseases (2; 4.4%), cord-related pathology/accident (1; 2.2%), and placental pathologies (1; 2.2%). There were 12 (26.7%) unexplained SBs throughout the study period, although the rate was significantly lower in the second decade (2; 10%) than in the first decade (10; 40%, P=0.002); otherwise, there were no other substantial differences in the causes of SB between the first and second decades. The causes of SB differed between MC and non-MC groups: fetal growth restriction (9; 33.3%) [P=0.014] and TTTS (7; 25.9%) [P=0.001] were the two most common causes of SB in MC multiple pregnancies. Whereas one-third of SBs in the non-MC group were unexplained, fetal growth restriction (4; 22.2%), congenital and genetic abnormalities (2; 11.1%), chorioamnionitis (2; 11.1%), and pre-eclampsia/hypertension (2; 11.1%) were common causes in the non-MC group.

Details of neonatal deaths in multiple pregnancies

The distribution of gestational ages at NND is shown in Table 4. In the '31 to 33 weeks' group, the overall

TABLE 3. Causes of stillbirth among multiple pregnancies with and without a monochorionic component, compared between 2000-2009 and 2010-2019

Cause	Total n=4280†	2000-2009 n=1676	2010-2019 n=2604	P value	MC n=1451	Non-MC n=2829	P value
Total stillbirths	45 (10.51)	25 (14.92)	20 (7.68)	0.023	27 (18.61)	18 (6.36)	<0.001
Congenital and genetic abnormalities	3 (0.70)	2 (1.19)	1 (0.38)	0.565	1 (0.69)	2 (0.71)	0.999
Chorioamnionitis	3 (0.70)	2 (1.19)	1 (0.38)	0.565	1 (0.69)	2 (0.71)	0.999
Fetal growth restriction	13 (3.04)	4 (2.39)	9 (3.46)	0.737	9 (6.20)	4 (1.41)	0.014
Unexplained	12 (2.80)	10 (5.97)	2 (0.77)	0.002	6 (4.14)	6 (2.12)	0.239
Pre-eclampsia /hypertension	3 (0.70)	1 (0.60)	2 (0.77)	0.999	1 (0.69)	2 (0.71)	0.999
Twin-to-twin transfusion syndrome	7 (1.64)	4 (2.39)	3 (1.15)	0.443	7 (4.82)	0	0.001
Other maternal medical diseases	2 (0.47)	0	2 (0.77)	0.523	2 (1.38)	0	0.115
Cord-related pathology/accident	1 (0.23)	1 (0.60)	0	0.392	0	1 (0.35)	0.999
Placental pathologies	1 (0.23)	1 (0.60)	0	0.392	0	1 (0.35)	0.999

Abbreviation: monochorionic = MC

* Data are presented as No. (/1000), unless otherwise specified

† Twins and triplets with uncertain chorioamnionicity (n=18) and the quadruplets (n=4) were excluded from the analysis

TABLE 4. Distributions of gestational age at livebirth and neonatal death, compared among multiple pregnancies*

Gestational age, wk	Livebirths					Neonatal death						
	All n=4257	2000-2009 n=1673	2010-2019 n=2584	Twin n=4111	Triplet n=142	All n=34	2000-2009 n=18	2010-2019 n=16	P value	Twin n=28	Triplet n=6	P value
24-27	76	29	47	65	11	20 (277.78)	7 (241.38)	13 (302.33)	0.766	14 (215.38)	6 (545.45)	0.031
28-30	151†	72	79	138	9	2 (13.25)	1 (13.89)	1 (12.66)	0.999	2 (14.49)	0	0.999
31-33	474	208	266	424	50	4 (8.33)	4 (19.23)	0	0.035	4 (9.43)	0	0.999
34-36	1332	494	838	1260	72	5 (3.75)	4 (8.10)	1 (1.19)	0.066	5 (3.96)	0	0.999
≥37	2224	870	1354	2224	0	3 (1.35)	2 (2.30)	1 (0.74)	0.565	3 (1.35)	0	-

* Data are presented as No. or No. (/1000), unless otherwise specified

† The quadruplets (n=4) were excluded from the analysis

NND rate was significantly higher in the first decade (19.23 per 1000 births) than in the second decade (0 per 1000 births; P=0.035). In the '24 to 27 weeks' group, the NND rate was significantly higher among triplet pregnancies (545.45 per 1000 births) than among twin pregnancies (215.38 per 1000 births; P=0.031). Preterm birth before 34 weeks of gestation in multiple pregnancies was significantly higher in the first decade (18.5%) than in the second decade (15.2%; P=0.006).

Regarding the causes of NND in multiple pregnancies, prematurity (23; 67.6%) was the most common cause, followed by congenital and genetic abnormalities (8; 23.6%), birth asphyxia (2; 5.9%), and sepsis (1; 2.9%) [Table 5 and Supplementary Fig b]. There were no significant differences in the incidences of various causes of NND between the first and second decades. However, a greater proportion of NNDs in the MC group was caused by prematurity, compared with the non-MC group (11.24 per 1000 births vs 2.49 per 1000 births; P=0.001) [Table 5].

Changes in maternal demographics during the study period

Between the first and second decades, there were several statistically significant trends in maternal demographics, including a higher maternal age in the second decade (31.6 ± 5.3 years vs 33.3 ± 5.2 years; P<0.001), as well as greater proportions of mothers aged ≥35 years (29.7% vs 43.4%; P<0.001) and ≥40 years (4.8% vs 8.0%; P=0.004). The overall mean booking body mass index was significantly lower in the second decade (23.1 ± 3.7 kg/m^2 vs 22.7 ± 3.3 kg/m^2; P=0.011). The prevalence of non-booked cases was also significantly lower in the second decade (11.2% vs 4.7%; P<0.001). Women of Chinese ethnicity remained the predominant group (96.9% vs 94.9%), but there was an increase in the proportion of deliveries by women of Southeast Asian ethnicity (1.3% vs 4.3%; P<0.001). The proportions of nulliparous women were similar (63.9% vs 67%; P=0.150). In the second decade, there were higher prevalences of chronic hypertension (0% vs 1.1%; P=0.006) and pre-eclampsia/gestational

TABLE 5. Causes of neonatal death among multiple pregnancies with and without a monochorionic component, compared between 2000-2009 and 2010-2019

Cause	Total n=4235	2000-2009 n=1651	2010-2019 n=2584	P value	MC n=1424	Non-MC n=2811	P value
Total NNDs	34	18	16		20	14	
Congenital and genetic abnormalities	8 (1.89)	6 (3.63)	2 (0.77)	0.063	2 (1.40)	6 (2.13)	0.725
Prematurity	23 (5.43)	9 (5.45)	14 (5.42)	0.999	16 (11.24)	7 (2.49)	0.001
Sepsis	1 (0.24)	1 (0.61)	0	0.390	1 (0.70)	0	0.336
Birth asphyxia	2 (0.47)	2 (1.21)	0	0.152	1 (0.70)	1 (0.36)	0.999

Abbreviations: monochorionic = MC; NND = neonatal death

* Data are presented as No. or No. (/1000), unless otherwise specified

hypertension (8.5% vs 11.2%; P=0.043), as well as an increase in the rate of caesarean delivery (65.0% vs 81.0%; P<0.001). Other differences in the prevalences of medical diseases are summarised in Supplementary Table 2 of the Appendix.

Discussion

Changes in the types of multiple pregnancies and their perinatal mortality rates

To our knowledge, this is the first large study concerning the epidemiology and patterns of perinatal mortality in multiple pregnancies during a 20-year period in Hong Kong. In the second decade, there were significantly more non-MC twin pregnancies, compared with the first decade; this was mainly because of the widespread use of artificial reproductive technology. However, there was no change in the number of non-MC triplet or quadruplet pregnancies; this finding was presumably related to changes in artificial reproductive technology practices that restricted the number of embryo transfers, controlled ovulation induction, and implemented fetal reduction (ie, from higher order pregnancies to twin pregnancies).[14] The probability of a spontaneous MC twin pregnancy is generally stable (~1 in 300).[15] The increased prevalence of MC twin pregnancies in this cohort is presumably related to the increased number of referrals received by the obstetric unit involved in this study, which is a specialised centre for the treatment of complicated twin pregnancies via fetoscopic laser coagulation of anastomoses or radiofrequency ablation of umbilical vessels for selective fetal reduction.[14,16-19] Embryos produced by artificial reproductive technology also have a higher probability of spitting and forming MC multiple pregnancies.[20] Compared with the perinatal mortality in singleton pregnancies during the same period, which we previously reported,[13] the respective perinatal mortality rates in twin pregnancies and triplet pregnancies were 3.6-fold and 10.0-fold higher (4.16 in 1000 births [singleton] vs 14.93 in 1000 births [twin] vs 41.67 in 1000 births [triplet]; P<0.05). The total perinatal mortality rate in twin pregnancies was 45.4% lower in the second decade than in the first decade (25.32 per 1000 births [2000-2009] vs 13.82 per 1000 births [2010-2019]). This difference was considerably larger than the 15.2% reduction we previously observed in singleton pregnancies (4.54 per 1000 births [2000-2009] vs 3.85 per 1000 births [2010-2019]).[13]

Changes in the stillbirth rates

The improvement in perinatal mortality in multiple pregnancies was a combined effect of reductions in SB and late NND. Compared with SB rates in twin and triplet pregnancies in the same obstetric unit between 1988 and 1992,[21] the SB rate for twin pregnancies substantially decreased from 23.2 per 1000 births (1988-1992) to 14.9 per 1000 births (2000-2009) and 7.53 per 1000 births (2010-2019). The SB rate for triplet pregnancies also substantially decreased from 66.7 per 1000 births (1988-1992) to 15.2 per 1000 births (2000-2009) and 12.8 per 1000 births (2010-2019). Our findings are comparable to results from the UK, where the national SB rate in twin pregnancies decreased from 17.58 per 1000 births (2000) to 6.16 per 1000 births (2016).[22]

The decline in SB rates since 1990 can be attributed to improvements in care, including the introduction of fetoscopic laser coagulation for TTTS (in 2002)[17,18] and the establishment of a specialised multiple pregnancy clinic with a standard protocol for close ultrasonographic monitoring (in the late 2000s). The establishment of this clinic ensured better care for these high-risk multiple pregnancies; the additional monitoring allowed earlier recognition of complications and greater access to timely treatment.[23] However, the effect of radiofrequency ablation of the umbilical vessels for selective fetal reduction, introduced in 2011, was not revealed in this study because many multiple pregnancies were regarded as singleton pregnancies after fetal reduction.[14,16,19,24]

In the second decade, the proportion of non-MC multiple pregnancies increased from 62.6% [1049/(1049+627)] to 68.4% [1780/(1780+824)]; this also reduced the overall perinatal mortality rate. Furthermore, non-MC multiple pregnancies had lower rates of total mortality (11.31 in 1000 births vs 32.39 in 1000 births; P<0.001), perinatal mortality (10.25 in 1000 births vs 26.88 in 1000 births; P<0.001), and SB (6.36 in 1000 births vs 18.61 in 1000 births; P<0.001), compared with MC multiple pregnancies. This is consistent with findings from the UK, where the SB rates were 3-5 in 1000 births (dichorionic twin pregnancies) and 18-26 in 1000 births (MC twin pregnancies) during the period of 2013-2016.

Comparison with singleton pregnancies

Notably, approximately half of the SBs in multiple pregnancies occurred between 24 and 27 weeks of gestation, whereas only 25% of SBs in singleton pregnancies occurred in this range of gestational ages.[13] This difference suggests that the underlying diseases associated with SB were more severe (with earlier onset) in multiple pregnancies than in singleton pregnancies. When comparing the aetiologies of SB between singleton and multiple pregnancies, the multiple pregnancies group had higher rates of SB caused by fetal growth restriction (3.04 in 1000 births vs 0.49 in 1000 births), pre-eclampsia/hypertension (0.70 in 1000 births vs 0.19 in 1000 births), other maternal medical diseases (0.47 in 1000 births vs 0.11 in 1000 births), and TTTS (specific to MC multiple pregnancies). In the second decade, the proportion of unexplained SBs in multiple pregnancies was significantly lower than in the first decade (40% [2000-2009] vs 10% [2010-2019]); this change was not observed in singleton pregnancies (33.3% [2000-2009] vs 39.1% [2010-2019]). We presumed that the difference was mainly related to the close monitoring provided in multiple pregnancies.

Whereas SBs in singleton pregnancies were associated with older maternal age and obesity, SBs in multiple pregnancies were associated with significantly younger maternal age, compared with livebirths in multiple pregnancies. Moreover, the proportion of mothers aged ≥35 years was significantly lower among multiple pregnancies with SBs than among multiple pregnancies with livebirths. This difference presumably can be attributed to the younger age of mothers with MC multiple pregnancies compared with mothers who had non-MC multiple pregnancies; moreover, a greater proportion of non-MC multiple pregnancies were produced by artificial reproductive technology.

Changes in neonatal death rates

As in singleton pregnancies, prematurity was the most common cause of NND in multiple pregnancies.[13] There was a significantly lower rate of preterm birth before 34 weeks of gestation in multiple pregnancies during the second decade (15.2%) than in the first decade (18.5%; P=0.006); accordingly, the rates of late NND and total NND were lower in the second decade. After stratification according to gestational age at birth, the NND rate was significantly higher in triplet pregnancies than in twin pregnancies among deliveries between 24 and 27 weeks of gestation. However, the NND rate did not significantly differ between singleton pregnancies (197.53 per 1000 births) and twin pregnancies (215.38 per 1000 births; P=0.743). Thus, there is an unclear effect of order of pregnancy on the NND rate in extreme preterm births; the degree of prematurity is the main factor that affects the NND rate.

The rate of caesarean delivery was significantly lower in the first decade than in the second decade (65.0% vs 81.0%; P<0.001). This difference was mainly related to an increase in the elective caesarean delivery rate for multiple pregnancies (23.7% vs 42.5%); the emergency caesarean delivery rate was similar between the first and second decades (41.3% vs 38.5%). Women with the first twin in cephalic presentation and overall stable condition were offered a trial of vaginal delivery and elective caesarean delivery. Because there is a generally consistent probability that the first fetus is in cephalic presentation, the higher rate of elective caesarean delivery was mainly related to patient choice and preference.

Strengths and limitations

This is the first large analysis of the prevalence and causes of SB and NND among multiple pregnancies in Hong Kong. Most data regarding chorioamnionicity, gestational age at SB, and basic maternal demographics are complete and accurate. The 20-year study period also allowed comparisons between the first and second decades. However, because our obstetric unit is the major referral centre for complicated MC cases, the number of MC cases in this study was higher than the number of cases in a nearby obstetric unit (0.6% vs 0.4% of all pregnancies); moreover, total perinatal mortality was higher in our obstetric unit (32.77 per 1000 births during 2010-2019 [Table 2], vs 19 per 1000 births during 2011-2018).[25] Notably, the analysis by the other obstetric unit excluded MC triplet pregnancies, monoamniotic twin pregnancies, and cases complicated by TTTS or lethal anomalies, all of which carried a high risk of perinatal mortality.[25] Furthermore, clinical practices might have changed during the 20-year study period, potentially influencing the classification of causes of SB. For example, the change from karyotyping to chromosomal microarray may have led to additional genetic disease diagnoses.[26] Additionally, some multiple pregnancies were reduced to singleton

pregnancies, either spontaneously or by medical intervention, before 24 weeks of gestation; these pregnancies were regarded as singleton pregnancies. Therefore, the effect of fetal reduction in these cases was unclear. Finally, although this large cohort provided extensive data concerning perinatal mortality among multiple pregnancies in Hong Kong, the dataset was insufficient for statistical evaluation of rare events. Nonetheless, these findings provide a basis for a territory-wide review of perinatal outcomes in multiple pregnancies.

Conclusion

The prevalence of multiple pregnancies increased from 1.41% in 2000-2009 to 1.91% in 2010-2019, but the total perinatal mortality rate decreased from 25.32 per 1000 births to 13.82 per 1000 births. This change in the total perinatal mortality rate was related to reductions in the rates of SB and NND, which resulted from improvements in antenatal care and neonatal intensive care.

Author contributions

Concept or design: SL Lau, TY Leung.
Acquisition of data: All authors.
Analysis or interpretation of data: SL Lau, STK Wong, WT Tse, TY Leung.
Drafting of the manuscript: SL Lau, TY Leung.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

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References

1. Collins J. Global epidemiology of multiple birth. Reprod Biomed Online 2007;15 Suppl 3:45-52.
2. Russo FM, Pozzi E, Pelizzoni F, et al. Stillbirths in singletons, dichorionic and monochorionic twins: a comparison of risks and causes. Eur J Obstet Gynecol Reprod Biol 2013;170:131-6.
3. Sherer DM. Adverse perinatal outcome of twin pregnancies according to chorionicity: review of the literature. Am J Perinatol 2001;18:23-37.
4. Hack KE, Derks JB, Elias SG, et al. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. BJOG 2008;115:58-67.
5. Lewi L, Jani J, Blickstein I, et al. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol 2008;199:514.e1-8.
6. Lee YM, Wylie BJ, Simpson LL, D'Alton ME. Twin chorionicity and the risk of stillbirth. Obstet Gynecol 2008;111:301-8.
7. Ananth CV, Chauhan SP. Epidemiology of twinning in developed countries. Semin Perinatol 2012;36:156-61.
8. Manktelow BN, Smith LK, Seaton SE, et al; on behalf of the MBRRACE-UK collaboration. MBRRACE-UK perinatal mortality surveillance report. UK perinatal deaths for births from January to December 2014. Available from: https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK-PMS-Report-2014.pdf. Accessed 1 Mar 2022.
9. Healthcare Quality Improvement Partnership Ltd. MBRRACE-UK. Perinatal mortality surveillance report 2018. Available from: https://www.hqip.org.uk/resource/mbrrace-uk-perinatal-mortality-surveillance-report-2018/. Accessed 1 Mar 2022.
10. Healthcare Quality Improvement Partnership Ltd. CMACE and CEMACH reports. Stillbirth, neonatal and post-neonatal mortality 2002-2003 from CEMACH. Available from: https://www.hqip.org.uk/resource/cmace-and-cemach-reports/. Accessed 1 Mar 2022.
11. National Collaborating Centre for Women's and Children's Health (UK). Multiple Pregnancy: The Management of Twin and Triplet Pregnancies in the Antenatal Period. London: RCOG Press; 2011.
12. Khalil A, Giallongo E, Bhide A, Papageorghiou AT, Thilaganathan B. Reduction in twin stillbirth following implementation of NICE guidance. Ultrasound Obstet Gynecol 2020;56:566-71.
13. Wong ST, Tse WT, Lau SL, Sahota DS, Leung TY. Stillbirth rate in singleton pregnancies: a 20-year retrospective study from a public obstetric unit in Hong Kong. Hong Kong Med J 2022;28:285-93.
14. Tse WT, Law LW, Sahota DS, Leung TY, Cheng YK. Triplet pregnancy with fetal reduction: experience in Hong Kong. Hong Kong Med J 2017;23:326-32.
15. Sperling L, Kiil C, Larsen LU, et al. Naturally conceived twins with monochorionic placentation have the highest risk of fetal loss. Ultrasound Obstet Gynecol 2006;28:644-52.
16. Ting YH, Poon LC, Tse WT, et al. Outcomes of radiofrequency ablation for selective fetal reduction before vs at or after 16 gestational weeks in complicated monochorionic pregnancy. Ultrasound Obstet Gynecol 2021;58:214-20.
17. Lau TK, Leung TY, Fung TY, Leung TN. Treatment of twin-twin transfusion syndrome by fetoscopic laser photocoagulation. Chin Med J (Engl) 2004;117:1431-4.
18. Yang X, Leung TY, Ngan Kee WD, Chen M, Chan LW, Lau TK. Fetoscopic laser photocoagulation in the management of twin-twin transfusion syndrome: local experience from Hong Kong. Hong Kong Med J 2010;16:275-81.
19. Lu J, Ting YH, Law KM, Lau TK, Leung TY. Radiofrequency ablation for selective reduction in complicated

monochorionic multiple pregnancies. Fetal Diagn Ther 2013;34:211-6.
20. Saravelos SH, Zhang T, Chung JP, et al. Monochorionic quadramniotic and triamniotic pregnancies following single embryo transfers: two case reports and a review of the literature. J Assist Reprod Genet 2016;33:27-32.
21. Lau TK, Li CY. A perinatal audit of stillbirths in a teaching hospital in Hong Kong. Aust N Z J Obstet Gynaecol 1994;34:416-21.
22. Kurinczuk JJ, Draper ES, Field DJ, et al. Experiences with maternal and perinatal death reviews in the UK—the MBRRACE-UK programme. BJOG 2014;121 Suppl 4:41-6.
23. Pan M, Chen M, Leung TY, Sahota DS, Ting YH, Lau TK. Outcome of monochorionic twin pregnancies with abnormal umbilical artery Doppler between 16 and 20 weeks of gestation. J Matern Fetal Neonatal Med 2012;25:277-80.
24. Ting YH, Lao TT, Law KM, Cheng YK, Lau TK, Leung TY. Pseudoamniotic band syndrome after in-utero intervention for twin-to-twin transfusion syndrome: case reports and literature review. Fetal Diagn Ther 2016;40:67-72.
25. Yu FN, Mak AS, Chan NM, Siu KL, Ma TW, Leung KY. Prospective risk of stillbirth and neonatal complications for monochorionic diamniotic and dichorionic diamniotic twins after 24 weeks of gestation. J Obstet Gynaecol Res 2021;47:3127-35.
26. Hui AS, Chau MH, Chan YM, et al. The role of chromosomal microarray analysis among fetuses with normal karyotype and single system anomaly or nonspecific sonographic findings. Acta Obstet Gynecol Scand 2021;100:235-43.

