APPENDIX.

Antenatal and obstetric care for multiple pregnancies

Chorioamnionicity was diagnosed antenatally by ultrasonography[1] and confirmed postnatally by placental histology. Depending on the presence of a monochorionic (MC) component, multiple pregnancies were sub-grouped into a MC group (monochorionic-diamniotic and monochorionic-monoamniotic twin, monochorionic-triamniotic triplet, and dichorionic-triamniotic triplet) and a non-MC group (dichorionic-diamniotic twin and trichorionic-triamniotic triplet).

Standard protocols for the antenatal care of multiple pregnancies were followed, according to their chorioamnionicity and order of pregnancy. Women with multiple pregnancy were offered ultrasound examination at 11+0 to 13+6 weeks of gestation to assess fetal viability, gestational age, and chorionicity; this examination was also conducted to exclude major congenital abnormalities. For multiple pregnancies conceived naturally, the gestational age was determined by the first day of the last menstrual period and adjusted by ultrasonography-based measurement of the crown-rump length or other biometric indicators in the larger twin.[2] For multiple pregnancies conceived by in vitro fertilisation, the gestational age was determined by the date of embryo transfer. Morphology scans were performed at approximately 20 weeks of gestation.[3] For MC multiple pregnancies, ultrasonography monitoring to identify potential twin-twin transfusion syndrome and selective fetal growth restriction was performed at 2-week intervals from 16 until 26 weeks of gestation, then at 1-week intervals until delivery. Ultrasonography monitoring included assessments of fetal growth, fluid volume, umbilical artery and middle cerebral artery Doppler findings, bladder size, and any hydropic features.[4] For non-MC multiple pregnancies, ultrasonography monitoring was provided at 4-week intervals for assessments of fetal growth, fluid volume (according to deepest vertical pool), and umbilical artery Doppler findings. During each visit, maternal weight and blood pressure were recorded; urine dipstick analysis was conducted to screen for albuminuria and glucosuria. In the event of antenatal complications, monitoring was increased and interventions were offered.

Down syndrome screening using second-trimester biochemical analysis was provided for women of advanced maternal age before 2009; in 2010, universal first-trimester combined screening was implemented.[5] Women with twin pregnancies could also attend private clinics to undergo non-invasive antenatal testing with cell-free DNA for more accurate results[6,7]; publicly available non-invasive antenatal testing was implemented in late 2019 for women who were considered high-risk based on first-trimester combined screening results. Other routine blood tests for all women with multiple pregnancy included assessments of thalassaemia, blood group, human immunodeficiency virus, syphilis, hepatitis B, and rubella, as well as the oral glucose tolerance test. Universal group B streptococcal screening was implemented in 2012.[8,9]

The mode of delivery was discussed at approximately 34 weeks of gestation depending on the presentation of the first twin and other maternal or fetal conditions. A trial of vaginal delivery and elective caesarean delivery were offered in cases where the first twin was in cephalic presentation and the overall condition was stable. The recommended gestational age at delivery depended on chorioamnionicity: 37 weeks for uncomplicated monochorionic-diamniotic twin pregnancies, 38 weeks for dichorionic diamniotic twin pregnancies, and 34 weeks for monochorionic-monoamniotic twin pregnancies and triplet pregnancies (by caesarean delivery). For multiple pregnancies in which a trial of vaginal delivery was attempted, continuous intrapartum fetal monitoring with cardiotocography was implemented except in cases that involved lethal fetal anomalies (eg, haemoglobin Bart syndrome, anencephaly, trisomy 13, or trisomy 18) or borderline fetal viability for which the parents declined emergency caesarean delivery. To differentiate the fetal heart rates of twins, the presenting twin was monitored with a fetal scalp electrode while the co-twin was monitored transabdominally in the usual manner. The preferred twin-to-twin delivery interval was ≤30 minutes.[10,11] A delayed delivery was considered for some extreme preterm twin pregnancies.[12]

The diagnosis of twin-twin transfusion syndrome was based on standard antenatal ultrasonography findings.[13] Fetal growth restriction was diagnosed when antenatal ultrasonography showed fetal abdominal circumference or estimated fetal weight below the third centile, or below the tenth centile combined with other abnormalities (eg, oligohydramnios or abnormal pulsatility index).[14,15] Additionally, selective fetal growth restriction in MC multiple pregnancies was defined as a difference of >20% in estimated fetal weight. In the absence of antenatal ultrasonographic fetal biometric measurements, fetal growth restriction was diagnosed when birthweight was below the third centile.[16,17]

Protocol for investigation of stillbirth and neonatal death

The standard protocol in our obstetric unit for

investigating the causes of stillbirth (SB) and neonatal death in multiple pregnancies was identical to our previously reported protocol for investigating such events in singleton pregnancies.[18] We also selected only one factor for each pregnancy as the primary cause of SB, as in our previous study of singleton pregnancies.[18] The primary cause was determined through prioritisation based on a combination of clinical judgement and laboratory results. Causes with the highest priority were lethal congenital malformations or genetic disorders, as well as emergencies (eg, cord prolapse, uterine rupture, or placental abruption). For example, if a case involved pre-eclampsia complicated by placental abruption, the primary cause was placental abruption. If fetal haemoglobin Bart syndrome was complicated by pre-eclampsia, the primary cause was haemoglobin Bart syndrome. Causes with the next highest priority were pre-eclampsia, medical diseases, and placental pathologies that may be associated with fetal growth restriction. Fetal growth restriction was regarded as the primary cause only when other underlying causes were not identified. When causes were difficult to determine, the final decision was made after case review by a panel of physicians. Stillbirths were considered unexplained after the exclusion of all other causes.

The underlying causes of SBs and neonatal deaths in multiple pregnancies were investigated, along with the associated maternal characteristics and risk factors. The rates of SBs and perinatal mortality in multiple pregnancies were compared between the first decade (2000-2009) and the second decade (2010-2019); they were also compared between MC and non-MC multiple pregnancies. All required information was retrieved from the obstetric unit's computerised antenatal record, which captured maternal demographic characteristics including ethnicity, maternal age, height, body weight, body mass index, underlying medical diseases, and obstetric history, as well as the details of each antenatal follow-up visit. The obstetric unit also utilised the hospital's Obstetric Specialty Clinical Information System to record maternal and perinatal outcomes after birth.[19] This study included all cases with perinatal mortality, regardless of whether they had been booked in our obstetric unit; however, booking status was incorporated into the analysis.

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SUPPLEMENTARY TABLE 1. Comparison of maternal demographic risk factors between livebirths and stillbirths among all multiple pregnancies from 2000 to 2019*

	Livebirths (excluding neonatal deaths), n=2066	All stillbirths, n=40†	P value	Difference/odds ratio (95% confidence interval)
Ethnicity			0.693	
Chinese	1976 (95.6%)	38 (95.0%)		Reference
Southeast Asian	66 (3.2%)	1 (2.5%)		0.79 (0.11-5.83)
Caucasian	24 (1.2%)	1 (2.5%)		2.17 (0.29-16.43)
Parity			0.203	
Nulliparous	1350 (65.3%)	30 (75.0%)		Reference
Multiparous	716 (34.7%)	10 (25.0%)		0.63 (0.31-1.29)
Maternal age, y				
Mean ± standard deviation	32.7 ± 5.3	30.3 ± 6.6	0.004	2.41 (0.76-4.07)
≤19	15 (0.7%)	1 (2.5%)	0.265	3.50 (0.45-27.19)
≥35	796 (38.5%)	7 (17.5%)	0.007	0.34 (0.15-0.77)
≥40	139 (6.7%)	2 (5.0%)	0.999	0.73 (0.17-3.06)
Body mass index, kg/m² ‡				
Mean ± standard deviation	22.9 ± 3.47	22.9 ± 3.73	0.992	-0.005 (-1.14 to 1.13)
<18.5	137 (6.9%)	1 (2.7%)	0.511	0.38 (0.05-2.78)
≥27.5	198 (9.9%)	4 (10.8%)	0.781	1.10 (0.39-3.15)
≥30	76 (3.8%)	3 (8.1%)	0.171	2.23 (0.67-7.44)
Non-booked cases	149 (7.2%)	2 (5.0%)	0.999	0.68 (0.16-2.83)
Underlying medical diseases				
Pre-existing diabetes mellitus	6 (0.3%)	0	0.999	-
Gestational diabetes mellitus	331 (16.0%)	4 (10.0%)	0.302	0.58 (0.21-1.65)
Chronic hypertension	14 (0.7%)	0	0.999	-
Pre-eclampsia/gestational hypertension	206 (10.0%)	7 (17.5%)	0.116	1.92 (0.84-4.38)
Cardiac diseases	13 (0.6%)	0	0.999	-
Renal diseases	25 (1.2%)	0	0.999	-
Liver diseases	7 (0.3%)	0	0.999	-
Respiratory diseases	36 (1.7%)	1 (2.5%)	0.511	1.45 (0.19-10.81)
Gastrointestinal diseases	5 (0.2%)	0	0.999	-
Neurological diseases	4 (0.2%)	0	0.999	-
Psychiatric diseases	16 (0.8%)	0	0.999	-
Immunological diseases	4 (0.2%)	0	0.999	-
Thyroid diseases	53 (2.6%)	1 (2.5%)	0.999	0.97 (0.13-7.22)

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

† Five mothers had stillbirths of both twins; thus, the number of mothers with stillbirth was 40

‡ Body mass index information was missing for 66 and three cases in the livebirth and stillbirth groups, respectively

SUPPLEMENTARY TABLE 2. Comparison of maternal characteristics and mode of delivery for all multiple pregnancies between 2000-2009 and 2010-2019*

	2000-2009 (n=837)	2010-2019 (n=1289)	P value
Ethnicity			
Chinese	811 (96.9%)	1223 (94.9%)	<0.001
Southeast Asian	11 (1.3%)	56 (4.3%)	
Caucasian	15 (1.8%)	10 (0.8%)	
Parity			
Nulliparous	535 (63.9%)	863 (67.0%)	0.150
Multiparous	302 (36.1%)	426 (33.0%)	
Maternal age, y			
Mean ± standard deviation	31.6 ± 5.3	33.3 ± 5.2	<0.001
≤19	13 (1.6%)	1 (0.1%)	<0.001
20-34	575 (68.7%)	729 (56.6%)	
35-39	209 (25.0%)	456 (35.4%)	
≥40	40 (4.8%)	103 (8.0%)	
Body mass index, kg/m^2 †			
Mean ± standard deviation	23.1 ± 3.7	22.7 ± 3.3	0.011
<18.5	57 (7.0%)	81 (6.5%)	0.082
18.5-<23.0	386 (47.6%)	649 (52.0%)	
23.0-<25.0	164 (20.2%)	257 (20.6%)	
25.0-<27.5	103 (12.7%)	153 (12.3%)	
27.5-<30	60 (7.4%)	67 (5.4%)	
≥30.0	41 (5.1%)	40 (3.2%)	
Non-booked cases	94 (11.2%)	61 (4.7%)	<0.001
Underlying medical diseases			
Pre-existing diabetes mellitus	3 (0.4%)	3 (0.2%)	0.685
Gestational diabetes mellitus	145 (17.3%)	194 (15.1%)	0.320
Chronic hypertension	0	14 (1.1%)	0.006
Pre-eclampsia/gestational hypertension	71 (8.5%)	144 (11.2%)	0.043
Cardiac diseases	7 (0.8%)	7 (0.5%)	0.588
Renal diseases	16 (1.9%)	10 (0.8%)	0.020
Liver diseases	2 (0.2%)	6 (0.5%)	0.492
Respiratory diseases	17 (2.0%)	20 (1.6%)	0.409
Gastrointestinal diseases	3 (0.4%)	2 (0.2%)	0.388
Neurological diseases	3 (0.4%)	1 (0.1%)	0.307
Psychiatric diseases	8 (1.0%)	8 (0.6%)	0.537
Immunological diseases	1 (0.1%)	3 (0.2%)	0.999
Thyroid diseases	12 (1.4%)	42 (3.3%)	0.009
Mode of delivery	n=1698 babies	n=2604 babies	
Normal vaginal	361 (21.3%)	341 (13.1%)	<0.001
Assisted vaginal	139 (8.2%)	62 (2.4%)	
Vaginal breech	94 (5.5%)	92 (3.5%)	
Elective caesarean	403 (23.7%)	1107 (42.5%)	
Emergency caesarean	701 (41.3%)	1002 (38.5%)	
All vaginal delivery	594 (35.0%)	495 (19.0%)	<0.001
All caesarean delivery	1104 (65.0%)	2109 (81.0%)	

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

† Body mass index information was missing for 26 and 42 cases in the first and second decades, respectively

SUPPLEMENTARY FIG. Distributions of the causes of stillbirth (a) and neonatal death (b) in multiple pregnancies