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Original Article

Placental pathologic features in macrosomia

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Abstract: The incidence of macrosomia (birthweight ≥4,000 g) has been increasing worldwide, and the long-term consequences of macrosomia are being revealed. However, little is known regarding placental pathology in macrosomic babies which may shed light to the important long-term health sequelae of macrosomia. This study aims to examine previously unexplored placental pathologic features in macrosomia. We analyzed data on 29248 women who delivered a singleton infant with complete data on placental pathology in the Collaborative Perinatal Project (CPP), a large prospective cohort study at 12 hospitals in the U.S. More than five percent [5.35%, 95% CI 5.16%, 5.53%] of women delivered a macrosomic neonate. Macrosomia had a large, thick and heavy placenta, long cord, more central insertion into the placenta of cord, more thrombosis in cut surface, fetal neutrophilic infiltration, pigment of macrophage cell, abnormal color of the cord and membrane, abnormal fetal surface related to the meconium stain, true cysts in cut surface and post maturity of the whole placenta. Odds ratios for the above placental features were significantly elevated after adjusting for potential confounders. Macrosomia is related to many placental pathologic lesions. This may be related to the long-term impact of macrosomia on health and disease risk in later life.

Keywords: Fetal origin of adult disease, macrosomia, pathological lesion, placenta

Introduction

Fetal macrosomia is increasingly common worldwide [1]. Remarkably, the US macrosomia rate has increased to 8% in 2014, with 320,701 newborns being affected [2]. It is associated with higher perinatal and maternal morbidity [3-5]. Macrosomic infants are also at increased risks of obesity and diabetes in later life [6, 7]. However, the mechanisms leading to macrosomia remain largely unknown. Placenta, the "diary of gestational life", not only reflects the intrauterine environment, but also provides valuable information on the causes and timing of many diseases in later life [8, 9]. Unfortunately, since routine placental pathology is not done in most studies, data on placental pathology in macrosomia are scarce. To the best of our knowledge, only a few studies examined the relationships between placental gross measures and birth weight [10-13], but not placental histopathology and birth weight. The aim of the present study is to examine previously unexplored placental pathologic features in macrosomia.

Materials and methods

Study population

We used data from the prospective cohort study known as the Collaborative Perinatal Project (CPP). Details of the study have been described elsewhere [14]. Briefly, CPP enrolled 46,021 women with 54,371 singleton pregnancies who received prenatal care at 12 centers in the U.S. from 1959 to 1966. Some of women delivered the newborn many times in this study. Demographic and socio-economic characteristics were collected by in-person interviews at the enrollment. Medical information was collected at each prenatal visit. After delivery, placental gross morphology was examined and samples were collected for histological examination by trained pathologists according to a standard protocol [15]. Obstetrical information (e.g., hypertensive disorders, diabetes) were obtain-

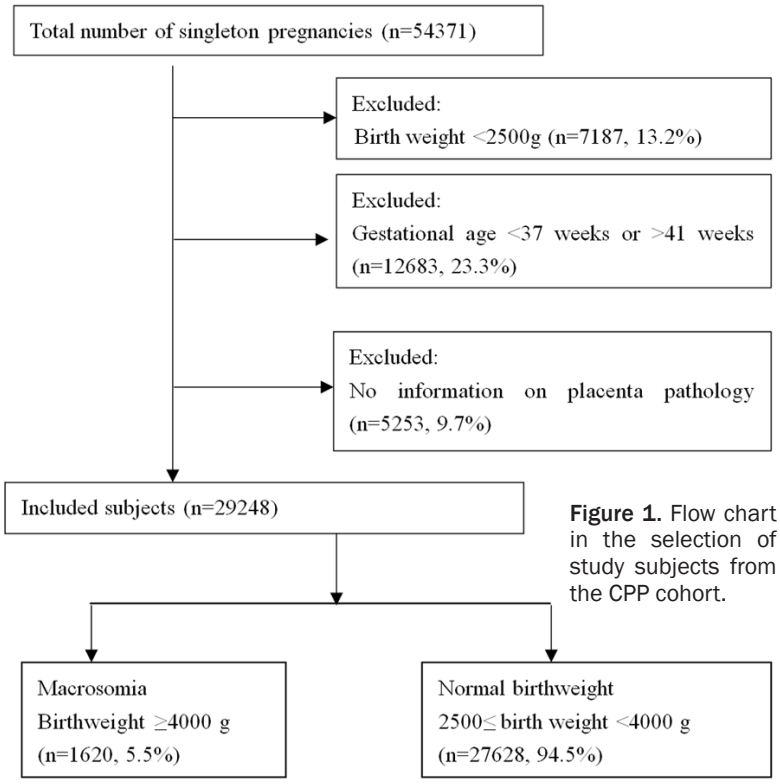

Figure 1. Flow chart in the selection of study subjects from the CPP cohort.

ed from clinical examination and laboratory testing [16].

The present analysis included live-born singletons with a gestational age between 37 and 41 weeks, birth weight ≥2500 grams, and complete placental pathology information, resulting in 29248 mother-child pairs for the final analysis (**Figure 1**). The CPP data are anonymized, rendering an ethical review unnecessary by the Institutional Review Board of our hospital.

Maternal and fetal anthropometric measures

At the enrollment, the pregnant women were asked to provide demographic information such as age, height, parity, smoking, race and pre-pregnancy weight. Newborn's birth weight was obtained within 1 h of delivery by the CPP observer of labour and delivery using calibrated scales [17]. We defined macrosomia as birth weight ≥4000 grams [18]. Pre-pregnancy BMI (kg/m^2) was classified as underweight (<18.5), normal (18.5 to 24.9), overweight (25.0 to 29.9) and obese (≥30) [19] . Adequacy of gestational weight gain was assessed according to the 2009 Institute of Medicine recommendations: 28-40 lb for women with BMI<18.5; 25-35 lb for BMI 18.5-24.9; 15-25 lb for BMI 25.0-29.9; and 11-20 lb for BMI≥30.0 kg/m^2 [20].

Placental pathologic measures

The placental pathology dataset contains 103 gross and microscopic measures, including the following categories: basic morphology, cord, membranes and fetal surface, maternal surface, cut surface, membranes, decidua, terminal villi and intervillous space. Placental pathology assessments in CPP were performed by a team of trained pathologists according to a detailed standard protocol [15]. Most of the pathologists were blinded to the clinical course, diagnosis or outcome. The following placental pathological lesions were identified on the basis of gross and microscopic examinations: gross measures, vascular and villous lesions of maternal or fetal origin, inflammatory cell infiltration, hemorrhage of maternal surface, calcification throughout cut surface, fibrin deposition of fetal membranes, meconium stain of the cord and fetal membranes, abnormal cord insertion, maturity of the placenta, abnormal type of insertion of membranes and true cysts in cut surface (Supplementary Table 1) [21]. Additionally, distance from the cord insertion to the closest placental margin was recorded to the nearest cm. Cord insertion was coded as membranous (velamentous), marginal or normal (inserted onto the chorionic disc). We combined these two variables into a single cord insertion distance measure (continuous variable), by recoding velamentous cord insertions as a negative distance value, cords inserted at the placental margin as '0' and progressively more central cords as its primary distance value [10]. Finally, an estimate of the chorionic plate area was calculated using the formula for the area (A) of an ellipse

$$A=\pi*d_L*d_S/4$$

Where d_L is the largest diameter and d_S is the smallest diameter [22].

Table 1. Maternal demographic characteristics and macrosomia prevalence in the Collaborative Perinatal Project, 1959-1976

	Macrosomia (n=1620)	Normal birthweight (n=27628)	Macrosomia (%)	*P*
Weight gain during pregnancy (%)				
Inadequate	363 (25.0)	12711 (51.1)	2.8	<0.0001
Adequate	586 (40.4)	8637 (34.7)	6.4	
Excessive	501 (34.6)	3513 (14.1)	12.5	
Pre-pregnancy BMI (%)				
<18.5	42 (2.9)	2317 (9.2)	1.8	<0.0001
18.5-24.9	853 (58.0)	17692 (69.9)	4.6	
25.0-29.9	361 (24.5)	3825 (15.1)	8.6	
≥30	216 (14.7)	1485 (5.9)	12.7	
Race (%)				
White	1092 (68.0)	14174 (51.6)	7.2	<0.0001
Black	447 (27.8)	11400 (41.5)	3.8	
Other	68 (4.2)	1920 (7.0)	3.4	
Marriage (%)				
Married	1375 (84.9)	21550 (78.0)	6.0	<0.0001
Other	245 (15.1)	6077 (22.0)	3.9	
Fetal sex (%)				
Male	1022 (63.1)	13954 (50.5)	6.8	<0.0001
Female	598 (36.9)	13674 (49.5)	4.2	
Socio-economic status (%)				
1 (lowest)	78 (4.9)	1693 (6.3)	4.4	<0.0001
2	407 (25.7)	7743 (28.6)	5.0	
3	477 (30.1)	8345 (30.8)	5.4	
4	383 (24.2)	5921 (21.9)	6.1	
5 (highest)	239 (15.1)	3380 (12.5)	6.6	
Parity (%)				
0	302 (18.7)	8448 (30.6)	3.5	<0.0001
1	315 (19.5)	6616 (24.0)	4.5	
2	302 (18.7)	4543 (16.5)	6.2	
3	241 (14.9)	3031 (11.0)	7.4	
4	163 (10.1)	1981 (7.2)	7.6	
≥5	294 (18.2)	2962 (10.7)	9.0	
Smoker (%)				
Nonsmoker	1075 (65.9)	14548 (53.0)	6.9	<0.0001
≤5 per day	204 (13.5)	3986 (14.5)	4.9	
6-10 per day	139 (9.0)	3239 (11.8)	4.1	
11-20 per day	147 (9.2)	4452 (16.2)	3.2	
21+ per day	38 (2.5)	1237 (4.5)	3.0	
Education (%)				
Less than high school (<10 years)	388 (24.3)	7167 (26.3)	5.1	0.015
High school (10-12 years)	951 (59.5)	16184 (59.4)	5.6	
College and above (>12 years)	259 (16.2)	3894 (14.3)	6.2	
Gestational age (week) (%)				
37	76 (4.7)	2458 (8.9)	3.0	<0.0001
38	126 (7.8)	4817 (17.4)	2.6	
39	269 (16.6)	7455 (27.0)	3.5	

40	570 (35.2)	7903 (28.6)	6.7	
41	579 (35.7)	4995 (18.1)	10.4	
Maternal age (year) (%)				
<20	201 (12.4)	5868 (21.2)	3.3	<0.0001
20-35	1251 (77.2)	20213 (73.2)	5.8	
>35	168 (10.4)	1547 (5.6)	9.8	
Chronic diabetes (%)	41 (2.5)	249 (0.9)	14.1	<0.0001
Chronic hypertension (%)	140 (8.7)	1999 (7.3)	6.6	0.03
Gestational hypertension (%)	382 (23.6)	5446 (19.8)	6.6	0.0002
Gestational diabetes (%)	63 (3.9)	249 (0.9)	20.2	<0.0001
Mode of delivery (%)				
Vaginal	1537 (94.9)	26220 (95.0)	5.5	0.96
Cesarean section	82 (5.1)	1391 (5.0)	5.6	

The numbers of missing value were 2457 for pre-pregnancy BMI, 2937 for weight gain during pregnancy, 582 for socio-economic status, 405 for education, 183 for smoking, and 147 for race.

Confounders/intermediates

Perinatal factors that may affect the relationship between fetal macrosomia and placental pathology were chosen as potential risk factors according to the literature [23]. They included maternal age at delivery, marital status at pregnancy (married or not), maternal race (white, black, and other), education (highest number of years of education reported: <10 years, 10-12 years, >12 years), fetal gender (male or female), parity (1-4), smoking during pregnancy (0, ≤5, 6-10, 11-20, 21+ cigarettes per day), socioeconomic status (a combined score of maternal education, occupation and family income, and was further classified into five categories: 1-5, lowest to highest [24]), pre-gestational BMI (underweight, normal, overweight and obese), gestational weight gain (inadequate, adequate, excessive), gestational diabetes (yes or no), chronic diabetes (yes or no), gestational hypertension (yes or no), chronic hypertension (yes or no), gestational age (weeks), delivery mode (vaginal delivery or cesarean section).

Statistical analysis

All analyses were carried out using SAS version 9.2 (SAS Institute Inc, Cary, NC). Frequencies were used for categorical variables; mean and standard deviations were calculated for continuous variables with a normal distribution, and median and interquartile ranges for continuous variables with a skewed data distribution. Chi-square, Student's T and Kruskal-Wallis tests (where appropriate) were used to compare macrosomic and normal birth weight infants. To assess the relationships between placental measures and macrosomia, logistic regression was performed (macrosomia as the outcome). As the placental parameters are measures of the same organ, they may not be independent. Therefore, in logistic regression models, each placental measure was entered individually, adjusting for significant maternal risk factors. In order to reduce the rate of false positive, a two-tailed probability value (p) of <0.01 was considered statistically significant.

Results

There were 2910 macrosomic newborns among 54371 singleton births, yielding an overall incidence of macrosomia of 5.35% (95% CI 5.16%, 5.53%). After applying a series of exclusion criteria, 29248 subjects remained in the final analysis (**Figure 1**). They were divided into macrosomia (birthweight ≥4000 g, n=1620) and normal birth weight (between 2500 and 4000 g, n=27628) groups.

Almost all maternal characteristics differed significantly between macrosomia and normal birth weight groups except for mode of delivery (**Table 1**). Women who were white, older, married, had a male fetus, higher pre-pregnancy BMI, higher gestational weight gain, higher socio-economic status, higher education level, longer gestational age, and did not smoke in pregnancy were more likely to have a macrosomia baby (P<0.01). In addition, women with gestational diabetes or gestational hypertension were more likely to deliver a macrosomic infant (P<0.001).

Table 2. Odds ratio of macrosomia for placental gross measures in the Collaborated Perinatal Project

Placental gross measures	Macrosomia (n=1620)	Normal birth weight (n=27628)	Crude OR (99% CI)	Adjusted, OR (99% CI)[†]
Placental weight				
≤90th percentile of CPP	826 (51.2)	25434 (92.4)	ref	ref
>90th percentile of CPP (560 g)	788 (48.8)	2093 (7.6)	11.59 (10.07, 13.35)	9.79 (8.40, 11.40)
Abnormal Chorionic disc shape				
Round or oval	1535 (94.8)	26459 (95.9)	ref	ref
Other abnormal shape	84 (5.2)	1126 (4.1)	1.29 (0.95, 1.74)	1.07 (0.78, 1.46)
Cord insertion into the placenta (median, interquartile) (cm)[‡]	6 (3)	5 (2)	1.13 (1.10, 1.17)	1.13 (1.09, 1.17)
Chorionic disc square				
≤90th percentile of CPP	1022 (63.6)	24823 (90.3)	ref	ref
>90th percentile of CPP (313 cm^2)	585 (36.4)	2679 (9.7)	5.30 (4.60, 6.12)	4.72 (4.04, 5.51)
Placental disc thickness				
≤90th percentile of CPP	1274 (79.4)	24765 (90.3)	ref	ref
>90th percentile of CPP (28 cm)	330 (20.6)	2673 (9.7)	2.40 (2.03, 2.84)	1.96 (1.64, 2.35)
Umbilical cord length				
≤90th percentile of CPP	1242 (77.1)	24466 (88.9)	ref	ref
>90th percentile of CPP (62 cm)	370 (23.0)	3057 (11.1)	2.39 (2.03, 2.80)	1.72 (1.45, 2.04)

Note: Descriptive data presented as n (%) except for cord insertion into the placenta which is presented as median (interquartile); [†]From logistic regression models adjusted for weight gain during pregnancy, pre-pregnant BMI, marital status, race, socio-economic status, education , smoking , parity, maternal age, chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension, fetal sex, gestational age and mode of delivery. [‡]Cord insertion into the placenta presented as median (interquartile).

Table 2 presents the distribution and odds ratio of macrosomia by placental gross pathological characteristics. After adjustment for confounders, the macrosomia group was more likely to have a larger, thicker and heavier placenta (adjusted OR=4.72, 1.96, 9.79, respectively), longer umbilical cord (adjusted OR=1.72) and longer distance from the cord insertion to the closest placental margin (adjusted OR= 1.13).

Table 3 shows the descriptive characteristics and odds ratio of macrosomia by placental vascular and villous measures. Based on the origin, they were further divided into vascular and villous lesions of maternal origin, and vascular and villous lesions of fetal origin. There were no significant differences in maternal villous lesions, and vascular and villous lesions of fetal origin between the two groups. In maternal vascular lesions, the placenta with infarct size ≥3 cm and infarct number ≥3 was associated with a lower risk for macrosomia (adjusted OR=0.64 and 0.67, respectively). Macrosomia was significantly associated with thrombosis in the cut surface (adjusted ORs=1.24). The vessel lesions and necrosis in decidua were similar between the macrosomia and normal birth weight groups.

Fetal neutrophilic infiltration in placenta was associated with a higher risk of macrosomia (adjusted ORs=1.20) (**Table 4**). But this was not the case in maternal neutrophilic or lymphocyte infiltration. Meconium pigment in macrophage cells and meconium stain of the cord, membrane and fetal surface were more likely to occur in macrosomia (adjusted OR=1.45 and 1.62, respectively). On the contrary, placental immaturity was associated with a lower risk of macrosomia (adjusted ORs=0.53). The prevalence of calcification throughout cut surface and fibrin deposition of fetal membranes was similar between the macrosomia and normal birth weight groups (**Table 4**).

Discussion

Main findings

Our study shows that the placenta of macrosomic newborns has more pathological abnormalities including meconium staining and maternal originthrombi than those of normal birth weight newborns. To our knowledge, this is the first study exploring the placental microscopic pathological characteristics in macrosomia.

The incidence of macrosomia as defined by birth weight >4000 g ranges from 1.3% to 8.0% in the literature [2, 25], which is consistent to ours (5.4%). We found that women who were married, of white race, had a male fetus, higher gestational weight gain or higher prepregnancy

Table 3. Odds ratio of macrosomia by placental vascular and villous measures in the Collaborated Perinatal Project

Placental vascular and villous lesions	Macrosomia (n=1620)	Normal birth weight (n=27628)	Crude OR (99% CI)	Adjusted OR (99% CI)†
Maternal origin vascular lesion				
Infarcts in cut surface				
Occurrence of vascular infarcts				
No	1232 (76.1)	21426 (77.6)	ref	ref
Yes	388 (24.0)	6200 (22.4)	1.09 (0.93, 1.27)	0.90 (0.76, 1.06)
Infarct size				
No infarct	1228 (75.9)	21379 (77.4)	ref	ref
Infarct size <3 cm	350 (21.6)	5340 (19.3)	1.14 (0.97, 1.34)	0.96 (0.81, 1.14)
Infarct size ≥3 cm	41 (2.5)	887 (3.2)	0.81 (0.53, 1.22)	0.64 (0.42, 0.99)
Infarct number ≥3				
No	1563 (96.5)	26466 (95.9)	ref	ref
Yes	57 (3.5)	1121 (4.1)	0.86 (0.60, 1.23)	0.67 (0.46, 0.97)
Thrombosis in cut surface				
No	1211 (75.9)	22464 (82.8)	ref	ref
Yes	384 (24.1)	4683 (17.3)	1.52 (1.30, 1.78)	1.24 (1.05, 1.46)
Vessel lesions in decidua				
No	1539 (97.5)	26155 (97.2)	ref	ref
Yes	40 (2.5)	754 (2.8)	0.90 (0.59, 1.38)	0.88 (0.56, 1.37)
Necrosis of decidua				
No	1434 (90.9)	24341 (90.2)	ref	ref
Yes	143 (9.1)	2633 (9.8)	0.92 (0.73, 1.16)	1.03 (0.81, 1.31)
Maternal origin villous lesion				
Villous infarcts				
No	1354 (84.7)	23878 (86.5)	ref	ref
Yes	264 (16.3)	3719 (13.5)	1.25 (1.05, 1.50)	1.20 (0.99, 1.45)
Excessive Syncytium-Nuclear clumping				
No	1579 (97.5)	26967 (97.7)	ref	ref
Yes	40 (2.5)	633 (2.3)	1.08 (0.71, 1.65)	0.96 (0.61, 1.50)
Fetal origin vascular lesion				
No	1577 (98.1)	27072 (98.5)	ref	ref
Yes	30 (1.9)	426 (1.6)	1.21 (0.74, 1.98)	1.17 (0.70, 1.96)
Fetal origin villous lesion				
No	1531 (94.6)	26450 (95.8)	ref	ref
Yes	87 (5.4)	1162 (4.2)	1.29 (0.96, 1.74)	1.18 (0.87, 1.61)

Note: Descriptive data presented as n (%). †From logistic regression models adjusted for weight gain during the pregnancy, pre-pregnant BMI, marital status, race, socio-economic status, education status, smoking, parity, maternal age, chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension, fetal sex, gestational age and mode of delivery.

BMI tended to have a higher risk of macrosomia. These factors were also found in other populations [23, 26]. Fetal macrosomia has long been associated with adverse perinatal outcomes [27].

Placental gross measures

The placenta is the most important maternal-fetal organ because it is the sole source of nutrients to the developing fetus and removes fetal waste products [8]. Several experimental evidences suggested that fetal adaptations occur in response to the failure of the maternal-placental supply of nutrients to match the fetal requirements [28, 29]. In an otherwise 'normal' pregnancy, placental structure may have changed in response to sub-clinical physiological insults so as to compensate. But because of the professionality and complexity of placen-

Table 4. Odds ratios of macrosomia in association with other placental pathological measures in the Collaborated Perinatal Project

Other placental pathological measures	Macrosomia (n=1620)	Normal birth weight (n=27628)	Crude OR (99% CI)	Adjusted OR (99% CI)†
Inflammatory cell infiltration				
Fetal neutrophilic infiltration				
No	1081 (72.7)	19955 (78.0)	ref	ref
Yes	407 (27.4)	5620 (22.0)	1.34 (1.15, 1.56)	1.20 (1.02, 1.41)
Maternal neutrophilic infiltration				
No	1188 (73.9)	20722 (75.4)	ref	ref
Yes	420 (26.1)	6778 (24.7)	1.08 (0.93, 1.26)	1.03 (0.88, 1.21)
Maternal Lymphocytic infiltration				
No	1073 (66.6)	17731 (64.4)	ref	ref
Yes	539 (33.4)	9788 (35.6)	0.91 (0.79, 1.05)	0.98 (0.84, 1.14)
Calcification throughout cut surface				
No	1438 (88.8)	24288 (88.0)	ref	ref
Yes	181 (11.2)	3298 (12.0)	0.93 (0.75, 1.14)	1.06 (0.85, 1.33)
Fibrin deposition of fetal membranes				
No	1481 (91.7)	25623 (92.9)	ref	ref
Yes	135 (8.4)	1959 (7.1)	1.19 (0.94, 1.52)	1.22 (0.95, 1.57)
Meconium				
Pigment of macrophage cell				
No	1493 (92.3)	26276 (95.2)	ref	ref
Yes	124 (7.7)	1326 (4.8)	1.65 (1.28, 2.12)	1.45 (1.11, 1.90)
Abnormal Color of cord and membrane and fetal surface related to the meconium				
No	1405 (87.3)	25640 (93.4)	ref	ref
Yes	204 (12.7)	1803 (6.6)	2.07 (1.69, 2.53)	1.62 (1.30, 2.01)
Maturity of the placenta				
Normal	1562 (96.7)	25750 (93.3)	ref	ref
Immaturity	53 (3.3)	1849 (6.7)	0.47 (0.33, 0.68)	0.53 (0.36, 0.78)
Abnormal type of insertion of membranes				
No	1478 (91.5)	25316 (91.8)	ref	ref
Yes	138 (8.5)	2274 (8.2)	1.04 (0.82, 1.32)	1.04 (0.81, 1.34)
True cysts in cut surface				
No	1519 (93.8)	26547 (96.1)	ref	ref
Yes	101 (6.2)	1067 (3.9)	1.65 (1.26, 2.18)	1.48 (1.10, 1.98)

Note: Descriptive data presented as n (%). †From logistic regression models adjusted for weight gain during the pregnancy, pre-pregnant BMI, marital status, race, socio-economic status, education status, smoking, parity, maternal age, chronic diabetes, gestational diabetes, chronic hypertension, gestational hypertension.

tal pathology, it is difficult to obtain comprehensive placental pathological information as a routine. As a result, placental structure as a potentially promising marker of clinical insult has been largely unexplored [11].

Our study used the comprehensive placental pathological information in a large population of CPP and demonstrated that some placental pathologic features are related to macrosomia. The larger chorion disc square, thicker placenta, longer length of cord and longer distance from the cord insertion to the closest placental margin are associated with a higher risk of macrosomia. This is consistent with the findings from previous studies [10-13, 30].

Placental microscopic measures

Macrosomia was associated with more frequent thrombosis in cut surface, fetal neutrophilic infiltration, true cysts in cut surface, pig-

ment of macrophage cell and abnormal color of cord, membrane and fetal surface stained by meconium. Evers [31] studied in appropriate gestational age (AGA)- and large for gestational age (LGA)-placentae of type 1 diabetic women and in AGA- and LGA-placentae of control women, and found that LGA-control placentae showed a high prevalence of histological abnormalities almost comparable to the diabetic placentae. This is partly consistent with our study findings.

Neutrophilic infiltration in umbilical vessel, meconium staining and chorionic vessel thrombi have been related to adverse perinatal or even child health outcomes [32-36]. For example, Ziadeh et al. [36] found that meconium staining of the amniotic fluid was associated with poor neonatal outcomes such as perinatal mortality and severe fetal acidemia. Meconium staining was associated with chorioamnionitis [37]. Acute chorioamnionitisis is one of the main causes of premature rupture of membranes and preterm delivery, and a risk factor for periventricular leucomalacia and cerebral palsy [38, 39]. Zhao et al. used LASSO to select placental measures which are predictive of childhood diseases. Among them, placental and membrane inflammation was a strong predictor of childhood health [9]. These findings have linked placental lesions to disease risk in later life [40]. Maybe these lesions that we found could explain why the macrosomia was associated with the higher risk of disease in later life. More linear studies on relationship of these placental lesions and outcomes of macrosomia babies were needed to confirm this hypothesis.

The prevalence of macrosomia was 5.35% in CPP while it is 8% in the US today [2]. And macrosomia today may have somewhat different etiologies from those of 50 years ago, as maternal obesity is more common [18]. Do our findings have any practical implications nowadays? It is difficult to assess because little has been published on placental pathology in macrosomia in more recent studies. In a cohort study conducted in 2010, Sandra et al. found that maternal obesity was associated with an increased risk of chronic villitis independent of diabetes [35], which is consistent with our finding. Thus, our results may serve as a stepstone for future studies on placenta pathological lesions in macrosomia, which may have long-term implications for health and disease risk in later life. It would be of interest to compare our findings with a contemporary large birth cohort with similarly rich data on placenta pathology in the future.

Strengths and limitations

To our knowledge, this is the largest study to examine placental pathology in macrosomia. To determine the relationships between variables with relatively low frequencies, a large sample size is required. Thus, the prospectively collected CPP data are particularly useful to study these relationships, not to mention that CPP is still the most comprehensive placenta database in the world. However, our study has limitations. First, the placental pathologies were performed in the 1960s. Some techniques and diagnostic criteria may have changed overtime. However, for most placental pathological lesions such as ischemia, thrombosis, and hemorrhage, the diagnostic criteria remain relatively unchanged. Most importantly, the variation in diagnostic criteria of placental lesions may unlikely be related to macrosomia, and therefore should not bias our findings.

In conclusion, macrosomia is associated with larger and thicker placenta, longer length of cord, higher prevalence of thrombosis in cut surface, fetal neutrophilic infiltration, meconium pigment of macrophage cell and meconium stain. These lesions may partly explain the long-term impact of macrosomia on health in later life.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Definition of placental pathological lesions in the Collaborated Perinatal Project, 1959-1966

Placental pathological lesions	Definition
Placental gross measures	
Placenta weight	Proportion of placental weight lower than 10th percentile of CPP (330 grams).
Abnormal Chorionic disc shape	round-to-oval or other shape (bipartite, tripartite, succenturiate, membranous, crescent or 'irregular')
Cord insertion	Distance from the cord insertion to the closest placental margin
Chorionic disc square	Proportion of placental square larger than 90th percentile or smaller than 10th percentile of CPP
Placental disc thickness	Proportion of placental thickness larger than 90th percentile or smaller than 10th percentile of CPP
Umbilical cord length	Proportion of cord length larger than 90th percentile or smaller than 10th percentile of CPP
Maternal origin vascular characteristics	
Infarcts in cut surface	
Occurrence of vascular infarcts	Infarcts in maternal surface or maternal floor infarcts in cut surface
Infarct size ≥3 cm	At least one infarct ≥3 cm in cut surface
Infarct number ≥3	Infarct number ≥3
Thrombosis in cut surface	Inter-villous thrombosis in cut surface or vessels thrombosis in decidua or Inter-villous thrombi (microscopy)
Vessel lesion in decidua	Vessels atheroma or fibrosis or thrombi in decidua
Necrosis of decidua	Necrosis in capsularis or basalis or at margin
Maternal origin villous characteristics	
Villous infarcts	Micro infarcts in terminal villi or Villous infarction in inter-villous space
Excessive Syncytium-Nuclear clumping	Excessive Syncytium-Nuclear clumping in decidua
Fetal origin vascular characteristics	Thrombosis in membrane vessels or fetal surface vessels or cord vessels
Fetal origin villous characteristics	Emergence of stromal fibrosis in terminal villous or Langhans layer in terminal villous
Inflammatory cell infiltration	
Fetal neutrophilic infiltration	Neutrophilic infiltration in umbilical vessels or cord substance or chorion and amnion of membrane roll or in placental surface
Maternal neutrophilic infiltration	Neutrophilic infiltration in decidua
Maternal Lymphocytic infiltration	Lymphocytic infiltration in capsularis or basalis or at margin
Calcification throughout cut surface	Calcification throughout cut surface
Fibrin deposition of fetal membranes	Sub-chorionic fibrin in membranes and fetal surface or cytotrophoblast of columns fibrin deposition in decidua
Meconium	
Pigment of macrophage cells	Macrophage with meconium pigment in amnion or chorion in membranes or decidua
Abnormal color of cord and membrane and fetal surface related to the meconium	Green color of cord and membrane and fetal surface
Maturity of the placenta	Apparent maturity of placenta in inter-villous space
Abnormal type of insertion of membranes	Abnormal type of insertion of membranes into the placenta disc: circum marginate or circumvallate
True cysts in cut surface	The number of true cysts in cut surface >0