Parental consanguinity in Hong Kong

KH Siong *, Sidney KC Au Yeung, TY Leung

ABSTRACT

Introduction: Consanguineous union increases the risk of genetic disorders in offspring. The present study aimed to evaluate the prevalence and characteristics of parental consanguinity in Hong Kong, and its effects on pregnancy, perinatal, and child health outcomes.

Methods: Pregnant women in consanguineous unions attending an obstetrics unit at a public hospital in Hong Kong were retrospectively studied. Their pregnancy, perinatal, and child health outcomes were compared with an ethnicity-matched control group of pregnant women in non-consanguineous unions.

Results: The overall prevalence of parental consanguinity was 0.6% (first cousins or closer, 78.4%; beyond first cousins, 21.6%). The majority were ethnic Pakistani (85.0%). Women in consanguineous unions were more likely to have an obstetric history of congenital abnormality (10.5%), unexplained intrauterine fetal demise (4.2%) and unexplained neonatal death (4.6%), or family history of congenital abnormality (4.6%). Offspring of consanguineous parents had significantly higher risk of recessive diseases (odds ratio [OR]=8.70, 95% confidence interval [CI]=1.06-71.36), structural abnormalities (OR=4.55, 95% CI=2.17-9.53) and developmental delay (OR=6.72, 95% CI=1.48-30.63), and significantly higher incidence of autistic spectrum disorder (2.1%; P=0.008).

Conclusions: It is essential that information on the increased risks associated with parental consanguinity is included in genetic counselling for consanguineous couples, so that they can make informed decisions.

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New knowledge added by this study

- The majority of consanguineous unions in Hong Kong are of Pakistani ethnicity.
- It is well known that, in addition to recessive genetic diseases, offspring of consanguineous unions have higher incidences of non–genetically confirmed structural abnormalities, developmental delay, and autism spectrum disorders. The present study confirms this in the Hong Kong population.

Implications for clinical practice or policy

- Identification of consanguineous couples is essential to ensure appropriate referral for genetic counselling and diagnosis.
- Health education and information about availability of carrier screening should be provided for consanguineous couples to make informed choices.

Introduction

'Consanguinity' is a term derived from the Latin word 'consanguineus', meaning 'of the same blood'. In medical genetics, consanguineous union is generally referred as a union between couples related as second cousins or closer.[1] The prevalence of consanguinity varies significantly worldwide, depending on cultural background, religious belief, and geography. The highest rates are estimated in the Near and Middle East and in Northern Africa, where 20% to 50% of marriages are consanguineous.[1,2] The prevalence in Southern Europe, South America, and Japan is about 1% to 5%, whereas Western European countries, North America, and Oceania have the lowest prevalence of <1%.[1,2]

Consanguineous union increases the risk of genetic disorders in offspring, especially for autosomal recessive diseases. However, recent studies suggest that parental consanguinity is also a risk factor for other adverse outcomes, even in developed multi-ethnic countries where the prevalence of consanguineous marriages is perceived as lower. For example, in Vienna where the background consanguinity rate was <1%, Posch et al[3] reported that 39.7% of consanguineous couples had obstetric history of congenital malformations or genetic disorders. Becker et al[4] reported that 6.1% of consanguineous couples were referred to a specialist centre in Germany for a history of major fetal anomalies. A 10-year retrospective analysis

conducted in Australia, where the consanguinity rate is 5.5%, concluded that parental consanguinity was associated with higher rates of threatened premature labour, fetal congenital abnormality, stillbirth, and perinatal mortality.[5] In that study, consanguinity was also found to be an independent risk factor of nearly 3-fold for stillbirth.

In Hong Kong, parental consanguinity is more frequent among non-Chinese ethnic minorities, which account for 8% of the total population.[6] Internationally, healthcare workers lack knowledge on the risks of consanguinity.[7-9] Inconsistencies in information provided during genetic counselling and screening has been observed.[10] Consanguineous couples are often unaware of the potential health hazards in their offspring.[11-13] The level of concern and awareness of the adverse effects of parental consanguinity among patients and physicians is low, and available data on consanguinity in Hong Kong are limited. Therefore, in the present study, we aimed to clarify the prevalence and characteristics of pregnancies from consanguineous unions in Hong Kong, and to assess the related effects on maternal, perinatal, and child health outcomes.

在香港父母乃血親通婚的情況

常家雄、歐陽錦全、梁德楊

引言：血親通婚會增加後裔患上遺傳基因毛病的風險。本研究旨在評估香港現時血親通婚的普遍情況和特點，及其對懷孕期、後裔嬰孩及兒童期健康的影響。

方法：在一所香港公立醫院產科部門進行對血親通婚之孕婦的回溯性研究，將她們的懷孕期、後裔嬰孩及兒童期健康結果與同一種族的非血親通婚之孕婦的結果作比較。

結果：血親通婚的普及率為0.6%（堂表通婚或更近親通婚佔78.4%；堂表以外通婚佔21.6%）。大部分血親通婚之孕婦為巴基斯坦裔（85.0%）。血親通婚之孕婦較常有先天缺陷（10.5%）、原因不明的宮內胎兒死亡（4.2%）、原因不明的新生兒死亡（4.6%）的產科病史，以及有先天缺陷的家族病史（4.6%）。血親通婚的後裔有明顯較高患有隱性遺傳病（對比值：8.70，95%置信區間：1.06-71.36）、結構缺陷（對比值：4.55，95%置信區間：2.17-9.53）和發展遲緩（對比值：6.72，置信區間：1.48-30.63）的風險，自閉症譜系障礙的患病率亦明顯較高（2.1%；P=0.008）。

結論：在遺傳諮詢的過程中，應對血親通婚夫婦提供他們後裔有較高健康風險的資訊，讓他們作出適合自己的檢查決定。

Methods

The Prenatal Diagnosis Clinic in Tuen Mun Hospital is responsible for counselling consanguineous couples. Dating ultrasound and counselling sessions for Down syndrome screening are arranged for all pregnant women who have their booking appointment in our locality. At the booking appointment, patients are also asked about consanguinity. Hospital-accredited interpreters are arranged for couples who are not fluent in Cantonese or English. Identification of consanguineous cases depends on self-reporting by couples. A pedigree chart is constructed for each case. Couples are counselled about the possible effects of parental consanguinity on pregnancy outcomes, and advised to attend antenatal care regularly.

A retrospective cohort study of all parental consanguinity cases over a 10-year period from 1 January 2007 to 31 December 2016 was conducted. The antenatal records of these cases were reviewed. Details were gathered about pregnancy loss, fetal congenital abnormalities, pregnancy and perinatal outcomes, and neonatal and childhood development in the preceding pregnancy. The family history of each case was also collected from patient records, including known genetic or congenital anomalies, or intellectual or developmental disabilities. A morphology scan was arranged for consanguineous cases. Each family pedigree was studied to determine the degree of parental consanguinity (Fig). Only couples fulfilling the definition of consanguineous unions (second cousins or closer) were included for analysis in the present study.

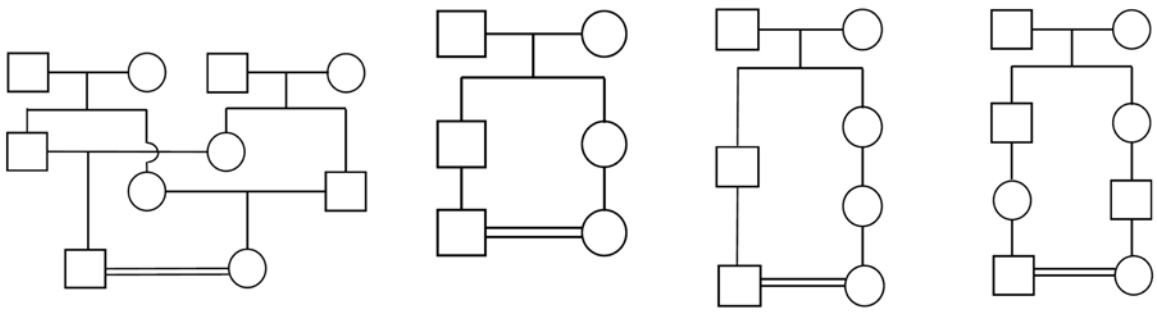

FIG. Family trees of consanguineous marriages with corresponding coefficients of inbreeding (F)

Socio-demographic characteristics were collected, including ethnicity, maternal and paternal age, religious beliefs, working status, education level, and occupation. Maternal antepartum and peripartum characteristics, and fetal and perinatal information were available. Information about the neonatal, infancy, and childhood outcomes of the offspring were retrieved from the public sector electronic record system.

The relationship between consanguinity and fetal, neonatal, infant, or childhood diseases that required long-term paediatric management was evaluated and categorised into one of three categories:

Category A—Improbable association with consanguinity: cases known to be caused by numerical or structural chromosomal abnormalities, or not to have an autosomal recessive mode of inheritance;

Category B—Probable association with consanguinity: cases known to have an autosomal recessive mode of inheritance, particularly when both parents were found to be the carriers of genetic disorders; and

Category C—Possible/unclear association with consanguinity: cases where the mode of inheritance was unclear, or when genetic testing was unremarkable.

The characteristics and outcomes of consanguineous cases were compared with a control group of non-consanguineous unions. The next record of a non-consanguineous case of the same ethnicity after that of a case of consanguineous union was selected as the control. This ensured the similar composition of ethnicity which might have socio-economic effects on the maternal and fetal outcomes within the study and control groups.[14] As some consanguineous couples might have contributed more than one pregnancies in our database, only adverse past obstetric outcome in the immediately preceding pregnancy was counted in the analysis, and any positive family history reported by such couples was counted as one case only, in order to prevent duplicated entries for multigravida women. Most previous studies have not evaluated the effects of closer consanguinity that might increase risks of hereditary disorders.[5,15,16] To evaluate the effect of degree of inbreeding, comparisons were made among 'first cousin or closer' (including first cousin and double first cousin), 'beyond first cousin' (including first cousin once removed and second cousin), and non-consanguineous relationships.

Approval of this study was granted by the research and ethics committee of the study hospital. Guidelines for reporting observational studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement were followed.

Statistical analysis was performed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], US). Cross-tabulation between degrees of consanguinity and the different variables was performed in order to evaluate the characteristics of the study population. Differences in continuous variables were compared using *t* test or one-way analysis of variance. Differences in categorical variables were analysed with Chi squared test or Fisher's exact test. Linear regression was carried out to adjust the collinearity among variables. Multivariate logistic regression analysis was used to determine the risk of consanguinity for adverse pregnancy and perinatal outcomes, with adjustment of significant confounders. Adjusted odds ratio (OR) with 95% confidence interval (CI) were calculated. Statistical significance was established for $P<0.05$.

Results

Of 56 657 fetuses, 334 (0.6%) were conceived by consanguineous parents; of these, the majority (85.0%, 284 of 334) were ethnic Pakistani (among whom the prevalence of consanguineous union is highest, at 30.5%), followed by Indian (6.2%), Nepalese (2.7%), Filipino (0.4%), and Chinese (0.04%) [Table 1]. Of all consanguineous unions, the majority were first cousin consanguineous unions (76.6%)

TABLE 1. Ethnicity and consanguinity in mothers of 56 657 fetuses from 2007 to 2016

Ethnicity	No. of fetuses	First cousin or closer (n=262, 78.4%)		Beyond first cousin (n=72, 21.6%)		Total parental consanguinity in ethnicity
		First cousin	Double first cousin	First cousin once removed	Second cousin	
All ethnicities	56 657	256 (76.6%)	6 (1.8%)	17 (5.1%)	55 (16.5%)	334 (0.6%)
Chinese	49 032	17	0	0	3	20 (0.04%)
Filipino	235	0	0	0	1	1 (0.4%)
Indian	177	11	0	0	0	11 (6.2%)
Nepalese	669	13	0	0	5	18 (2.7%)
Pakistani	931	215	6	17	46	284 (30.5%)
Others	5613	0	0	0	0	0

and double first cousin unions (1.8%); together, these were categorised as first cousin or closer (≤1C) unions. The remainder were categorised as beyond first cousin (>1C) unions, and included first cousin once removed unions (5.1%), and second cousin unions (16.5%). Comparison of background variables including maternal and paternal age, education level, religion, length of stay in Hong Kong, marital status, working status, occupation, parity, and body mass index showed no significant differences between the consanguineous group and the non-consanguineous control group (Table 2).

TABLE 2. Background characteristics of 334 fetuses with consanguineous parents and 334 control fetuses with non-consanguineous parents*

Characteristics	Non-consanguineous parents (n=334)	Consanguineous parents (n=334)	P value
Maternal age (years)	28.4 ± 5.25	28.3 ± 5.37	0.776
<20	16 (4.8%)	12 (3.6%)	0.638
20-35	282 (84.4%)	281 (84.1%)	
≥35	36 (10.8%)	41 (12.3%)	
Maternal education level			
Elementary	105 (31.4%)	117 (35.0%)	0.600
Secondary	171 (51.2%)	164 (49.1%)	
Tertiary	58 (17.4%)	53 (15.9%)	
Maternal religion			
Buddhist	18 (5.4%)	18 (5.3%)	0.192
Christian	3 (0.9%)	1 (0.3%)	
Hindu	14 (4.2%)	9 (2.7%)	
Muslim	277 (82.9%)	276 (82.6%)	
Nil	10 (3.0%)	3 (0.9%)	
Not reported	12 (3.6%)	27 (8.2%)	
Maternal length of stay in Hong Kong (years)	8.89 ± 8.88	8.69 ± 8.79	0.772
Married	334 (100%)	334 (100%)	-
Working mother	35 (10.5%)	28 (8.4%)	0.354
Paternal age (years)	33.0 ± 6.54	31.6 ± 5.52	0.070
Paternal occupation			
Unskilled manual	77 (23.1%)	116 (34.7%)	0.810
Skilled manual/professional	82 (24.6%)	119 (35.6%)	
Self-employed	43 (12.8%)	51 (15.3%)	
Unemployed	23 (6.9%)	34 (10.2%)	
Not reported	109 (32.6%)	14 (4.2%)	
Parity			
0	83 (24.9%)	95 (28.4%)	0.248
1-2	169 (50.6%)	153 (45.9%)	
≥3	82 (24.5%)	86 (25.7%)	
Maternal body mass index (kg/m^2)			
<18.5	19 (5.7%)	21 (6.3%)	0.727
18.5 to <25	146 (43.7%)	128 (38.3%)	
25 to <30	103 (30.8%)	114 (34.1%)	
30 to <35	47 (14.1%)	54 (16.2%)	
35 to <40	14 (4.2%)	14 (4.2%)	
≥40	5 (1.5%)	3 (0.9%)	
Spontaneous conception	334 (100%)	334 (100%)	-
Maternal smoking/substance abuse	0	0	-

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

Women in consanguineous unions were significantly more likely to have experienced congenital abnormality (10.5% vs 0.4%; P<0.001), unexplained intrauterine fetal demise (4.2% vs 0.4%; P=0.005) and neonatal death (4.6% vs 1.2%; P=0.024) in the preceding pregnancy, and family history of congenital abnormality (4.6% vs 0%; P<0.001) than were non-consanguineous controls (Table 3). Down syndrome screening was offered to all women, but the attendance was only about one-fifth for all groups.

In terms of major maternal and perinatal complications, there were no significant differences between the non-consanguineous control group and the overall consanguineous group or the subgroups, except that pregnancies of ≤1C unions were more often complicated with pre-eclampsia (4.2% vs 1.2%; P=0.02) than were those of the non-consanguineous control group (Table 4).

Altogether there were 58 fetuses and 14 fetuses having different abnormalities, from 55 consanguineous and 14 control couples respectively (Table 5). Offspring of consanguineous couples had a higher risk of having category C disorders (OR=4.60; 95% CI=2.35-9.00) or category B disorders (OR=8.70; 95% CI=1.06-71.36), compared with those of non-consanguineous couples. The overall prevalence of category C disorders (14.7%) was higher than that of category B disorders (2.4%). Compared with the non-consanguineous control group, the prevalence of category C disorders was significantly higher in the ≤1C subgroup (OR=5.59; 95% CI=2.83-11.06); it was lower in the >1C subgroup, but the difference was not significant.

The prevalence of structural malformations was higher in the consanguineous group than that in the non-consanguineous control group, especially for those abnormalities involving cardiovascular, musculoskeletal, and urological systems (Table 5). Parental consanguinity also significantly increased the risk of developmental delay in offspring of consanguineous couples (OR=6.72, 95% CI=1.48-30.63) and in those of ≤1C couples (OR=7.64, 95% CI=1.64-35.58). Autism spectrum disorder was more prevalent in offspring of consanguineous couples (2.1%) than in those of non-consanguineous couples (0%) [P=0.008]. The diseases recorded in the consanguineous group and in the control group are detailed in online supplementary Appendices 1 and 2, respectively.

TABLE 3. Pregnancy characteristics of 334 fetuses with consanguineous parents and 334 control fetuses with non-consanguineous parents*

Characteristics	Non-consanguineous parents (n=334)	Consanguineous parents (n=334)	P value	First cousin or closer (n=262)	P value†	Beyond first cousin (n=72)	P value†
T1 miscarriage in the preceding pregnancy	72 (27.1%)‡	82 (32.7%)‡	0.164	71 (35.5%)‡	0.051	11 (21.6%)‡	0.431
T2 miscarriage in the preceding pregnancy	2 (0.8%)‡	6 (2.4%)‡	0.131	5 (2.5%)‡	0.125	1 (2.0%)‡	0.414
Preceding child with congenital abnormality	1 (0.4%)§	25 (10.5%)§	<0.001	22 (11.6%)§	<0.001	3 (6.1%)§	0.001
Preceding child with ID/DD	2 (0.8%)§	6 (2.5%)§	0.135	6 (3.2%)§	0.066	0§	0.531
Unexplained IUFD in the preceding pregnancy	1 (0.4%)§	10 (4.2%)§	0.005	9 (4.7%)§	0.002	1 (2.0%)§	0.196
Unexplained NND in the preceding pregnancy	3 (1.2%)§	11 (4.6%)§	0.024	11 (5.8%)§	0.006	0§	0.442
Family history of congenital abnormality	0	9 (4.6%)‖	<0.001	5 (3.3%)‖	0.001	4 (9.1%)‖	<0.001
Family history of ID/DD	0	2 (1.0%)‖	0.064	1 (0.7%)‖	0.138	1 (2.3%)‖	0.005
Multiple pregnancy	4 (1.2%)	6 (1.8%)	0.524	4 (1.5%)	0.729	2 (2.8%)	0.314
DSS performed	78 (23.4%)	65 (19.5%)	0.220	52 (19.8%)	0.304	13 (18.1%)	0.328
Structural scan performed	56 (16.8%)	192 (57.5%)	<0.001	153 (58.4%)	<0.001	39 (54.2%)	<0.001

Abbreviations: DSS = Down syndrome screening; ID/DD = intellectual disability or developmental delay; IUFD = intrauterine fetal demise; NND = neonatal death; T1 = first trimester; T2 = second trimester

* Data are shown as No. (%), unless otherwise specified

† Comparison with non-consanguineous controls

‡ Primigravida women excluded in the calculation, only multigravida women used for analysis (non-consanguineous, 266; overall consanguineous, 251; first cousin or closer, 200; beyond first cousin, 51)

§ Nulliparous women excluded in the calculation, multiparous women used for analysis (non-consanguineous, 251; overall consanguineous, 239; first cousin or closer, 190; beyond first cousin, 49)

‖ Positive family history reported by a multigravida woman was counted as one case only to avoid duplicated data entries (non-consanguineous, 334; overall consanguineous, 196; first cousin or closer, 152; beyond first cousin, 44)

TABLE 4. Maternal and perinatal outcomes of 334 fetuses with consanguineous parents and 334 control fetuses with non-consanguineous parents*

Outcomes	Non-consanguineous parents (n=334)	Consanguineous parents (n=334)	P value	First cousin or closer (n=262)	P value†	Beyond first cousin (n=72)	P value†
Diabetes	46 (13.8%)	59 (17.7%)	0.167	51 (19.5%)	0.062	8 (11.1%)	0.546
Hypertensive disorders	20 (6.0%)	17 (5.1%)	0.612	11 (4.2%)	0.329	6 (8.3%)	0.461
Pre-eclampsia	4 (1.2%)	11 (3.3%)	0.068	11 (4.2%)	0.020	0	0.351
APH	8 (2.4%)	14 (4.2%)	0.193	10 (3.8%)	0.314	4 (5.6%)	0.145
TOP	0	2 (0.6%)	0.157	2 (0.8%)	0.110	0	-
Miscarriage	0	1 (0.3%)	0.317	1 (0.4%)	0.258	0	-
IUFD	2 (0.6%)	1 (0.3%)	0.563	1 (0.4%)	0.710	0	0.510
Preterm labour	32 (9.6%)	36 (10.8%)	0.609	27 (10.3%)	0.769	9 (12.5%)	0.456
GA at delivery (weeks)	38.5 ± 2.31	38.5 ± 1.94	0.791	38.4 ± 2.02	0.766	38.5 ± 1.63	0.978
Spontaneous labour	185 (55.4%)	163 (48.8%)	0.88	127 (48.5%)	0.093	36 (50%)	0.405
MOD							
Normal VD	208 (62.3%)	199 (59.6%)	0.493	157 (59.9%)	0.707	42 (58.3%)	0.376
Instrumental VD	19 (5.7%)	15 (4.5%)		13 (5.0%)		2 (2.8%)	
Caesarean section	107 (32.0%)	120 (35.9%)		92 (35.1%)		28 (38.9%)	
PPH	14 (4.2%)	13 (3.9%)	0.844	10 (3.8%)	0.817	3 (4.2%)	0.992
Birth weight (kg)	3.11 ± 0.59	3.07 ± 0.54	0.365	3.07 ± 0.55	0.409	3.07 ± 0.47	0.584
IUGR/SGA baby	24 (7.2%)	33 (9.9%)	0.213	28 (10.7%)	0.133	5 (6.9%)	0.943
Sex							
Female	160 (47.9%)	163 (48.8%)	0.816	122 (46.6%)	0.745	41 (56.9%)	0.164
Male	174 (52.1%)	171 (51.2%)		140 (53.4%)		31 (43.1%)	
AS <7 at 1 minute	15 (4.5%)	10 (3.0%)	0.308	9 (3.4%)	0.515	1 (1.4%)	0.220
AS <7 at 5 minutes	2 (0.6%)	0	0.157	0	0.210	0	0.510
NICU admission	9 (2.7%)	16 (4.8%)	0.154	12 (4.6%)	0.215	4 (5.6%)	0.211
Neonatal sepsis	7 (2.1%)	7 (2.1%)	1.000	7 (2.7%)	0.645	0	0.215
Neonatal RDS	7 (2.1%)	8 (2.4%)	0.794	6 (2.3%)	0.872	2 (2.8%)	0.721
Neonatal jaundice	29 (8.7%)	42 (12.6%)	0.103	35 (13.4%)	0.067	7 (9.7%)	0.778
Neonatal death	3 (0.9%)	5 (1.5%)	0.477	3 (1.1%)	0.764	2 (2.8%)	0.190

Abbreviations: APH = antepartum haemorrhage; AS = Apgar score; GA = gestational age; IUFD = intrauterine fetal demise; IUGR = intrauterine growth restriction; MOD = mode of delivery; NICU = neonatal intensive care unit; PPH = postpartum haemorrhage; RDS = respiratory distress syndrome; SGA = small for gestational age; TOP = termination of pregnancy; VD = vaginal delivery

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

† Comparison with non-consanguineous controls

Discussion

To the best of our knowledge, this is the first comprehensive study in Hong Kong describing the prevalence of parental consanguinity. Our results support those of previous studies that revealed a higher prevalence of parental consanguinity in certain ethnic groups, and the higher prevalence of known genetic disorders (category B) among their offspring. In addition, our study has revealed that the prevalence of fetal structural abnormalities, developmental delay, and autism spectrum disorders (category C) are also high. This has implications for prenatal counselling and diagnosis, and related healthcare services.

Our comparison of maternal age and parity showed no significant difference between the consanguineous group and control group. This is in contrast to findings by Islam et al[16] and Hosseini-Chavoshi et al,[17] who found that women in consanguineous unions were younger and of higher parity in Iran and Oman, where the consanguinity rate was more than 30%. Studies in India and Pakistan populations also showed that mothers in consanguineous relationships were more likely to be socially and economically disadvantaged.[11,18] The similarity in the socio-economic characteristics

TABLE 5. Causative association of abnormalities with degree of parental consanguinity in 334 fetuses with consanguineous parents and 334 control fetuses with non-consanguineous parents

Abnormalities	Non-consanguineous parents (n=334)	Consanguineous parents (n=334)	OR (95% CI)	P value	First cousin or closer (n=262)	OR* (95% CI)	P value	Beyond first cousin (n=72)	OR* (95% CI)	P value
Category A: Improbable association with consanguinity	1 (0.3%)	1 (0.3%)	1.31 (0.08-21.13)	0.847	1 (0.4%)	1.79 (0.11-28.86)	0.681	0	<0.001	0.997
Category B: Probable association with consanguinity	1 (0.3%)	8 (2.4%)	8.70 (1.06-71.36)	0.044	7 (2.7%)	9.89 (1.18-83.01)	0.035	1 (1.4%)	5.43 (0.33-89.18)	0.236
Category C: Possible/unclear association with consanguinity†	12 (3.6%)	49 (14.7%)	4.60 (2.35-9.00)	<0.001	45 (17.2%)	5.59 (2.83-11.06)	<0.001	4 (5.6%)	1.77 (0.54-5.80)	0.348
Isolated involvement‡	12 (3.6%)	41 (12.3%)	3.70 (1.86-7.33)	<0.001	38 (14.5%)	4.44 (2.21-8.90)	<0.001	3 (4.2%)	1.42 (0.38-5.28)	0.605
Multiple involvement‡	0	8 (2.4%)		0.004§	7 (2.7%)		0.003§	1 (1.4%)		0.027§
Structural abnormalities†	10 (3.0%)	38 (11.4%)	4.55 (2.17-9.53)	<0.001	35 (13.4%)	5.49 (2.59-11.62)	<0.001	3 (4.2%)	1.73 (0.45-6.65)	0.426
Cardiovascular	7 (2.1%)	19 (5.7%)	3.05 (1.22-7.61)	0.017	17 (6.5%)	3.55 (1.40-9.04)	0.008	2 (2.8%)	1.72 (0.34-8.78)	0.514
Craniofacial	2 (0.6%)	7 (2.1%)	3.10 (0.60-16.03)	0.178	6 (2.3%)	3.84 (0.72-20.52)	0.116	1 (1.4%)	1.23 (0.08-18.80)	0.883
Musculoskeletal	1 (0.3%)	9 (2.7%)	9.53 (1.10-82.34)	0.040	9 (3.4%)	12.48 (1.42-110.03)	0.023	0	0.00	0.997
Gastrointestinal	0	2 (0.6%)		0.157§	2 (0.8%)		0.108§	0	-	
Urological	0	6 (1.8%)		0.014§	6 (2.3%)		0.005§	0	-	
Non-syndromic sensorineural hearing loss	0	3 (0.9%)		0.083§	3 (1.1%)		0.050§	0	-	
Developmental and behavioural disorders†	2 (0.6%)	14 (4.2%)	6.72 (1.48-30.63)	0.014	12 (4.6%)	7.64 (1.64-35.58)	0.001	2 (2.8%)	4.11 (0.53-31.91)	0.178
Developmental delay	2 (0.6%)	14 (4.2%)	6.72 (1.48-30.63)	0.014	12 (4.6%)	7.64 (1.64-35.58)	0.001	2 (2.8%)	4.11 (0.53-31.91)	0.178
Autism spectrum disorder	0	7 (2.1%)		0.008§	6 (2.3%)		0.005§	1 (1.4%)		0.027§
Attention deficit hyperactivity disorder	0	2 (0.6%)		0.157§	2 (0.8%)		0.108§	0	-	

Abbreviations: 95% CI = confidence interval; OR = odds ratio

* Comparison with non-consanguineous controls

† A case may have clinical manifestations in more than one subcategory

‡ Subcategories used for analysis include cardiovascular, craniofacial, musculoskeletal, gastrointestinal, urological, developmental and behavioural, and hearing disorders

§ No cases in the control group, Chi squared test is used instead to compare groups

between the consanguineous and non-consanguineous unions of our study indicates that socio-economic factors are unlikely to be causes of the poorer fetal outcomes, both in the index pregnancy and the preceding pregnancy, found in our consanguineous group.

We identified eight offspring with autosomal recessive diseases in the consanguineous group, including three cases of beta-thalassaemia major and five cases of other rarer diseases (online supplementary Appendix 1). Although the carrier status of thalassaemia can be screened by low mean corpuscular volume of red blood cells, the carrier status of other recessive disorders can be more complex. For some disorders, comprehensive genetic carrier screening using exome sequencing is required.[4,19-21] Our data provide useful information for preconception counselling for consanguineous couples. However, exome sequencing is expensive, and this screening test is not yet available in public

hospitals. Health education and information about the availability of carrier screening should be provided to all pregnant women, regardless of cultural, religious, or socio-economic background. Once a consanguineous couple is diagnosed to be the carrier of a genetic disease, they should be encouraged to discuss carrier screening with their siblings, who may also carry the same recessive gene and be in consanguineous union. Access to obstetric care and genetic counselling services in prenatal diagnosis clinics allows couples to make informed choices. Knowledge on various cultural, religious, or socio-economic issues allows healthcare workers to provide appropriate support and to best advise patients.

Our results revealed that category C disorders are more prevalent among offspring of consanguineous couples, especially in the ≤1C subgroup. Fetal structural ultrasonographic examination should be offered to ≤1C couples, especially for the cardiovascular, urological, and skeletal systems.[22-26] Detailed genetic counselling and investigation services must be offered to ≤1C couples if fetal abnormalities are detected.[3,4]

Our results revealed increased risk of developmental and behavioural disorders for offspring of consanguineous couples. However, disorders such as developmental delay and autism spectrum disorder are not diagnosable before birth. Preconception and prenatal counselling should be offered to consanguineous couples, who should also be reminded about regular postnatal follow-up examinations, in order to avoid any delay in diagnosing any developmental or behavioural disorders.[27]

Pakistani ethnicity accounted for only 1.6% of all fetuses but 85% of consanguineous couples in our study. According to the Hong Kong 2016 population by-census, 0.25% of the total Hong Kong population was of Pakistani ethnicity.[6] However, the majority of this local Pakistani population is within potentially reproductive age-groups (15-24 years, 19.2%; 25-34 years, 14.9%; 35-44 years, 21.3%), and they tend to have more children per couple than do ethnic Chinese couples.[6] It is essential to include information about the increased risks of parental consanguinity during the antenatal care and provide appropriate genetic counselling once a consanguineous couple is identified.

In addition to poor fetal outcomes, we also found a 3-fold increased risk of pre-eclampsia among women in ≤1C unions. Familial aggregation and possible genetic correlation of pre-eclampsia have been observed, but the exact effect of consanguinity remains controversial.[28,29] Mumtaz et al[15] suggested that parental consanguinity is a risk factor of 1.6-fold for preterm birth at less than 33 weeks of gestation. Low birth weight has also been associated with first-cousin relationships, but the risk increase was found to be marginal (OR=1.36)[30]. Our study did not confirm higher incidences of antepartum, peripartum, neonatal and perinatal complications in overall consanguinity. Findings on the effect of consanguinity on various complications are inconsistent, especially when these complications are multifactorial in pathogenesis.[5,15,27,29,30]

One limitation of our study is the retrospective nature that might have led to incompleteness of information for analysis, especially when previous pregnancies were not in Hong Kong. Another limitation is that some of the fetal abnormalities classified under category C may in fact be category B disorders, as some of them recurred in the same couples (online supplementary Appendix 1); the majority of category C disorders did not receive genetic investigations. However, there is a high dependence on public health service in our locality, and this facilitated data retrieval of postnatal, infancy, and childhood outcomes of the offspring. Different types of parental consanguinity were also included in our analysis to provide the stratified risks according to the degree of inbreeding. Collection of socio-economic characteristics was also comprehensive. The same composition of ethnicity in both the consanguineous and control groups further minimised the socio-economic confounding effects in the analysis. Another limitation is that the genetic data were often incomplete or not up-to-date for the studied cases, which were recorded from 2007 to 2016.

It is recommended that a territory-wide prospective study is conducted on consanguineous couples to further delineate their healthcare needs in Hong Kong.

Conclusions

Identification of consanguineous couples is essential to ensure appropriate referral for preconception or prenatal counselling and diagnosis. Our study showed the majority of consanguineous unions in Hong Kong are of Pakistani ethnicity. International studies have reported that in addition to recessive genetic diseases, offspring of consanguineous unions have higher incidences of non–genetically confirmed structural abnormalities, developmental delay, and autism spectrum disorders. The present study confirms this in the Hong Kong population. Information on the increased risks associated with parental consanguinity should be included in genetic counselling for consanguineous couples, so that they can make informed decisions.

Author contributions

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.

Concept or design of the study: All authors.
Acquisition of data: KH Siong.
Analysis or interpretation of data: KH Siong, TY Leung.
Drafting of the manuscript: KH Siong, TY Leung.
Critical revision for important intellectual content: All authors.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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