Research Article ISSN 2639-9342

Gynecology & Reproductive Health

Maternal Obesity and the Risk of Selected Foetal Abnormalities (Neural Tube Defects and Orofacial Clefts) In Malaysia: A Retrospective Observational Study

Yi Rou Bah[1], Glenn Jing Yan Lye[2], Sisyena Anusha Gunaravi[3], Steven Toh[4], Vigneswari Vijayan[1], Grace Soon En Ting[1], Su Ming Tham[1], Nisha Angela Dominic[1], Ravichandran Jeganathan[5] and Valliammai Jayanthi Thirunavuk Arasoo[1*]

[1]*Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru, Johor, Malaysia.*

[2]*Faculty of Medicine, University of Southampton, United Kingdom.*

[3]*School of Medicine, Dentistry and Nursing, University of Glasgow, United Kingdom.*

[4]*School of Medicine, Faculty of Health and Life Sciences, University of Liverpool, United Kingdom.*

[5]*Department of Obstetrics and Gynaecology, Hospital Sultanah Aminah, Johor Bahru, Johor, Malaysia.*

[*]Correspondence:
Valliammai Jayanthi Thirunavuk Arasoo, Clinical School Johor Bahru, Monash University Malaysia, No. 8, Masjid Sultan Abu Bakar, 80100 Johor Bahru, Johor, Malaysia, +607-219 0600.

Received: 02 July 2021; **Accepted:** 30 July 2021

Citation: Bah YR, Lye GJY, Gunaravi SA, et al. Maternal Obesity and the Risk of Selected Foetal Abnormalities (Neural Tube Defects and Orofacial Clefts) In Malaysia: A Retrospective Observational Study. Gynecol Reprod Health. 2021; 5(4): 1-8.

ABSTRACT

Objective: *To evaluate the association between maternal obesity and the risk of selected foetal abnormalities (neural tube defects and orofacial clefts) in Malaysia.*

Materials and Methods: *We conducted a single-centre retrospective observational study on all women who delivered at Hospital Sultanah Aminah Johor Bahru, Malaysia from 1st January 2017 to 31st December 2018. The presence of neural tube defects (NTD) and orofacial clefts (OC) were identified from medical records, including all live births, stillbirths and terminations of pregnancy. All deliveries during the study period were reviewed to collect data on maternal weight, height and demographics. We performed multiple logistic regression to estimate factors contributing to selected anomalies.*

Results: *A total of 28,228 pregnancies were included. There were 57 NTD-affected pregnancies and 34 OC-affected pregnancies identified during the two-year study period. There was no statistically significant association found between maternal obesity and the occurrence of NTDs or OCs. Pre-gestational diabetes had a significant association with NTD-affected pregnancies (aOR 3.454, 95% CI [1.017, 11.725], p=0.091). The highest incidence rate of NTDs was among Malaysian Indians (2.540 per 1,000 deliveries). Malaysian Chinese and Malaysians of other ethnicities were found to have a significantly higher risk of having OC-affected pregnancies with aOR of 2.371 (95% CI [1.035-5.428], p=0.024) and 4.910 (95% CI [1.454-16.579], p=0.024) respectively.*

Conclusion: *Our study showed no significant association between maternal obesity and selected foetal abnormalities (NTD and OC), and that pre-gestational diabetes is a significant risk factor for NTD in Malaysia.*

Keywords
Cleft Lip, Cleft Palate, Foetal Abnormalities, Maternal Obesity, Neural Tube Defects.

Introduction
Over 1.9 billion people in the world are overweight (BMI>25), out of over 650 million are obese (BMI>30) [1]. 30% of adults in Malaysia are overweight, with almost one-fifth being obese [2]. The number of obese and overweight women in their childbearing age is increasing. Obese mothers are at significantly higher risk of gestational diabetes, gestational hypertension, thromboembolic events and miscarriages whilst their infants have a higher risk of foetal abnormalities and macrosomia [3-7].

Foetal abnormalities encompass a wide array of structural and functional defects that develop in utero [8]. Each year, approximately 7.9 million infants worldwide are born with a birth defect [9]. In Malaysia, neural tube defects (NTD) and orofacial clefts (OC) are among the most common and debilitating foetal abnormalities reported [10,11]. NTDs involve the failure of closure of the neural tube during the 3rd and 4th week of gestation [12]. This results in infant death or long-term disability depending on the anatomical site of the lesion [12]. OC results from abnormal facial development in embryogenesis between the 6th and 12th gestational week [13].

Maternal obesity is a risk factor for numerous foetal abnormalities, including NTDs and OCs [14-16]. A meta-analysis of 8 case-control studies and 4 cohort studies found that obese mothers have a 70% higher risk of having an infant affected by NTDs (OR 1.70, 95%CI 1.34-2.15), with severe obesity increasing the risk three-fold (OR 3.11, 95%CI 1.75-5.46) [17]. Another meta-analysis reported that obese women have a significantly higher risk of having an OC-affected pregnancy (OR 1.18, 95%CI 1.11-1.26) [18].

There is a distinct lack of studies evaluating the association of maternal obesity and foetal abnormalities in Malaysia, despite having the highest prevalence of obesity in Southeast Asia [19]. Most studies reporting the association are based on the Western population. Another team studied the prevalence of NTDs in Malaysia and the demographics of the mothers but maternal obesity as a risk factor for NTDs was not assessed due to incomplete data records [20]. The association between maternal BMI and orofacial clefts were also not addressed in recent epidemiological studies when evaluating the aetiology of orofacial clefts in Malaysia [21,22].

This study investigated the association between maternal obesity and selected foetal abnormalities – NTDs and OCs in Malaysia. Malaysia is unique as the population is multi-ethnic. The outcome of this study can serve as a guide for future studies related to NTDs and OCs and aid pre-pregnancy counselling for obese women.

Materials and Methods
This is a single-centre retrospective observational study. We included all women with a singleton birth and terminations of pregnancy for selected foetal anomalies at Hospital Sultanah Aminah Johor Bahru (HSAJB), Malaysia between 1st January 2017 and 31st December 2018. HSAJB is a public tertiary health facility and the main referral hospital for the southern region of Malaysia. Multiple pregnancies were excluded in the study as they have a higher risk of congenital anomalies compared to singleton pregnancies [23]. Information on all births was collected retrospectively from hospital records.

Details of all deliveries in HSAJB are recorded on birth notification slips which are then entered into the National Obstetric Registry (NOR) database. We retrieved all birth notification slips and manually extracted information on maternal age, ethnicity, weight and height during the first antenatal check-up, parity, gestational age and diabetic status for all deliveries between 1st January 2017 and 31st December 2018.

We included all live births, stillbirths and terminations of pregnancy due to NTDs or OCs by searching the consensus records of Labour Room, Obstetric Ward, Gynaecological Ward and Neonatal Ward for cases with a confirmed diagnosis of NTDs or OCs. The diagnoses of NTDs and OCs were made by clinicians through clinical examinations and imaging modalities. For terminations of pregnancy due to NTDs or OCs, a confirmed prenatal diagnosis of NTDs or OCs must be made by an obstetrician antenatally based on a detailed ultrasound scan. The data was later matched with data collected from birth notifications slips and medical records using the mother's identification number and hospital registration number.

The main independent variable in this study is maternal pre-pregnancy body mass index (BMI) recorded in the birth notification slips. Asian BMI cut-off points recommended by WHO were used to estimate obesity-related risks as the study is based upon an Asian population [24].

The covariates in this study were maternal age, ethnicity, maternal diabetic status, gestational age and parity. The ethnicity of the mothers was categorized into Malay, Chinese, Indian, others and non-Malaysians. Other ethnic groups included Iban, Kadazan and other indigenous groups in Malaysia. Maternal diabetic status was categorized into pre-existing diabetes, gestational diabetes and no diabetes. Gestational age was dichotomized into <37 weeks and ≥ 37 weeks.

A descriptive analysis was carried out for the entire study population on maternal characteristics including age, ethnicity, BMI, diabetic status, gestational age and parity. The incidence of NTDs and OCs in the study population were calculated and stratified by ethnicity and expressed as incidence per 1,000 births.

Two separate multiple logistic regression models were used to estimate the factors associated with NTDs and OCs respectively. For each regression model, binary logistic regressions were used to calculate crude odds ratios (ORs) for each variable

before selecting variables to be included in the multiple logistic regression. Only variables that had a p-value <0.25 in the binary logistic regressions or were clinically significant were included in the multiple regression models. The reference group for each variable were Malay ethnicity, normal BMI, gestational age >37 weeks, non-diabetic and non-primigravida. Adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated.

Statistical analyses were performed using IBM SPSS Statistics Version 25. Data entry and organization were done using Microsoft Excel. P<0.05 was considered statistically significant.

Results

There was a total of 28,228 singleton deliveries in Hospital Sultanah Aminah Johor Bahru between 1st January 2017 and 31st December 2018. 57 cases of neural tube defects and 34 cases of orofacial clefts were identified. The women in the study population had an average age of 29.2. Most of them were of Malay ethnicity (71.3%), overweight (29.7%), delivered beyond gestational age of 37 weeks (89%), non-diabetic (79.6%) and multiparous (68.8%). Summary of characteristics of the study population, NTD cases and OC cases can be found in Table 1.

Among the 57 identified pregnancies affected by NTDs, 40 (70.2%) were live births, 3 (5.3%) were stillbirths and 14 (24.5%) ended in termination of pregnancies (TOP). The incidence of NTDs in this study population was 2.019 per 1,000 pregnancies. After excluding termination of pregnancies and stillbirths, the incidence of NTD was 1.417 per 1,000 live births. Table 2 shows the incidence of NTDs based on ethnicities. The highest incidence rate of NTDs was among the Indians (2.540 per 1,000 deliveries), followed by Malays (2.136 per 1,000 deliveries), non-Malaysians (1.646 per 1,000 deliveries) and Chinese (1.530 per 1,000 deliveries). The commonest subtype of NTD was hydrocephalus (39.4%), followed by anencephaly (33.3%), spina bifida (21.2%), myelomeningocele (3%) and encephalocele (3%) (Figure 1).

The incidence of orofacial clefts in this study population was 1.204 per 1,000 live births. Stratifying by ethnicity, the incidence of orofacial clefts is the highest among Malaysians of other ethnics (4.870 per 1,000 deliveries), followed by Chinese (2.754 per 1,000

Table 1: Summary of characteristics of study population, NTD cases and OC cases.

Characteristics	General population (N=28228) Mean ± SD[a]	NTD[a] cases (N=57) Mean ± SD	OC[a] cases (N=34) Mean ± SD
Maternal age (years)	29.17 ± 5.44	29.18 ± 5.55	29.50 ± 5.02
	n (%)	n (%)	n (%)
Ethnicity			
Malay	20130 (71.3%)	43 (75.4%)	20 (58.5%)
Chinese	3268 (11.6%)	5 (8.8%)	9 (26.5%)
Indian	2362 (8.4%)	6 (10.5%)	1 (2.9%)
Others	616 (2.2%)	0 (0%)	3 (8.8%)
Non-Malaysians	1823 (6.5%)	3 (5.3%)	1 (2.9%)
Missing	29 (1%)	0 (0%)	0 (0%)
Maternal BMI[b]			
Underweight (<18.5)	2176 (7.7%)	2 (3.5%)	2 (5.9%)
Normal (18.5-22.9)	7769 (27.5%)	17 (29.8%)	12 (35.3%)
Overweight (23-27.4)	8375 (29.7%)	9 (15.8%)	10 (29.4%)
Obese 1 (27.5-32.4)	5349 (18.9%)	19 (33.3%)	7 (20.6%)
Obese 2 (32.5-37.4)	2238 (7.9%)	5 (8.8%)	1 (2.9%)
Obese 3 (>37.5)	939 (3.3%)	3 (5.3%)	1 (2.9%)
Missing	1382 (4.9%)	2 (3.5%)	1 (2.9%)
Gestational age			
<37weeks	2900 (10.3%)	23 (40.4%)	5 (14.7%)
>37 weeks	25109 (89%)	33 (57.9%)	29 (85.3%)
Missing	219 (0.8%)	1 (1.8%)	0 (0%)
Diabetic status			
No diabetes	22467 (79.6%)	44 (77.2%)	30 (88.2%)
GDM	5443 (19.3%)	10 (17.5%)	4 (11.8%)
Pre-existing diabetes	240 (0.9%)	3 (5.3%)	0 (0%)
Missing	78 (0.3%)	0 (0%)	0 (0%)
Parity			
Primigravida	8789 (31.1%)	14 (24.6%)	12 (35.3%)
More than one parity	19429 (68.8%)	43 (75.4%)	22 (64.7%)

[a]NTD, neural tube defects; OC, orofacial clefts; SD, standard deviation.
[b]WHO recommended Asian cut-off points for maternal body mass index (BMI) were used, with unit kg/m^2.

Table 2: Incidence rate of neural tube defects in the study population stratified by ethnicity.

Ethnicity	Total number of NTD[a] cases, n (%)	Total number of deliveries	Incidence per 1,000 deliveries
All ethnicities	57 (100%)	28228	2.019
Malay	43 (75.4%)	20130	2.136
Chinese	5 (8.8%)	3268	1.530
Indian	6 (10.5%)	2362	2.540
Others	0 (0%)	616	0
Non-Malaysians	3 (5.3%)	1823	1.646

[a]NTD, neural tube defects.
[b]Others include Iban, Kadazan, Orang Asli and other indigenous groups in Malaysia.

Table 3: Incidence rate of orofacial clefts in the study population stratified by ethnicity.

Ethnicity	Total number of OC[a] cases	Total number of deliveries	Incidence per 1,000 deliveries
All ethnicities	34	28228	1.204
Malay	20	20130	0.994
Chinese	9	3268	2.754
Indian	1	2362	0.423
Others[b]	3	616	4.870
Non-Malaysian	1	1823	0.549

[a]OC, orofacial clefts.
[b]Others include Iban, Kadazan, Orang Asli and other indigenous groups in Malaysia.

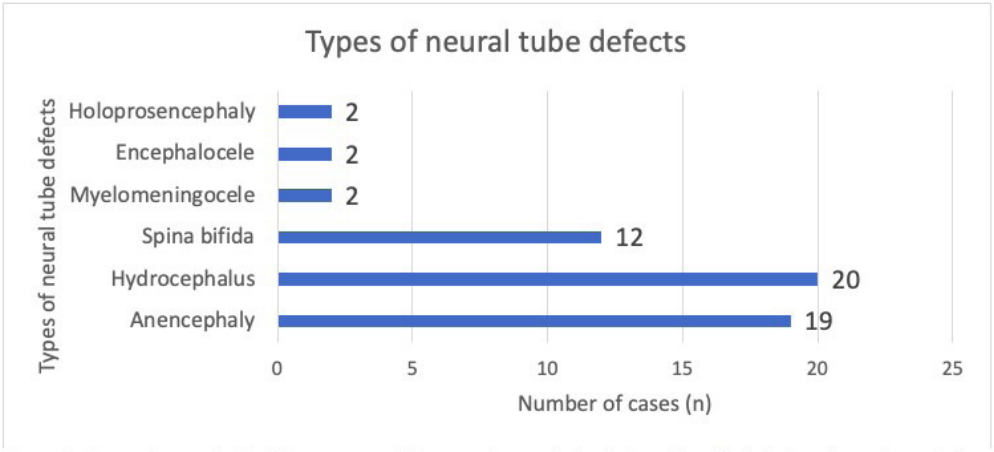

Figure 1: Types of neural tube defects among 57 cases of neural tube defects identified during the study period. Values are number of cases (n).

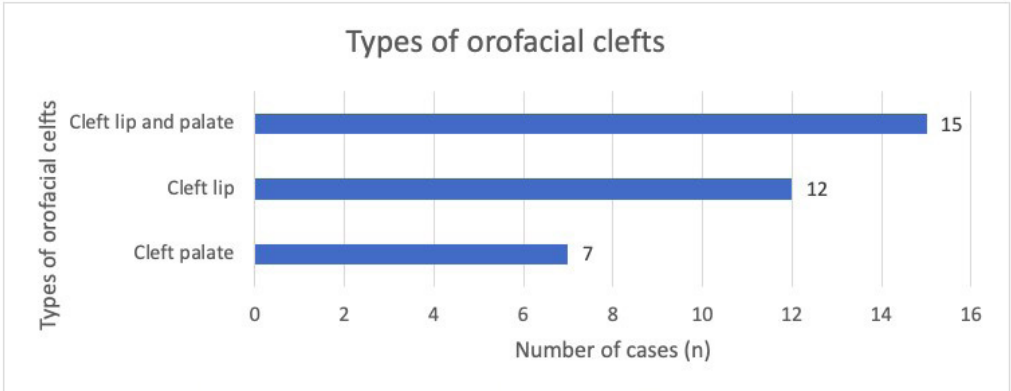

Figure 2: Types of orofacial clefts among 34 cases of orofacial clefts identified during the study period. Values are number of cases (n).

Table 4: Factors associated with pregnancy affected by neural tube defects.

		Crude OR[a] (95% CI)	P	Adjusted OR[b] (95% CI)	P
Age		1.00 (0.954-1.049)	0.995	Excluded[c]	
Ethnicity	Malay	Reference	0.923	Excluded[c]	
	Chinese	0.716 (0.283-1.808)			
	Indian	1.190 (0.506-2.798)			
	Others	<0.001			
	Non-Malaysians	0.770 (0.239-2.484)			
BMI	Underweight	0.420 (0.097-1.817)	0.054	0.394 (0.091-1.709)	
	Normal	Reference		Reference	0.068
	Overweight	0.491 (0.219-1.101)		0.496 (0.220-1.115)	
	Obese class 1	1.626 (0.844-3.130)		1.594 (0.814-3.122)	
	Obese class 2	1.021 (0.376-2.771)		0.949 (0.343-2.624)	
	Obese class 3	1.462 (0.0.428-4.997)		1.372 (0.393-4.791)	
Gestational age	>37 weeks	Reference	<0.001	Reference	<0.001
	<37weeks	6.075 (3.562-10.360)		5.816 (3.366-10.049)	
Diabetic status	No diabetes	Reference	0.007	Reference	0.091
	GDM	0.938 (0.472-1.865)		0.803 (0.395-1.631)	
	Pre-existing diabetes	6.451 (1.989-20.920)		3.454 (1.017-11.725)	
Parity	Not primigravida	Reference	0.285	Excluded[c]	
	Primigravida	0.719 (0.393-1.315)			

[a]Binary logistic regressions were used to calculate crude ORs.
[b]Multiple logistic regression Enter method applied. No multicollinearity detected. Hosmer-Lemeshow test, (p=0.258), classification table (overall correctly classified = 99.8%) and area under ROC curve (72.2%) was applied to test the model fitness.
[c]Age, ethnicity and parity were excluded in the multiple logistic regression model as their crude ORs were <0.25 and not clinically significant.

Table 5: Factors associated with pregnancy affected by orofacial clefts.

		Crude OR[a] (95% CI)	P	Adjusted OR[b] (95% CI)	P
Age		1.011 (0.951-1.075)	0.724	Excluded[§]	
Ethnicity	Malay	Reference	0.009	Reference	0.024
	Chinese	2.777 (1.263-6.103)		2.371 (1.035-5.428)	
	Indian	0.426 (0.057-3.175)		0.443 (0.059-3.302)	
	Others	4.921 (1.458-16.604)		4.910 (1.454-16.579)	
	Non-Malaysians	0.552 (0.074-4.114)		0.566 (0.076-4.231)	
BMI	Underweight	0.595 (0.133-2.659)	0.871	0.620 (0.139-2.779)	0.924
	Normal	Reference		Reference	
	Overweight	0.773 (0.334-1.790)		0.843 (0.363-1.960)	
	Obese class 1	0.847 (0.333-2.153)		1.008 (0.390-2.604)	
	Obese class 2	0.289 (0.038-2.224)		0.354 (0.046-2.757)	
	Obese class 3	0.689 (0.090-5.306)		0.875 (0.111-6.874)	
Gestational age	>37 weeks	Reference	0.408	Excluded[c]	
	<37weeks	1.494 (0.578-3.862)			
Diabetic status	No diabetes	Reference	0.533	Reference	0.612
	GDM	0.550 (0.194-1.562)		0.584 (0.201-1.691)	
	Pre-existing diabetes	<0.001		<0.001	
Parity	Not primigravida	Reference	0.602	Excluded[§]	
	Primigravida	1.206 (0.597-2.438)			

[a]Binary Logistic Regressions were used to calculate crude ORs.
[b]Multiple Logistic Regression enter method applied. No multi collinearity detected. Hosmer-Lemeshow test, (p=0.740), classification table (overall correctly classified = 99.9%) and area under ROC curve (66.3%) was applied to test the model fitness.
[c]Age, gestational age and parity were excluded in the multiple logistic regression model as their crude ORs were <0.25 and not clinically significant.

deliveries), Malay (0.994 per 1,000 deliveries), non-Malaysian (0.549 per 1,000 deliveries) and Indian (0.423 per 1,000 deliveries) (Table 3). Figure 2 shows that among the 34 cases of orofacial clefts, 15 were combined cleft lip and palate, 12 were isolated cleft lip and 7 were isolated cleft palate.

Table 4 shows the ORs and aORs for a pregnancy affected by a Neural Tube Defect. The model was adjusted for maternal BMI, gestational age, and diabetic status. Our results show that being overweight and obese at the start of pregnancy has no significant association with the risk of NTD in the offspring (p=0.068).

However, there is a significant association between gestational age <37 weeks and pregnancies affected by NTD with aOR of 5.816 (95% CI 3.366-10.049, p<0.001). Pre-existing diabetes is also significantly associated with a higher risk of NTD in the offspring with aOR of 3.454 (95% CI 1.017-11.725, p=0.091).

The ORs and aORs for a pregnancy affected by orofacial clefts are tabulated in Table 5. Adjustments were made for ethnicity, maternal BMI and diabetic status. Being overweight and obese has no significant association with the risk of OC in the offspring (p=0.924). Malaysian Chinese and Malaysians of other ethnicities were significantly associated with OC-affected pregnancy with aOR of 2.371 (95% CI 1.035-5.428, p=0.024) and 4.910 (95% CI 1.454-16.579, p=0.024) respectively.

Discussion

This study evaluated the association between maternal obesity and the risk of neural tube defects and orofacial clefts in the Malaysian population. Our results showed no significant association between maternal obesity and the presence of the two selected anomalies in our study population. Additionally, pre-existing diabetes and gestational age of <37 weeks were found to be significantly associated with an NTD-affected pregnancy while Malaysian Chinese and other Malaysian ethnicities were found to have an increased risk for pregnancies affected by orofacial clefts.

The incidence of NTDs in our study population was 2.019 per 1,000 pregnancies and 1.417 per 1,000 live births. The incidence rate is comparable to the estimated prevalence of spina bifida in University Malaya Medical Centre (UMMC) that ranges between 1.87 and 8.9 per live births, from 2003 to 2016 [25]. Based on data from 32 government hospitals documented in the Malaysian National Neonatal Registry in 2009, the incidence rate of NTDs was estimated as 0.42 per 1,000 live births. This data included hospitals from both urban and rural areas, as compared to our study, which focussed on a single tertiary and referral hospital [20]. Hence, this could explain the higher incidence rate of NTDs in our study population compared to the ones reported by them.

When stratified by ethnicity, Indians had the highest incidence rate (2.54 per 1,000 deliveries), followed by Malays (2.14 per 1,000 deliveries), non-Malaysians (1.65 per 1,000 deliveries) and Chinese (1.53 per 1,000 deliveries). This is consistent with findings from another retrospective analysis in the same hospital (HSA) in 2015, where the incidence of NTDs was highest among Indians (3.02 per 1,000 deliveries), then Chinese (2.16 per 1,000 deliveries) and Malays (0.99 per deliveries) [26]. This is similarly observed in the United Kingdom, where Indian and Bangladeshi mothers had 1.84- and 2.86-times higher incidence of an NTD-affected pregnancy, compared to Caucasian mothers [27].

The incidence of OCs in this study population was 1.2 per 1,000 deliveries. The National Oral Health Survey of School Children 1998 reported that orofacial clefts occurred in every 1 in 941 births, which is equivalent to an incidence rate of 1.06 per 1,000 births [28]. Previously, an incidence rate of 1.24 per 1,00 live births was reported in a single maternity hospital in Kuala Lumpur [29]. There were no other recent studies that report the incidence rate of OCs in Malaysia.

The highest incidence rate was recorded among Malaysians of other ethnicities in our study cohort (4.87 per 1,000 deliveries), followed by Chinese (2.75 per 1,000 deliveries), Malays (0.99 per 1,000 deliveries), non-Malaysians (0.55 per 1,000 deliveries) and Indians (0.42 per 1,000 deliveries). Another Malaysian study reported the highest incidence rate of OCs among Chinese (1.90 per 1,000 deliveries) and lowest among Malays (0.98 per 1,000 deliveries) [29]. Further studies should include a larger sample size to better assess the risk of OCs in different ethnic groups. Like the two other studies that evaluated the characteristics of orofacial clefts in Malaysia [21,22], we also found that combined cleft lip and palate is the most common form of OCs identified.

Although our results reported a significant association between gestational age <37 weeks and NTDs, this could be explained by the inclusion of cases of stillbirths and termination of pregnancies due to NTDs in the statistical analyses, as 70.6% of them occurred before 37 weeks of gestation. Pregnancies affected by major birth defects are twice as common in preterm babies than term babies [30].

Most of the mothers with pregnancies affected by NTDs or OCs were multigravida (75.4% and 64.7% respectively). This is consistent with the findings from the other retrospective study performed in HSAJB, where 70.6% of the mothers with NTD-affected pregnancies were multiparous [26]. Although the underlying mechanism of this causal link is unclear, studies have reported that increasing parity increases the risk of congenital heart disease and orofacial clefts [31,32]. Several observational studies have shown that primiparous women were more likely to comply with folic acid supplementation compared to women who had given birth before [33-35]. Multiparous women were thought to have a more casual attitude towards their subsequent pregnancies and gave less attention to nutrient supplementations. Moreover, women with greater parity were more likely to have a shorter interpregnancy interval, which in itself was a risk factor for birth defects [36].

Our study has several strengths. Firstly, the availability of individual clinical data allows for analysis that is more comprehensive. As compared to the previous study done in HSAJB [26], we were able to measure the magnitude of effect of each maternal factor on the risk of NTDs and OCs. Additionally, the weight and height of all mothers were measured and recorded from their first antenatal encounter and this reduced the possibility of recall bias. For NTDs, we included live births, stillbirths and terminations of pregnancies. This is a better estimate of all pregnancies affected by NTDs, allowing a more accurate assessment of the risk factors.

This research, however, has some limitations. Firstly, this study

involves participants from a single centre for two years. Moreover, the status of folic acid supplementation could not be obtained, as it is not routinely recorded in our medical records. The detailed information regarding individual glycaemic control among mothers with gestational diabetes or pre-existing diabetes were not available, therefore we could not comment on the association between glycaemic control and the presence of NTDs/OCs.

Our study is noteworthy because it is one of the first studies to investigate the association between maternal obesity and selected foetal abnormalities in Malaysia as many observational studies correlating maternal obesity with NTDs and OCs were in Western nations. The underlying mechanism thus remains unclear. Folic acid deficiency, raised serum insulin, chronic hypoxia and raised inflammatory mediators have been postulated to be the contributors to birth defects [37-39]. Our results suggest that maternal obesity may not be a significant contributor to NTDs or OCs and it may be due to undiagnosed diabetes or other factors such as epigenetics that were not assessed in this study. Even though our study had not found any significant link between maternal BMI and anomaly rates, evidence showed that maternal obesity can lead to a spectrum of adverse pregnancy outcomes [3-6,40,41]. We also observed an upward trend in the rate of obesity among pregnant women in our population. Therefore, these findings highlight the need for pragmatic interventions that are focused on achieving optimum weight and euglycemia before conceiving. This suggests a role not only for weight-reduction strategies but also the consideration of screening for diabetes in obese women contemplating pregnancy.

Future studies should include a larger sample size from multiple healthcare settings. Other possible risk factors such as folic acid supplementation, glycaemic control, diet and cigarette smoking should also be assessed to better understand the multifactorial contributors to congenital abnormalities.

In conclusion, the findings of this study showed that there was no significant association between maternal obesity and the occurrence of selected anomalies (NTDs and OCs) in our population. Rather, we found that maternal pregestational diabetes is associated with a 3-fold increased risk of neural tube defects in the offspring.

Acknowledgement

The team of authors acknowledge and thank Sister Sharifah and Matron Rahimah from the Department of Obstetrics and Gynaecology as well as staff from the Medical Records Department of Hospital Sultanah Aminah Johor Bahru for their help in gaining access to the required data.

Ethical approval

All authors hereby declare that necessary ethical approval has been obtained from the Malaysian Medical Research Ethics Committee (NMRRID: NMRR-17-583-34577) and Monash University Human Research Ethics Committee (Project ID: 9581).

References

1. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. https://www.moh.gov.my/moh/resources/nhmsreport-2015vol2.pdf
3. Weiss J, Malone F, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate-a population-based screening study. Am J Obstet Gynecol. 2004; 190: 1091-1097.
4. Burke Y, Perlow J. Obesity and Pregnancy. Curr Womens Health Rev. 2017; 13: 25-33.
5. Stotland N. Obesity and Pregnancy. Br Med J. 2009; 338: 107-110.
6. Adamo K, Ferraro Z, Brett K. Can We Modify the Intrauterine Environment to Halt the Intergenerational Cycle of Obesity? Int J Environ Res Public Health. 2012; 9: 1263-1307.
7. Hunt S, Hellwig J. Maternal Obesity and Macrosomia. Nurs Womens Health. 2018; 22: 15.
8. https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies
9. https://www.marchofdimes.org/global-Report-on-Birth-Defects-the-Hidden-Toll-of-Dying-and-Disabled-Children-Full-Report.Pdf
10. Thong M, Ho J, Khatijah N. A population-based study of birth defects in Malaysia. Ann Hum Biol. 2005; 32: 180-187.
11. Zakaria R, Lim M, Ali N, et al. Mortality In Children Under 5: Prevalence Of Congenital Malformations And Its Associated Demographic Variables. Int J Public Health Res. 2017; 7.
12. Thompson D. Postnatal management and outcome for neural tube defects including spina bifida and encephalocoeles. Prenat Diagn. 2009; 29: 412-419.
13. Tolarova M, Al-Kharafi L, Tolar M, et al. Pediatric Cleft Lip and Palate. Medscape. 2020.
14. Stothard K, Tennant P, Bell R, et al. Maternal Overweight and Obesity and the Risk of Congenital Anomalies. JAMA. 2009; 301: 636.
15. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. Br Med J. 2017; 357: j2563.
16. Hildén K, Hanson U, Persson M, et al. Gestational diabetes and adiposity are independent risk factors for perinatal outcomes: a population based cohort study in Sweden. Diabetic Medicine. 2019; 36: 151-157.
17. Rasmussen S, Chu S, Kim S, et al. Maternal obesity and risk of neural tube defects: a metaanalysis. Am J Obstet Gynecol. 2008; 198: 611-619.
18. Blanco R, Colombo A, Suazo J. Maternal obesity is a risk factor for orofacial clefts: a meta-analysis. British Journal of Oral and Maxillofacial Surgery. 2015; 53: 699-704.
19. Tan S, Mohd-Sidik S, Rampal L, et al. Are Malaysians Getting Fatter and Rounder? An Updated Systematic Review (2009-2015). Malaysian Journal of Medicine and Health Sciences.

2019; 15: 63-77.

20. Boo N, Cheah I, Thong M. Neural Tube Defects in Malaysia: Data from the Malaysian National Neonatal Registry. J Trop Pediatr. 2013; 59: 338-342.
21. Shah S, Abdul Rahman Z, Mirani S, et al. Demographic data on the characterization of oral clefts in Malaysia. Pakistan Oral Dental Journal. 2015; 35: 108-110.
22. Shah S, Mirani S, Sahito M. Evaluating Occurrence of Variable Cleft Lip and Palate Types Among Ethnic Groups of Malaysia. Journal of The Pakistan Dental Association. 2018; 27: 9-12.
23. Glinianaia S, Rankin J, Wright C. Congenital anomalies in twins: a register-based study. Human Reproduction. 2008; 23: 1306-1311.
24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet. 2004; 363: 157-163.
25. Sahmat A, Gunasekaran R, Mohd-Zin S, et al. The Prevalence and Distribution of Spina Bifida in a Single Major Referral Center in Malaysia. Front Pediatr. 2017; 5.
26. Thee L, Dominic N, Periasamy S, et al. Maternal Obesity and Neural Tube Defects -A Malaysian Perspective (Interim Analysis). Asian Research Journal of Gynaecology and Obstetrics. 2020; 3: 14-24.
27. Peake J, Knowles R, Shawe J, et al. Maternal ethnicity and the prevalence of British pregnancies affected by neural tube defects. Birth Defects Res. 2021.
28. http://ohd.moh.gov.my/images/pdf/xtvtnsop/Oral-Healthcare-for-Schoolchildren-in-Malaysia-2006.pdf
29. Arshad A, Khoo B. A study of cleft lip and palate in neonates born in a large Malaysian maternity hospital over a 2-year period. Plast Reconstr Surg. 1991; 88: 931.
30. Honein M, Kirby R, Meyer R, et al. The Association Between Major Birth Defects and Preterm Birth. Matern Child Health J. 2008; 13: 164-175.
31. Feng Y, Yu D, Chen T, et al. Maternal Parity and the Risk of Congenital Heart Defects in Offspring: A Dose-Response Meta-Analysis of Epidemiological Observational Studies. PLoS One. 2014; 9: e108944.
32. Vieira A, Orioli I. Birth order and oral clefts: A meta analysis. Teratology. 2002; 66: 209-216.
33. Carmichael S, Shaw G, Yang W, et al. Correlates of intake of folic acid-containing supplements among pregnant women. Am J Obstet Gynecol. 2006; 194: 203-210.
34. Knudsen V, Hansen H, Ovesen L, et al. Iron supplement use among Danish pregnant women. Public Health Nutr. 2007; 10: 1104-1110.
35. Lutsey P, Dawe D, Villate E, et al. Iron supplementation compliance among pregnant women in Bicol, Philippines. Public Health Nutr. 2008; 11: 76-82.
36. Grisaru-Granovsky S, Gordon E, Haklai Z, et al. Effect of interpregnancy interval on adverse perinatal outcomes-a national study. Contraception. 2009; 80: 512-518.
37. Waller D, Dawson T. Relationship between Maternal Obesity and Adverse Pregnancy Outcomes. Nestlé Nutrition Workshop Series Pediatric Program-The Impact of Maternal Nutrition on the Offspring. 2005; 55: 197-211.
38. Waller D, Mills J, Simpson J, et al. Are obese women at higher risk for producing malformed offspring? Am J Obstet Gynecol. 1994; 170: 541-548.
39. Watkins M, Rasmussen S, Honein M, et al. Maternal obesity and risk for birth defects. Pediatrics. 2003; 111: 1152-1158.
40. Cedergren M. Maternal Morbid Obesity and the Risk of Adverse Pregnancy Outcome. Obstetrics & Gynecology. 2004; 103: 219-224.
41. Stephansson O, Dickman P, Johansson A, et al. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. Am J Obstet Gynecol. 2001; 184: 463-469.