Is Maternal Obesity Associated With Fetal Congenital Lung Malformations?

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Abstract

Background

Previous data demonstrated an increased incidence in congenital lung malformations (CLM) and hypothesised a link with maternal obesity.

Method

A retrospective case-control study (1994-2017) including all cases of CLM and matched controls (N=114 pregnancies). For each diagnosis of a baby diagnosed antenatally with CLM, two controls were selected. Primary outcome measure was mean Body Mass Index of women of affected pregnancies.

Results

The women in affected pregnancies had a greater BMI (26.7 ±5.2kg/m^2 (n=38)) than the control women (24.6±4.7 kg/m2 (n=76)) (p=0.03). 60.5% (n=46) of women in the control group and 39.5% (n=15) women in the CLM group had a normal BMI (<25kg/m^2). Women with a BMI > 25kg/m^2 had a 1.53 relative risk (RR) of having an affected baby (p=0.02, 95% CI 1.05-2.24).

Conclusion

Obesity is not associated with increased rates of CLM. There is a small clinical difference in the BMI of women affected by CLM.

Introduction

Maternal obesity (defined as a Body Mass Index (BMI) of 30 kg/m^2 or more at the first antenatal consultation) increases health risks for the mother and is known to have implications for the developing fetus [1]. Half of all women of childbearing age in England are either overweight or obese [2] and the resulting prevalence of obesity in pregnancy has seen an increase from 9–10% in the early 1990s to 16–19% in the 2000s [34].

Several congenital malformations are known to be associated with maternal obesity, even when adjusting for confounders such as socio-economic status and education [5]. The most commonly quoted of these are neural tube and cardiac and cardiac defects, but abnormalities in the fetal chest have received little attention. In a recent review of congenital abnormalities in obese women, only three of 39 studies studied the fetal chest and all of these examined only congenital diaphragmatic hernia.

Congenital lung malformations (CLM), comprise mainly of congenital pulmonary airway malformation (CPAM, formally known as cystic adenomatoid malformation) and broncho-pulmonary sequestration (BPS) [67] and they arise during abnormal embryological development [89]. Whilst the underlying mechanism is not fully understood, altered airway morphogenesis in CLM leads to characteristic

dysplastic airway formation [10]. If maternal body mass or diet disrupts the regulation of organogenesis at a cellular level, this may influence the incidence of CLM.

Over the past two decades, an increase in the rate of antenatally detected CLM of up to three-fold has been described [11]. This increased incidence persists despite adjustments made for increased detection rate due to better antenatal recognition because of improved ultrasound resolution and operator experience.

Objective

To assess whether there is an association with obesity at the beginning of pregnancy and the rate of Congenital Lung Malformations (CLM).

Methods

A search was performed using the regional congenital anomaly register WANDA (Wessex Antenatally Detected Anomalies) and the tertiary Fetal Medicine Unit records (1994-2018). The geographical area covered by WANDA was the former Wessex Health Region including ten maternity services in central southern England and the Channel Islands. Data was collected prospectively from the regional fetal medicine unit and sonographers in each maternity unit of all suspected fetal anomalies which are potentially diagnosable in utero. Each centre reported back to a primary database, managed locally, and to a central database EUROCAT (European Surveillance Of Congenital Abnormalities). Cases with intrauterine fetal death, termination of pregnancy and postnatal death are included where there was an antenatal abnormality identified, or a new postnatal diagnosis made. Follow up was performed until one year of life in the majority of cases. Additional information was obtained from the wider multi-disciplinary team, including surgeons, neonatologists and pathologists. Routine anomaly scans were performed using specific protocols in all but one of the hospitals until 2008, and all units subsequently.

All recorded antenatal congenital anomalies classified as lung or thoracic anomalies diagnosed in live births, stillbirths and terminations of pregnancy were included. The records were hand-searched to ascertain whether this was a CLM. The total number of babies born with CLM were recorded and for each baby born with CLM, two controls were selected by choosing the baby born immediately preceding and following the affected baby (cases) from the local birth register of the Princess Anne Hospital. Maternal and fetal demographics were collected from the hospital electronic delivery summary for each woman and her baby. This included a height and weight measurements which was recorded at the woman's initial first trimester appointment. A woman only has this information recorded in the tertiary centre if she either books or delivers in that hospital, and therefore only these women could be included and so outborn babies were excluded.

Ethical approval to maintain and use this data has been obtained from the Trent Multicentre Research Ethics Committee (Ethics number 09/H0405/48).

Statistics

Data handling was performed using PRISM Version 6.0a (2012) and SPSS Version 21 (2012). Student's T Test was used for comparisons of linear dependence. Statistical significance was defined as $p \leq 0.05$. Results are presented as either range or mean ± standard deviation.

Odd ratio (OR) was calculated by the method described by Altman 1999 [12] ($OR = D_e N_n / D_n N_e$ (where D is 'diseased', or CLM, N is 'normal' or control, n is 'non-exposed' or BMI <25/<30, e is 'exposed' or BMI≥25/≥30)[13]).

Results

Between 1994 and 2018, 137 isolated cases of antenatally diagnosed echogenic congenital lung lesions were recorded in the Wessex area. The overall prevalence was 0.2/1000 births (1994-2017, population data for 2018 not yet available). We had complete data for 38 women who delivered locally (at the Princess Anne Hospital). The remaining women booked and delivered at their local maternity unit so we had no demographic data for them and so they could not be included. Three (7.8%) cases occurred in one fetus of a twin pregnancy and the remainder were singletons (n=35, 96.2%). 37 (97.4%) babies were diagnosed postnatally with Congenital Pulmonary Airway Malformation (CPAM), and one with bronchopulmonary sequestration (2.6%). There were complete data recorded for 76 control pregnancies.

The mean BMI of the study population (women with CLM affected babies and controls) was 25.2kg/m^2 (17.5-43.6 ± 4.9, range ± standard deviation). This was comparative to the mean BMI of all delivered women 2008-2018, compiled from the local hospital database (25.9kg/m^2, 15.1-63.1 ± 5.68). The women in the affected pregnancies had a greater BMI (26.7 ±5.2kg/m^2 (n=38)) than the control women (24.6±4.7 kg/m^2, mean ± standard deviation (n=76)) (p=0.03) see Figure 1. Rates of BMI ≥25 were significantly higher among cases than controls (23/38 or 60.5% vs 30/76 or 39.4%, P=0.03). Using the proportion of women with a normal BMI compared with the proportion of women with a BMI above 25kg/m^2 in each group (ELL vs controls) there is a 2.35 odds ratio (OR) of having an affected baby (p=0.04, 95% CI 1.06-5.22). The percentage of obese mothers (BMI≥30) was 26.3% in the CLM (n=10) affected pregnancies and 18.4% (n=14) in the control group. Although there were more obese women in the pregnancies affected by CLM, this was non-significant (OR 1.58, p=0.33).

The mean age of all women was 29.0 years (17.5-43.6 ± 4.9) with no difference between cases (29.7±6.1) and controls (28.7±5.6) (p=0.40) (Table 1). Of the pregnancies affected by CLM, mean gestation at delivery was 38.9 completed weeks (range 34-41), with no difference between the mean gestation of case and control pregnancies (controls, mean gestation controls, 39.1 completed weeks, range 29-42) (p=0.43). There was no difference between the cases and controls in mode of delivery, female:male ratio, birthweight, maternal smoking status or ethnicity. For details see Table 1. 56 (49.1%) of babies born were female and 58 (50.9%) male, with no gender difference between women with babies

having CLM and controls (p=0.51). The mean birthweight was 3300.3g (920.0-4320.0 ± 620.2), again with no difference between babies born with (3268.8 ± 716.6) or without CLM (3316.1 ± 570.5) (p=0.70).

Discussion

We describe an association between maternal BMI in the first trimester of pregnancy and the incidence of CLM. Women with pregnancies affected by CLM had a greater BMI, 26.7 ±5.2kg/m^2 (n=38) compared with women with unaffected pregnancies 24.6±4.7 kg/m^2 (n=76) (p=0.03) but this effect was not, 'dose-dependent' and CLM were not more common in obese women. There was no difference in the gestation, smoking status nor age of these women. Birthweight was not different between cases and controls.

This study used high-quality population-based data from a 24-year period and investigates the association between the occurrence of CLM and maternal weight. The diverse population studied covers a large geographical area inhabited by almost three million, displaying a range of social classes, cultural practices and behavioural norms. This increases the generalisability of our data to the population at large.

Some infants diagnosed with CLM postnatally may not have been recognised until months or years after birth and not be reported to the registry. This would artificially reduce the prevalence of CLM but we would expect this to be at least equivalent in cases and controls, if not more common in obese women as maternal obesity might contribute to cases being missed antenatally because of impaired ultrasound views. In addition, our dataset is limited by small sample size (only 24 women were obese).

Pre-pregnancy obesity is associated with a wide range of adverse pregnancy outcomes, including birth defects. The aetiology of these are likely complex and multifactorial. Specific cell-adhesion molecules are important during the process of lung development in utero. In CLM these processes are dysfunctional and result in a failed interaction between the mesenchyme and epithelium [14] with a resultant lack of maturation and bronchial atresia [15]. It is thought that altered gene expression of regulatory embryonic transcription factors, notably a member of the Homeobox (HOX) gene family, HOXB5, is exhibited in CLM [16-18]. HOX proteins control the formation of specific structures in the area where they are expressed, they are involved in the construction of the embryo along the anterior-posterior axis [1920]. Increased expression of HOXB5 gene is associated with the occurrence of CLM, whilst aberrant HOX proteins are part of the mechanism involved in the development of CLM [17]. The encoded protein functions as a sequence-specific transcription factor that is involved in lung and gut development.

In obesity, impaired adipose tissue function may promote disease through ectopic lipid accumulation and excess release of adipokines, resulting in systemic low-grade inflammation, insulin resistance and organ dysfunction[21]. Homeobox transcription factors act as important regulators of adipose tissue function, and HOXB has been suggested to have a role in obesity and is associated with elevated BMI [2223]. A disruption in the exposure to genes which predominates in the 'adult' fat stores may dysregulate the functioning off the offspring, predating birth. No data exists to prove or disprove this hypothesis, but it is

a plausible link which warrants consideration in molecular studies. This may, in part explain why maternal BMI was higher, in the CLM affected pregnancies, although this was not seen when examining the obese groups alone. Whilst the number of obese women were not statically significantly different between the CLM affected pregnancies and the control women, the numbers in this study were small and in a larger sample size may become increasingly relevant.

The long-term effects of maternal obesity have profound implications, and this public health problem is only likely to worsen. Increasing evidence implicates maternal obesity as a major determinant of offspring health during childhood and later adult life, as may be the case with the increased incidence of congenital abnormalities. Raised BMI in pregnancy is associated with complex metabolic and inflammatory changes, which could affect organogenesis [24], whilst epigenetic processes may alter fetal and infant development when exposed to an 'obesogenic' environment [25].

Conclusion

For the first time the association between maternal BMI in the first trimester and the incidence of CLM has been described, but a link with matenrla obesity has not been proven. Further work is needed to determine the relationship between maternity adiposity and CLM.

Declarations

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Ethics

Ethical approval to maintain and use this data has been obtained from the Trent Multicentre Research Ethics Committee (Ethics number 09/H0405/48).

Conflict of Interest statement

No authors have conflicts of interest to declare and all authors can take responsibility for the integrity of the data. We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. This manuscript contains only original unpublished work and is not being submitted for publication elsewhere.

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Contributions to authorship

LJS developed the idea, performed data extraction and statistical analysis, interpreted data and wrote the manuscript. DTH conceived the idea, led the project and performed revision of the manuscript. RP, MPS and DGW contributed to interpretation of data, revised the manuscript critically, and all authors approved the version for publication.

All authors had full access to all of the data (including statistical reports and tables) in the study and can take affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data

The anonymised datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1 The maternal and pregnancy demographic differences between the CLM affected pregnancies and controls. *p≤ 0.05

	Control (n=76)	Case (n=38)	P value
BMI	24.6 (17.5-37.2)	26.7 (19.5-43.6)	0.03*
Maternal age (years)	28.7 (17.0 -40.0)	29.7 (18.5-43.0)	0.40
Gestation at delivery (completed weeks)	39.3 (29.0-42.0, ± 2.1)	38.9 (33.0-42.0 ±2.0)	0.43
Baby weight (kg)	3317.7 (1265.0-4315.0 ± 552.3)	3268.8 (1485.0-4320.0 ± 716.6)	0.70
Female:Male (ratio)	39:37	17:21	0.60
Induced labour (yes)	17 (22.3%)	7 (18.4)	0.62
Mode of Delivery			Vaginal birth vs LSCS
Spontaneous vaginal delivery	49 (64.5)	23 (60.5)	0.14
Ventouse	4 (5.3)	1 (2.6)	
Forceps	8 (10.5)	2 (5.3)	
Emergency Lower segment Caesarean Section (LSCS)	12 (15.8)	8 (21.1)	
Elective Lower segment Caesarean Section	3 (3.9)	4 (10.5)	
Parity (%)			Nulliparous vs parous
0	26 (44.8)	15 (39.5)	0.16
1	18 (31.0)	16 (42.1)	
2	11 (19.0)	1 (7.9)	
≤3	3 (5.2)	4 (10.5)	
Smoking status (%)			Smoker vs non-smoker
During pregnancy	15 (19.7)	7 (18.4)	0.87
Never	43 (56.6)	21 (55.3)	
Stopped >1 year ago	9 (11.8)	4 (10.5)	
Stopped in last year	2 (2.6)	3 (7.9)	
Stopped when pregnant	7 (9.2)	3 (7.9)	
Ethnicity (%)			
White British	51 (67.1)	32 (84.2)	

White other	11 (14.5)	1 (2.6)
Asian	8 (10.4)	2 (5.2)
African	1 (1.3)	0
Other	4 (3.9)	0
Not stated	1 (1.3)	3 (8.0)

Figures

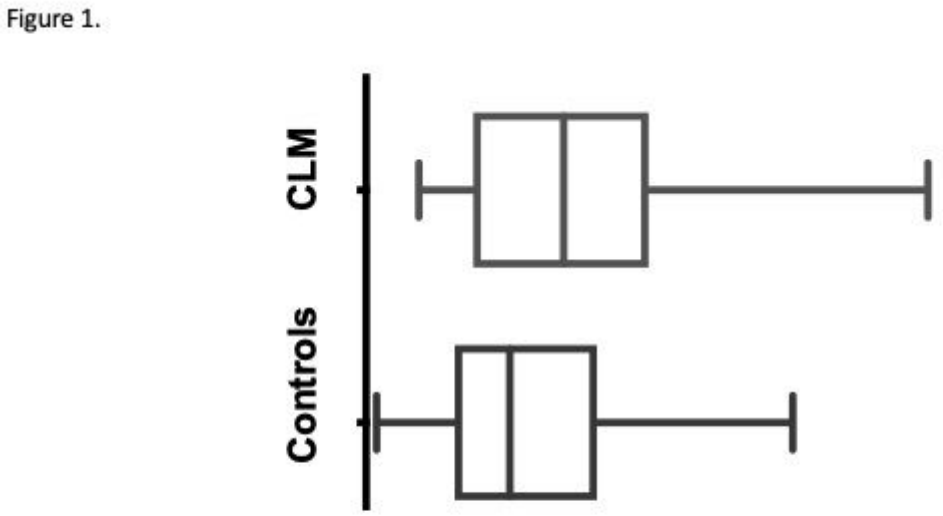

Figure 1

A box and whisker plot to show the mean BMI of women of affected babies compared with control women