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REVIEW ARTICLE

Maternal Obesity and Congenital Anomalies: Its Implications and Future Trends

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ABSTRACT

Objectives: To find the current body of evidence for maternal obesity's association with and its burden on congenital malformations and to estimate its financial and mortality implications as well as future trend.

Materials and methods: Thorough search and review of current literature with deductive interpretations.

Results and evidence: Obesity is associated with certain types of congenital anomalies like neural tube defects (NTD), congenital heart defects (CHDs), orofacial defects, etc. The burden in absolute numbers for major CHD and NTD attributable to obesity can be estimated to be 0.42 to 1.05 and 0.588 to 1.12 per 10,000 births respectively.

Remarks and conclusion: Contribution of maternal obesity on perinatal mortality could be anywhere from 6 to 20 per 1,00,000 births. However, its economic implications could be substantial. Current trend indicates that contribution of obesity to certain congenital anomalies may increase in future.

Keywords: Congenital anomalies, Congenital anomaly trends, Implication of congenital malformations, Maternal obesity.

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INTRODUCTION

Overweight and obesity have been growing rapidly in the world in the past few decades accounting for about 1.4 billion overweight people of which 200 million men and 300 million women were obese.[1] In the UK and USA, about 33 to 40% of all pregnant women are overweight or obese;[2-4] whereas in India and China, the burden is anywhere between 8 and 26%.[5,6] Besides the overall long-term risk for diabetes, cardiovascular disease and cancer, overweight and obesity are also associated with many pregnancy and birth complications.

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OBJECTIVES

Various studies have shown association of obesity with some types of congenital anomalies. But, the exact burden of obesity on congenital anomalies, its financial and mortality implications are not well documented in the literature. Aim of our present work is to review current literature to find the body of evidence associating maternal obesity with congenital malformations and overall burden of obesity on congenital malformations, their implications and future trends.

LITERATURE SEARCH AND SELECTION

The primary source of materials has been through Aarhus University Hospital (www.ascag.as.aaa.dk), Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/), and www.google.com. References from the original articles were freely used. Key search words were 'obesity and congenital anomalies', 'congenital anomalies associated with obesity', 'burden/contribution of obesity on congenital anomalies', 'implications of congenital anomalies', 'future trends in congenital anomalies', etc. Out of 50 odd papers 24 current and contemporary papers published between 1999 and 2012 were selected for review and divided according to study design. 6 prospective/cohort studies, 13 retrospective/case control studies, 1 cross-sectional study, 2 review articles and 2 meta-analyses are included in the comparative list.

Obesity—Definition

Overweight and obesity are defined as abnormal/excessive accumulation of fat that poses a health-risk. They are classified according to body mass index (BMI) defined as weight in kilograms divided by height in meter,[2] i.e. BMI = kg/m^2.[1,7] The standard World Health organization (WHO) classification of BMI is widely

Table 1: Classification of adult underweight, normal weight, overweight and obesity according to BMI aligned after WHO classification

Classification	*BMI (kg/m^2)*
Underweight	<18.50
Normal weight	18.50–24.99
Overweight	25.00–29.99
Obese	>30.00
Class I	30.00–34.99
Class II	35.00–39.99
Class III	>40.00

followed[8] where BMI > 25 and > 30 are defined as overweight and obesity respectively (Table 1).

Most studies in our review categorized or matched prepregnancy BMI according to the WHO classification. Moor et al, however, categorized obesity as BMI > 28; Watkins and Botto clubbed overweight and obesity together with BMI > 26, Ray et al in quartiles and deciles, Biggio as per weight in lb and Feldman according to lb or kg.[9-13]

Obesity and Congenital Anomalies—Current Evidence

World Health Organization defines congenital anomalies as structural or functional anomalies, including metabolic disorders, present at birth.[14] Twenty-two studies in our review reported association of congenital defects with obesity. Eleven studies reported association with neural tube defects (NTD), nine studies with congenital heart defects (CHD), five studies with orofacial, four studies with musculoskeletal, one study with renal and obstructive and one study with eye anomalies. Six studies reported multisystem anomalies of which NTD, CHD and orofacial-anomalies were predominant. Most studies reported either an overall increase in congenital defects or specific congenital anomalies associated with obesity (Table 2).

Odds ratio (OR) for NTDs ranged from lowest 1.7 (95% CI 1.34 – 2.15) for all NTDs to highest 3.5 (95% CI 1.2 – 10.3) for spina bifida (11 studies), for CHD from lowest 1.15 (95% CI 1.07 – 1.23) to highest 2.0 (95% CI 1.2 – 3.4) (9 studies) and for orofacial clefts from lowest 1.2 (95% CI 1.09 – 1.31) for septal defects to highest 3.71 (95% CI 1.05 – 13.10) for cleft lip (5 studies). Several studies have also mentioned that compounding factors along with obesity increase the risk of congenital anomalies. Moore et al have mentioned a three-fold increased risk of congenital anomalies when diabetes and obesity are combined with PR = 3.1 (95% CI 1.2 – 7.6) but no significant association with either obesity (BMI > 28) or diabetes alone.[9] Multiplicative interaction with diabetes has also been noted by Anderson et al.[15] Hyperinsulinemia appears to be an independent risk factor for NTD and may be the driving force of observed risk of NTD in obese.[16] Honein et al[17] found increased risk of renal and obstructive anomalies with joint exposures to high BMI and subfertility but not for either exposure alone (Table 3).

Feldman et al however did not find any statistically significant difference between obese and nonobese using different cut-off points for obesity.[13] Biggio et al using obesity criteria of either BMI > 29 kg/m^2 or 200 lb cut-off found no significant independent association between obesity and major congenital anomalies.[12] Shaw et al found no association with major congenital anomalies except for an overall increase in NTD.[18]

LIMITATIONS

There are many inherent limitations in the reviewed studies. Obesity has been defined differently by different studies, although 17 studies matched WHO criteria of obesity. Three studies included termination of pregnancy for fetal anomalies (TOPFA), late miscarriage, still birth and live births in their studies whereas three other studies included all but late miscarriage. Studies relied on self-reported height and weight which can be fraught with under-reporting and recall bias. Association of obesity with individual anomaly-subtypes lacks adequate power.

Burden of Obesity on Congenital Anomalies

Congenital anomalies affect approximately 1 in 33 births corresponding to about 3.2 million birth defect related disabilities every year.[14] Prevalence of major congenital anomalies in Europe was 23.9 per 1,000 births from 2003 to 2007 and 20.9 per 1,000 births from 2007 to 2011. The most common anomaly has been nonchromosomal CHD at 6.5/1000 for 2003 to 2007 and 5.8/1000 for 2007 to 2011. NTDs stand at about 0.77/1000 for 2007 to 2011.[19,20] In the UK major CHD rate is from 14.1 to 35 per 10,000 births and open NTD (spina bifida) is from 6 to 11.5 per 10,000 births.[21-23]

An estimated 3.0% (0.5 – 5.4) of CHDs and 9.8% (5.6 – 14.1) of NTDs in England are attributable to maternal obesity (BMI > 30 kg/m^2) with absolute risks for the same being 75 (95% CI = 66 – 84) and 19 (95% CI = 1.6 – 2.2) per 10,000 births respectively.[24] Absolute number of nonchromosomal CHD and NTD are 489 and 299 respectively (BINOCAR 2010).[22] Extrapolation to previously mentioned UK data shows that major CHD and NTD attributable to obesity can be approximated to 0.42 to 1.05 and 0.588 to 1.12 per 10,000 births or roughly 15 and 29 respectively per 642397 births (averaged) per year in England and Wales from 1998 to 2008.[25] In the USA, where prevalence of NTD and CHD is approximately

Table 2: Overview of the studies

Study authors	*Pub. year*	*No. cases*	*Prepregn weight/BMI*	*Inclusion criteria*	*Overall*	*NTD*	*CHD*	*Orofacial*	*MSK others*		*Comment*
Prospective/ cohort study											
Moore et al	Epidemiology 2000;11:689-694	22,951 pregnancies	BMI 3 months before conception <25, 25–<28, and >28 kg/m^2	Amniocentesis, alpha fetoprotein, congenital anomalies, other defects, deaths or fetal losses	None for BMI > 28 (PR 0.95; CI = 0.62 –1.5)	None	None except septal defects	PR 2.2 (95% CI 0.91–5.4)	PR 1.5 (95% CI 5 0.69 –3.4)	club foot	Obesity and diabetes PR 3.1 (95% CI 1.2–7.6)
Rankin et al	International J Obesity 2010; 34:1371-1380	41,013	<18.5, 18.5–<24.9, 25–29.9, >30	Late miscarriage (>20 weeks), MTP for fetal anomaly, live and still births		1.85 (0.66-5.21)	1.16 (0.84–1.59) VSD 1.56 (1.01–2.40)	1.76 (0.84–3.66), cleft lip 3.71 (1.05–13.10)	1.77 (0.16–19.98)	Eye 11.36 (2.25–57.28)	
Feldman et al	Fetal Diagn Ther 1999;14: 185-189	72,915 consecutive cases	Lb 100–140, 141–180, 181–220, 221–260, 261–300		Differences between maternal weights range not significant (÷2 = 5.997, p = 0.19, power = 0.99) Differences between obese and nonobese not significant for all three analyses						
Mandal et al	J Assoc Phys Ind 2011;59:486-489	422 cases, 422 controls	Obese > 30 kg		5 (1.2%) malformed						
Owens et al	Diabetes Care 2010;33: 577-579	2,329	Obese > 30		37 (1.6%); OR 2.47 (1.09–5.60, p = 0.03)						
Villamor et al	Am J Epidemiol 2008; 167(11): 1305-1311	220,328	Obese > 30			Orofacial anomalies Adjusted odds-isolated CP and all CP > 2.3 times for 3 BMI units gain between pregnancies, vis a vis BMI change −1 to <1 units					
Retrospective/case-control study											
Shaw et al	Pediatric and Perinatal Epidemiol 2000; 14:234-239	1052,343	Obese > 29 self reported by mother	Live and still births, elective MTPs	No significant association with other anomalies	Positive assoc with overall NTD (95%)CI 0.26–0.79					
Mills et al	Am J Clin Nutr 2010;91: 1543-1549	1536,828	Obese > 30, morbidly obese > 40	Live births			>30 OR 1.15 (1.07–1.23); >40 OR 1.33 (1.15–1.54)				

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Study authors	*Pub. year*	*No. cases*	*Prepregn weight/BMI*	*Inclusion criteria*	*Overall*	*NTD*	*CHD*	*Orofacial*	*MSK others*		*Comment*
Anderson et al	Epidemiology 2005;16(1): 87–92	cases 477 controls 497	Obese > 30		NTDS Anencephaly OR 2.3 CI (1.2–4.3), spina bifida OR 2.8 CI (1.7–4.5), hydrocephaly OR 2.7 CI (1.5–5.0)						
Watkins et al	Pediatrics 2003; 111:1152–1158		Obese > 30 diabetics excluded	Deliveries with and without birth defects	Spina bifida OR 3.5 CI (1.2–10.3)		OR 2.0 CI (1.2–3.4)				Ompha-locele OR 3.3 CI (1.0–10.3)
Cedergen MI, Kallen BA	Obes Res 2003; 11(9):1065-1071	812457	Obese > 29, morbidly obese >35	All deliveries	CHDs OR 1.18 CI (1.09–1.27), for severe CHD OR 1.23 CI (1.05–1.44); For morbid obesity OR 1.40 CI (1.22–1.64) and for severe CHD OR 1.69 CI (1.27–2.26)						Only ASD and VSD are significant
Watkins ML, Botto LD	Epidemiology 2001;12(4): 439-446	1049 cases 3029 control	>26 overweight and obese	Deliveries			Overweight and obese OR 1.36 CI (0.95–1.93).				
Hendricks et al	Epidemiology 2001;12(6): 630-635	149 cases 178 controls	Obese > 30			OR 1.73 CI (1.03–2.92)				Hyperinsu-linemia is an independent risk for NTD-OR 1.91 CI (1.21–3.01)	
Honein et al	Birth defects: Res A Clin Mol Teratol 2003;67(8): 572-577	169 cases 2763 controls	High BMI > 25, obese > 30	Deliveries	Only associated with joint exposure to subfertility and high BMI				Renal anomalies OR 5.8 CI (2.0–16.3). Obstructive anomalies OR 8.5 CI (2.9–24.7)		

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Study authors	*Pub. year*	*No. cases*	*Prepregn weight/BMI*	*Inclusion criteria*	*Overall*	*NTD*	*CHD*	*Orofacial*	*MSK others*		*Comment*
McMahon et al	Birth defects. Res A Clin Mol Teratol 2013 Feb;97:115–122	179 cases 288 controls	Obese > 30	Deliveries and MTP for anomalies		OR 2.06 CI (1.12–3.81)					
Waller et al	Arch Pediatr Adolesc Med 2007;161(8): 745-750	ongoing	Obese > 30	Deliveries	Adjusted after exclusion of diabetes	Spina bifida: OR 2.09; 95% CI, 1.63–2.70	OR, 1.26; 95% CI 1.11–1.43		Limb reduct OR, 1.16; CI, 0.89–1.52	Omphalo: OR 1.27; 95% CI (0.83–1.96)	
Cedergen MI, Kallen BA	The Cleft Palate-Craniofacial J 2005;42:367-371	1686 cases 988,171 controls	Obese > 29	Live and still births			Orofacial clefts 1686 cases @ 1.7/1000 births. CP occurred in 36%, CL in 25% and CLP in 38%				
Best et al	BJOG 2012;119: 1503-1511	132885 pregnancies	Obese > 30	Late miscarriage, MTP for anomaly, live and still births	Antenatal anomaly detection 59.7%, 52.6%, 48.1% and 45.8% in underweight, normal BMI, overweight and obese, respectively						
Ray et al	Obstet Gynecol 2005 Feb;105(2): 261-265	420,362 women	Weight quartiles and deciles	Live and still births, MTPs antenatal USG, fetal autopsies and delivery records	NTDs: 292 open NTDs Q2: 57.1 –64.1 (101,513) a OR 2.1 (1.4–3.2). Adjusted odds ratio (OR) for NTD 1.2 [95% (CI) 1.1—1.3] per 10 kg incremental rise in maternal weight						
Cross-sectional study											
Biggio et al	Obstetrics and Gynecol 2010; 115(3):290-296	41,902	Obese > 29 or > 200 lb	Deliveries, MTPs					Comment No significant independent association between maternal obesity by either definition and the presence of a major congenital anomaly		

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Study authors	*Pub. year*	*No. cases*	*Prepregn weight/BMI*	*Inclusion criteria*	*Overall*	*NTD*	*CHD*	*Orofacial*	*MSK others*	*Comment*
(Review and mata-analysis)										
Ruager-Martin et al	Early Human Development, 2010;86(11):715-722				NTD, CHD, orofacial clefts, hydro-cephalus					
Leddy et al	Rev Obstet Gynecol 2008 Fall;1(4):170-178				NTDs 1.8 (1.1–3.0), spina bifida 2.6 (1.5–4.5); Omphalo 3.3 (1.0–10.3)			1.2 (1.1–1.3)		
Stothard et al	JAMA 2009 Feb 11;301(6):636-650	18 studies	BMI matched to WHO criteria	Heterogenicity of OR 0.0–62.9%	1.87 (1.62–2.15) Affect size greater for spina bifida than anencephaly	1.3 (1.12–1.51) septal anomaly more common than other	Septal 1.2 (1.09–1.31); CP 1.23 (1.03–1.47); CL and CP 1.2 (1.03–1.40)	Limb reduction 1.34 (1.03–1.73)	Hydrocephalus 1.68 (1.19–2.36)	

Table 3: Risks of specific anomalies

Authors	*Anomalies NTD*	*OR*	*95% CI*	*Comment*
Rankin et al		1.85	0.66–5.21	
Shaw et al	Positive association with overall NTD		0.26–0.79	Multivitamin and diabetes did not significantly alter findings
Anderson et al	Anencephaly	2.3	1.2–4.3	OR is higher with simultaneous diabetes showing multiplicative interaction
	Spina bifida	2.8	1.7–4.5	
	Hydrocephaly	2.7	1.5–5.0	
Watkins et al	Spina bifida	3.5	1.2–10.3	
Hendricks et al		1.73	1.03–2.92	Hyperinsulinemia independent risk for NTD —OR 1.91 CI (1.21–3.01)—may be driving force of risk of NTD in obese
McMahon et al		2.06	1.12–3.81	
Waller et al	Spina bifida	2.09	1.63–2.70	
Ray et al	adjusted odds ratio (aOR)-Q2: 57.1-64.1 (101,513)	2.1	1.4–3.2	For the highest compared with lowest weight deciles (adjusted OR 3.3, 95% CI 1.7–6.2)
	aOR for NTD per 10 kg rise in maternal weight	1.2	1.1–1.3	
Leddy et al	Overall	1.8	1.1–3.0	
	Spina bifida	2.6	1.5–4.5	
Rasmussen et al	Overweight	1.22	0.99–1.49	
	Obese	1.7	1.34–2.15	
	Severely obese	3.11	1.75–5.46	
Stothard et al		1.87	1.62–2.15	Affect size greater for spina bifida than anencephaly
	CHD	OR	95% CI	Comment
Moore et al	None except septal defects	NA	NA	
Rankin et al	CHD most common anomaly	1.16	0.84–1.59	
	VSD	1.56	1.01–2.40	
Mills et al	BMI > 30	1.15	1.07–1.23	Includes all CHD, all LV- & RV-outflow obstructions, ASD, hypoplastic lt heart, ao stenosis, pulm stenosis, TOF
	BMI > 40	1.33	1.15–1.54	
Watkins et al		2.0	1.2–3.4	
Cedergen MI, Kallen BA	Obese Overall CHD	1.18	1.09–1.27	Only ASD and VSD are significant
	Severe CHD	1.23	1.05–1.44	
	Morbidly obese Overall CHD	1.40	1.22–1.64	
	Severe CHD	1.69	1.27–2.26	
Watkins ML, Botto LD	Overweight and obese	1.36	0.95–1.93	Use of multivitamin did not effect reduction of anomalies among overweight and obese
Waller et al		1.26	1.11–1.43	
Leddy et al		1.2	1.1–1.3	
Stothard et al		1.3	1.12–1.51	Septal anomaly more common than other
	Orofacial	OR	95% CI	comment
Moore et al		PR 5 2.2	0.91–5.4	
Rankin et al	Overall	1.76	0.84–3.66	
	Cleft lip	3.71	1.05–13.10	
Villamor et al	Adjusted odds for both isolated CP and all CP were >2.3 times higher for 3 BMI units weight-gain between pregnancies compared to BMI change between −1 and <1 units			Increase of 3 BMI units ~ a gain of 8 kg (17.6 pounds)
Cedergen MI, Kallen BA	1686 cases @ 1.7/1000 births. CP occurred in 36%, CL in 25%, and CLP in 38%			1408 (84%) were isolated (i.e. cleft was the only major malformation)
Stothard et al	Septal	1.2	1.09–1.31	
	Cleft palate	1.23	1.03–1.47	
	Cleft lip and palate	1.2	1.03–1.40	

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Authors	*Anomalies NTD*	*OR*	*95% CI*	*Comment*
Moore et al	MSK	PR 1.5	0.69–3.4	
Rankin et al	MSK	1.77	0.16–19.98	
Waller et al	Limb reduction	1.16	0.89–1.52	
Stothard et al	Limb reduction	1.34	1.03–1.73	
Rankin et al	Eye	11.36	2.25–57.28	
Honein et al	Renal anomalies	5.8	2.0–16.3	
	Obstructive anomalies	8.5	2.9–24.7	
	Nonspecific/overall anomalies	OR/PR	95% CI	Comment
Moore et al	None for BMI > 28 alone	PR 0.	0.62–1.5	3 times more risk combined
	Combined obesity and Diabetes	PR 3.1	1.2–7.6	
Owens et al	37 (1.6%) had congenital malformations)	OR 2.47	1.09–5.60	p = 0.03
Shaw et al	Positive association with overall NTD		0.26–0.79	No significant association with other anomalies.
Best et al	Antenatal detection of any anomaly			67 (4.0%) anomalies occurred in women who were underweight, 793 (47.0%) in women who were of recommended BMI, 468 (27.8%) in women who were overweight and 358 (21.2%) in women who were obese
Ruager et al	NTD, CHD, orofacial clefts, hydrocephalus			

0.5 – 1.0 and 8 per 1,000 births respectively, maternal obesity may result in around 600 NTD and 800 CHD each year.[26]

Contribution to Mortality

Congenital malformations including chromosomal abnormalities contributed to 5107 (21%) of total 24,586 infant deaths in the US during 2009 to 2010.[27] EUROCAT 2007 to 2011 shows a total perinatal mortality due to congenital anomalies to be 0.87 per 1000 births. Congenital anomalies are the second most common cause of infant deaths overall with a rate of 1.39/1000 live births in 2007 and the leading cause of postneonatal death at 0.52/1000 live births.[28] Approximately, 3% of pregnancies and infants are diagnosed with congenital anomalies of which 7% results in stillbirth or infant death.[29] Since contribution of obesity on congenital anomalies varies from 3% (for CHD) to 10% (for NTD), the effect of obesity on infant death and stillbirth could be anywhere between 6 per 1,00,000 (for CHD) to 20 per 1,00,000 (for NTDs).

ECONOMIC IMPLICATIONS

Although the absolute number of congenital anomalies is not very large, economic and healthcare impact may be substantial due to specialized care needs of many children and adults living with these anomalies.[26] Estimated medical cost for an infant with any CHD was about 1,00,000 USD in 2005 (for the privately insured) and higher for a major cardiac anomaly. Total hospitalization cost for all individuals with CHD was 1.4 billion USD in 2004.[34]

FUTURE TRENDS

Birth-defects-prevalence in Europe has decreased from 23.9/10000 to 20.9/10000 between 2003-2007 and 2007-2011.[19,20] Birth-defects-mortality has also declined at least in the developed world. It has declined from 255.4/100,000 live births in 1979 to 134.0/100,000 in 2007 in the USA.[30] On the contrary, obesity in women of childbearing age has been increasing steadily. Health Survey for England (HSE) shows prevalence of obesity among women between 16 and 44 years has increased from about 12% in 1993 to about 20% in 2010.[31] Similar trends are also seen in the US where estimated age adjusted prevalence of obesity in women >20 years have increased from 25% during 1988 to 1994 to about 36% in 2007 to 2008.[32] Fisher et al showed a continued upward trend of obesity-prevalence among prepregnant women from 17.6% in 2003 to 20.5% in 2009 ($p < 0.001$).[33] Thus while the prevalence of congenital anomalies and associated infant mortality due to them is declining, obesity (including among women in the childbearing age) is showing a continually upward trend globally. This means that contribution of obesity on congenital anomalies is likely to increase in future particularly as the effects of obesity on maternal and child health become more evident in future.

SUMMARY REMARKS AND CONCLUSION

- Obesity is increasing globally including among women in the reproductive age group.
- Obesity has been shown to contribute to certain types of congenital malformations particularly NTD, CHD and orofacial defects.

- Although absolute numbers of congenital anomalies caused by obesity are probably low, healthcare costs are substantial.
- While overall prevalence of congenital anomalies is declining steadily over decades, obesity on the other hand has shown an upward trend. Therefore, contribution of obesity to congenital anomalies may increase in future.

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