Review Article

Burden of Maternal Obesity on Congenital Anomalies: Implications and Future Trend

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ABSTRACT

Obesity is linked to certain congenital anomalies viz. neural tube defects (NTD), congenital heart disease (CHD) and oro-facial anomalies. However the exact burden of obesity on congenital anomalies, its economic implications and future trend have not been well documented before. We present a thorough review of the current literature with deductive interpretations to arrive at the following observations. Congenital anomalies in general are a leading cause of infant and child mortality but they are on decline in many countries. However maternal obesity is on the rise. As a result, the share of maternal obesity contributing to congenital anomalies is likely to increase in future. Maternal obesity can therefore significantly contribute to perinatal mortality and its economic, social and psychological impact can be substantial.

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Introduction

Various studies have shown an association between obesity and some types of congenital anomalies, but the exact burden of obesity on congenital anomalies or its implications on infant and child mortality or economic implications are sparsely discussed and documented. The conditions of overweight and obesity have been growing rapidly worldwide in the past few decades, accounting for about 1.4 billion overweight people as of 2008, of whom 200 million men and 300 million women were obese. Obesity is considered the fifth leading risk factor for global death [1]. In the U.K. and U.S. about 33–40% of all pregnant women are overweight or obese [2-4] whereas in rapidly developing nations like India and China the burden is anywhere from 8–26% [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 including congenital anomalies. The aim of the present work is to review the current literature in order to find the body of evidence associating maternal obesity with congenital malformations and the overall burden of obesity on congenital malformations, infant and child mortality, economic implications, and future trends.

Materials and Methods

Literature Search and Selection: The primary sources of materials were obtained from Aarhus University Hospital (www.ascag.as.aaa.dk), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), and www.google.com. References and cross references from the original articles were also 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*, *obesity in pregnant women*, *future trends in congenital anomalies*, etc. Out of approximately 50 papers sorted out for initial review, only current and contemporary papers (24 altogether) published between 1999 and 2012 were selected. Studies were divided according to study design. There were 6 prospective/cohort studies, 13 retrospective/case control studies, 1 cross-sectional study, 2 review articles, and 2 meta- analyses included in the comparative list.

Obesity Definition: Overweight and obesity are defined as abnormal or 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 meters squared, i.e., BMI=kg/m2 [1,7]. The standard World Health Organization (WHO) classification of BMI is widely followed, where BMI ≥ 25 and ≥ 30 are defined as overweight and obese, respectively (Table 1) [8]. Most studies in our review categorized pre-pregnancy BMI according to the WHO classification or matched to it, though some studies did deviate from it. Moore et al categorized obesity as BMI ≥ 28 [9].Watkins and Botto combined overweight and obesity together in a group with BMI >26 [10]. Ray et al categorized weight in quartiles and deciles [11], Biggio as per weight in pounds (lb) [12] and Feldman according to lb or kg [13].

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

Classification		BMI (kg/m2)
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

Results

WHO defines congenital anomalies as structural or functional anomalies, including metabolic disorders, present at birth [14]. Twenty-one studies in our review reported an association of congenital defects with obesity. Eleven studies reported association with neural tube defects (NTDs), 9 studies with congenital heart defects (CHDs), 5 studies with orofacial, 4 studies with musculoskeletal, 1 study with renal and obstructive, and 1 study with eye anomalies. Six studies reported multisystem anomalies, of which NTDs, CHDs, and orofacial anomalies were predominant. Most studies included in this review reported either an overall increase in congenital defects or specific congenital anomalies associated with obesity. The odds ratio (OR) for NTDs ranged from a lowest of 1.7 (95% CI 1.34– 2.15) for all NTDs to a highest of 3.5 (95% CI 1.2–10.3) for spina bifida (11 studies), for CHDs from a lowest of 1.15 (95% CI 1.07–1.23) to a highest of 2.0 (95% CI 1.2–3.4) (9 studies), and for orofacial clefts from a lowest of 1.2 (95% CI 1.09–1.31) for septal defects to a highest of 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 mentioned a 3-fold increased risk of congenital anomalies when diabetes and obesity were combined, with an OR of 3.1 (95% CI 1.2–7.6), but no significant association with either obesity (BMI ≥ 28) or diabetes alone [9]. A 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 the observed risk of NTDs in the obese [16]. Honein et al found an increased risk of renal and obstructive anomalies with combined exposure to high BMI and subfertility but not for either exposure alone (Table 2) [17]. Feldman et al, however, did not find any statistically significant difference between the obese and the non-obese using different cut-off points for obesity [13]. Biggio et al, using an obesity criteria of either BMI >29 kg/m2 or 200 lb (00 kg) 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 NTDs [18]. (Table 3)

TABLE 2: OVERVIEW OF THE STUDIES INCLUDED IN THE REVIEW

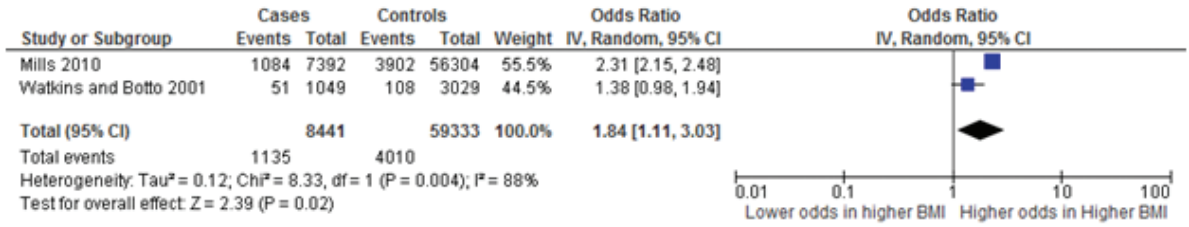
Authors	No. Cases	Inclusion	Overall	NTD	CHD	Orofacial	Msk	Others	Comment
REVIEW & METANALYSIS									
Stothard et al	18 studies		Heterogenicity of OR 0.0 - 62.9%	1.87 (1.62-2.15) Affect size greater for Spina Bifida than Anencephaly	1.3 (1.12-1.51) Septal anomaly more common than other	septal 1.2 (1.09-1.31); CP 1.23 (1.03-1.47); CL + CP 1.2 (1.03-1.40)	limb reduction 1.34 (1.03-1.73)	Hydrocephalus 1.68 (1.19-2.36)	
Leddy et al			NTD: 1.8 (1.1-3.0), Spina bifida 2.6(1.5-4.5)		1.2(1.1-1.3)			Omphalo 3.3 (1.0-10.3)	
PROSPECTIVE/COHORT STUDY									
Moore et al	22,951 preg	Amnio, AFP, anomalies, deaths or fetal loss	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 + Diabetes - PR 3.1(95% CI 1.2-7.6)
Rankin et al	41013	miscarriage (> 20 wks), TOPFA, live & still births	CVS ,urinary, nervous, digestive, orofacial	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	72,915 consecutive cases		Differences in weights ranges not statistically significant (÷2 = 5.997, p = 0.19, power = 0.99). Obese and non-obese difference statistically not significant						
Mandal et al.	422 cases,422 controls		5 (1.2%) congenitally malformed.						
Owens et al	2,329 women		37 (1.6%) ; OR 2.47 (1.09 –5.60, P = 0.03)						
Villamor et al	220,328			OROFACIAL: Adjusted odds - isolated CP & all CP > 2.3 times for 3 BMI units gain between pregnancies, visa vis BMI change −1 to <1 units				COMMENT 3 BMI units ~ 8 kg (17.6 pounds) for ave. height (1.65 m) woman who weighed 63 kg at the first pregnancy	
RETROSPECTIVE / CASE CONTROL STUDY									
Shaw et al	1052343 +additional 208387 for clefts	live and still births, TOPFA	+ve assoc. with overall NTD - 95% CI 0.26-0.79. No significant assoc. with other anomalies		COMMENT: Multivitamin & Diabetes didn't significantly alter findings				
Mills et al	1536828	live births			CHD: > 30 OR 1.15 (1.07-1.23); > 40 OR 1.33 (1.15-1.54)				
Anderson et a	cases 477 controls 497		NTD: 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)					COMMENT: OR is higher with simultaneous diabetes showing multiplicative interaction	
Watkins et al		Deliveries with/without birth defects		Spina bifida OR 3.5 CI (1.2-10.3)	OR 2.0 CI (1.2-3.4)				Omphalocele OR 3.3 CI (1.0-10.3)
Cedergen MI, Kallen BA	812457	All deliveries			CHD: 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) & for severe CHD OR 1.69 CI (1.27-2.26) Only ASD and VSD are significant				
Watkins ML, Botto LD	1049 cases vs 3029 control	Deliveries			Overweight & Obese OR 1.36 CI (0.95-1.93).			COMMENT: multivitamin didn't reduce of anomalies among overweight and Obese	

Hendricks et al	149 cases & 178 controls			OR 1.73 CI (1.03-2.92			COMMENT: Hyperinsulinemia independent risk for NTD-OR 1.91 CI (1.21-3.01)		
Honein et al	169 cases & 2763 controls	Deliveries	Only assoc. with joint exposure to subfertility & high BMI				Renal anomalies OR 5.8 CI (2.0-16.3). Obstructive anom. OR 8.5 CI (2.9-24.7).		No assoc. for single exposure
McMahon et al	179 cases & 288 controls	Deliveries and TOPFA		OR 2.06 CI (1.12-3.81)					
Waller et al	on-going	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 red. OR, 1.16; CI, 0.89-1.52	omphalo: OR 1.27; 95% CI, 0.83-1.96)	
Cedergen MI, Kallen BA	1686 cases and 988,171 controls	live and still births				OROFACIAL CLEFTS 1686 cases @ 1.7/1000 births. CP occurred in 36%, CL in 25%, and CLP in 38%		COMMENT 1408 (84%) of the orofacial clefts were isolated (i.e., the cleft was the only major congenital malformation present).	
Best et al	132885 pregnancies	late miscarriage, TOPFA, Live/ still births	Antenatal anomaly detection 59.7%, 52.6%, 48.1% and 45.8% in under-wt, normal BMI, overweight and obese, respectively				COMMENT 67 (4.0%) anomalies occurred in underweight, 793(47.0%) in recommended BMI, 468(27.8%) in overweight and 358 (21.2%) in obese.		
Ray et al.	420,362 women	Live/Still births, MTPs, USG, fetal autopsies	NTDs : 292 open NTDs Q2: 57.1–64.1 (101,513) aOR 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.					COMMENT For the highest compared with lowest weight deciles (adjusted OR 3.3, 95% CI 1.7-6.2)	

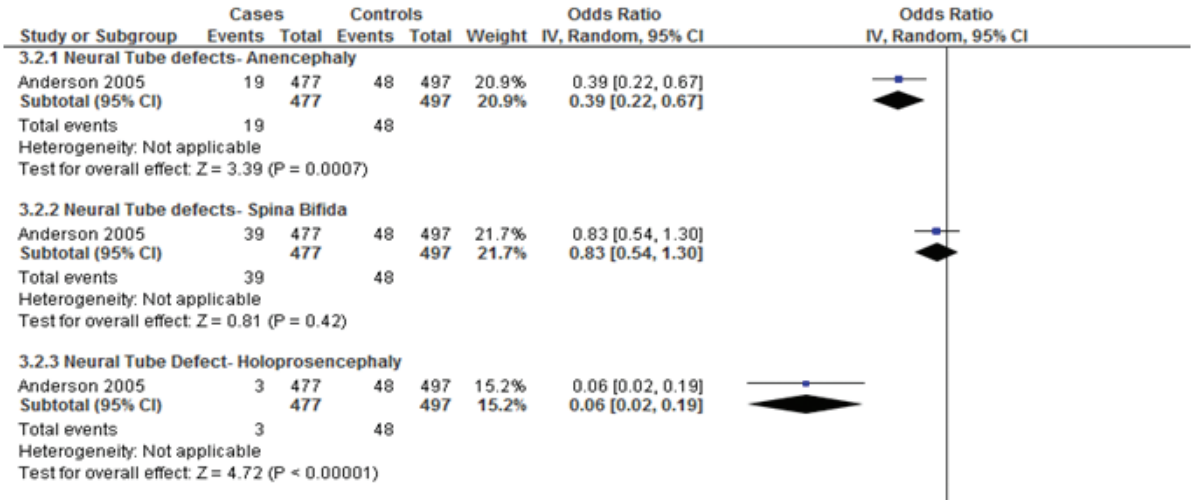
TABLE 3: Graphical representation of data (Forest plot) by study design showing association of maternal obesity with various congenital anomalies

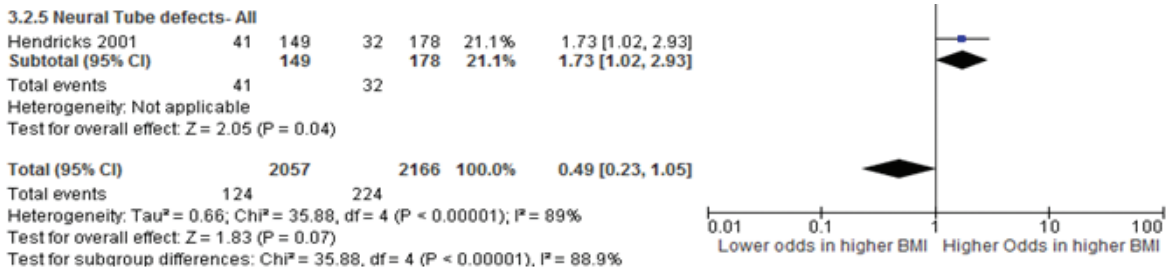
1. Case-control data:

1.1 Congenital Heart Disease (CHD)



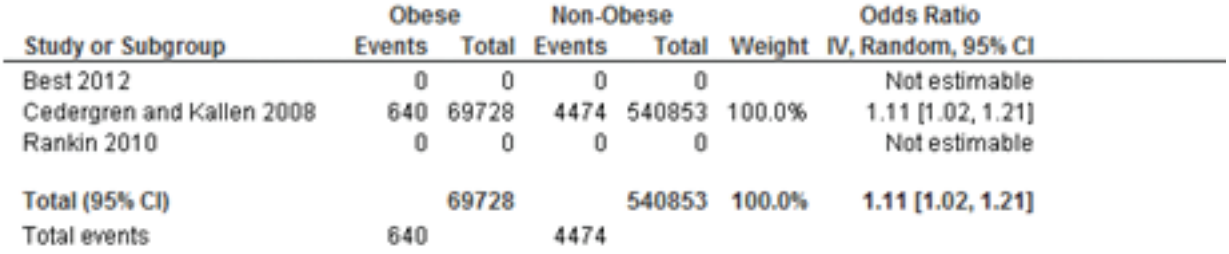
1.2 Neural Tube Defects



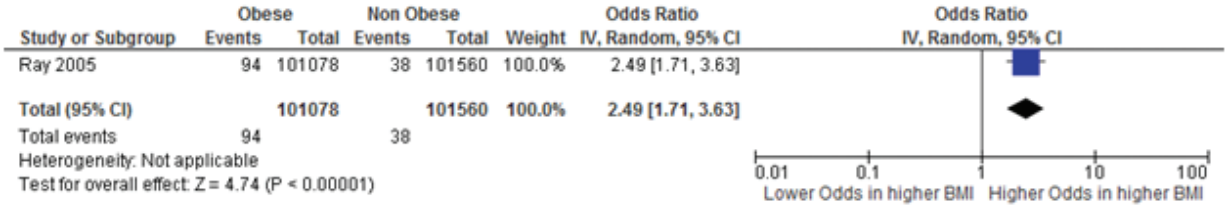


2. Prospective/ Longitudinal Data

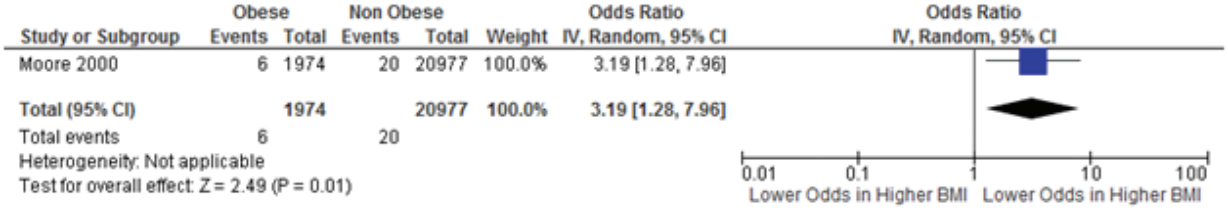
2.1 CHD



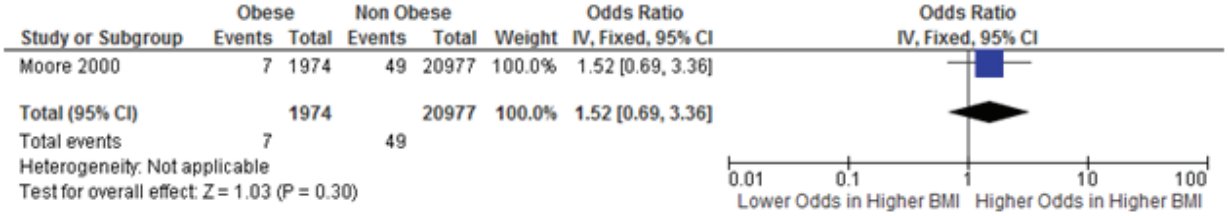
2.2 Neural Tube defects



2.3 Craniofacial Anomalies



2.4 Musculoskeletal Anomalies



Discussion

Limitations: There are many inherent limitations in the reviewed studies. Obesity has been defined differently by different studies, although 17 studies matched the WHO criteria of obesity. Three studies included termination of pregnancy for fetal anomalies, late miscarriage, stillbirth, and live births in their studies, whereas 3 other studies included all but late miscarriage. Studies relied on self-reported height and weight, which can be fraught with underreporting 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]. The prevalence of major congenital anomalies in Europe was 23.9 per 1,000 births from 2003–2007 and 20.9 per 1,000 births from 2007–2011. The most common anomaly has been non-chromosomal CHD, at 6.5/ 1,000 for 2003–2007 and 5.8/1,000 for 2007–2011. NTDs stand at about 0.77/1,000 for 2007–2011 [19,20]. In the U.K. the major CHD rate is from 14.1–35 per 10,000 births, and the open NTD rate (spina bifida) is from 6–11.5 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/m2), 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]. The absolute numbers of non-chromosomal CHD and NTD are 489 and 299 per 10,000 total births, respectively (British Isles Network of Congenital Anomaly Registers [BINOCAR] 2010) [22]. Extrapolation to previously mentioned U.K. data shows that major CHD and NTD attributable to obesity can be approximated to 0.42–1.05 and 0.588–1.12 per 10,000 births or, in absolute numbers, roughly 15 and 29, respectively, per 642,397 births (averaged) per year in England and Wales from 1998–2008 [25]. In the U.S., where the prevalence of NTDs and CHDs is approximately 0.5–1.0 and 8 per 1,000 births, respectively, maternal obesity may result in around 600 NTDs and 800 CHDs each year [26].

***Contribution to Mortality*:** Congenital malformations, including chromosomal abnormalities, contributed to 5,107 (21%) of a total of 24,586 infant deaths in the U.S. from 2009–2010 [27]. European Registry of Congenital Anomalies and Twins (EUROCAT) 2007–2011 shows a total perinatal mortality due to congenital anomalies to be 0.93 per 1,000 births (Table 4). Congenital anomalies are the second-most-common cause of infant deaths overall with a rate of 1.39/1,000 live births in 2007 and the leading cause of postneonatal death at 0.52/1,000 live births [28]. Approximately 3% of pregnancies and infants are diagnosed with congenital anomalies, of which 7% result 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 still- birth could be anywhere between 6 per 100,000 (for CHD) to 20 per 100,000 (for NTDs).

Economic Implications: Although the absolute number of congenital anomalies is not very large, economic and healthcare impact may be substantial due to the specialized care needs of many children and adults living with these anomalies [26]. The estimated medical cost for an infant with any CHD was about 100,000 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 [30].

Besides, social and psychological consequences due to congenital anomalies can be substantial and add to the overall burden.

Future Trends: The birth defect prevalence in Europe has decreased from 23.9/10,000 to 20.9/10,000 between 2003–2007 and 2007–2011 [19,20]. Birth defect 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 U.S [31]. On the contrary, obesity in women of childbearing age has been increasing steadily. Health Survey for England (HSE) shows that the prevalence of obesity among women aged 16–44 has increased from about 12% in 1993 to about 20% in 2010 [32]. Similar trends are also seen in the U.S., where the

TABLE 4: ABRIDGED EUROCAT PREVALENCE DATA ON ANOMALIES (2007-2011)

Category	LB N	FD N	TOPFA N	LB+FD+ TOPFA N	LB+FD+ TOPFA rate (95% CI)/ 10000 births	LB+FD+ TOPFA Excluding Chromosomal N	LB+FD+ TOPFA rate (95% CI)/ 10000 births Excluding Chromosomal
ALL	106753	2115	18982	127850	208.72 (207.58-209.87)	109746	179.17 (178.11-180.23
NTD	1667	185	3009	4861	7.94 (7.71-8.16	4699	7.67 (7.45-7.89
CHD	36364	548	2900	39812	65.00 (64.36-65.64)	35298	57.63 (57.03-58.23)

Source: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables

LB = Live birth, FD = Fetal death, TOPFA = Termination of Pregnancy for Fetal Anomaly following prenatal diagnosis. N = Number, CI = Confidence Interval.

estimated age- adjusted prevalence of obesity in women ≥ 20 years has increased from 25% during 1988–1994 to about 36% in 2007–2008 [33]. Fisher et al showed a continued upward trend of obesity prevalence among prepregnant women from 17.6% in 2003 to 20.5% in 2009 ($p<0.001$) [34]. Thus, while the prevalence of congenital anomalies and associated infant mortality due to them is declining, obesity (including that among women of childbearing age) is showing a continually upward trend globally. This means that the contribution of obesity to congenital anomalies is likely to increase in the future.

Conclusion

In 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. While the 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 and consequently to perinatal and child mortality may increase in the future. Although absolute numbers of congenital anomalies caused by obesity are probably low, the healthcare costs are substantial.

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NONE

Competing Interests

NOT DECLARED

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