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Review article

Smoking: A modifiable risk factor for gestational diabetes? -A review

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ABSTRACT

Back ground: Gestational diabetes mellitus, characterized by glucose intolerance during pregnancy has many risk factors associated with it. Some studies have shown a strong association between smoking and glucose intolerance during pregnancy. We sought to examine the role of smoking as modifiable risk factor for gestational diabetes.
Method: A systematic review of articles published upto 2010 using pub med, Embase, Science direct along with manual search through literature contributed to the present study. We focused on studies related to the effect of smoking on gestational diabetes and heterogeneity analysis was performed.
Results: We analyzed data from 39 studies and 14 were included in the review. Majority of the studies indicate smoking as dose-dependent modifiable risk factor for gestational diabetes. Other studies do not support this finding.
Conclusion: On the analysis of different studies regarding smoking and gestational diabetes, Current data give enough evidence to support the fact that smoking may be considered as a modifiable risk factor for gestational diabetes.

Contents

1. Introduction

Diabetes is a growing public health concern worldwide, with prevalence rates increasing rapidly in most regions. People with diabetes experience considerably worse health outcomes and have a shorter life expectancy than the general population. This is largely attributable to a 2-4 times greater risk of cardiovascular disease, which accounts for two-thirds of deaths among people with diabetes [1]. Established diabetes mellitus, either type 1 or 2, is the most common pre-existing medical condition in pregnant women. According to the United States Centers for Disease Control (CDC), its frequency is 2-5 per 1000 pregnancies. Nevertheless, this calculation was published in 1990 and has most likely increased by 40%in view of the present epidemic of worldwide obesity [2].

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(including gestational diabetes and preeclampsia), delivery complications (induction of labour, dystocia and cesarean delivery), and is also associated with increased risks of stillbirth, very preterm birth, and macrosomia.

3.1. Risk related to obesity

The World Health Organization (WHO) estimated in the year 2000 that as many as 300 million people worldwide were clinically obese. European countries are now following the health compromising trends found in the USA with as many as 30% of adults classified as overweight and obese. Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. As a rule, women have more body fat than men, and it is widely agreed that men with >30% body fat and women with>25% body fat are obese. The WHO and the National Institutes of Health define: underweight as a body mass index (BMI; kg/m2)_18.5, normal weight as a BMI of 18.524.9, overweight as a BMI of2529.9, and obesity as a BMI of _30. Obesity is further characterized by BMI into class I (3034.9), class II (3539.9), and class III (>40). The WHO's latest reports indicate that in 2005 w1.6 billion adults (aged _ 15 years) were overweight and at least 400 million adults were obese. This international agency also projects that by 2015; w2.3 billion adults will be overweight and more than 700million will be obese. Results from the latest 20032004 United States National Health and Nutrition Examination Survey (NHANES) indicate that 66.3% of adults are overweight (BMI_ 25), and 32.2% are obese (BMI _30). The prevalence of overweight and obesity among adults aged 2074 years in the USA has increased from 47.0% (in the 19761980 survey) to 66.3% (in the 20032004 survey). Over the same period, the prevalence of obesity has doubled among women from 16.5% to 33.2%.

Preterm birth, defined as delivery occurring at less than 37weeks of gestation was studied and results show that from 2004 to 2007, the rate of obesity among older mothers increased slightly from 19.8 to 21.8(p for trend <0.01) and that of preterm from 9.7 to 10.2 (p for trend = 0.1472) (Figure. 1). [9]

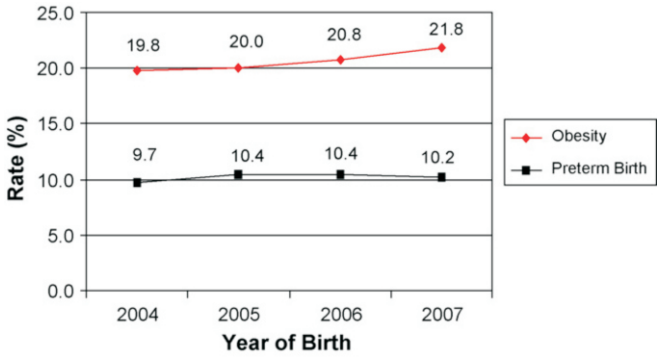

Figure. 1. Percentage of obesity and pre term birth among older mothers, 2004-2007. [9]

The complications of diabetes affecting the mother and fetus are well known. Maternal complications include preterm labor, pre-eclampsia, nephropathy, birth trauma, cesarean section; and postoperative wound complications, among others. Fetal complications include fetal wastage from early pregnancy loss or congenital anomalies, macrosomia, shoulder dystocia, stillbirth, growth restriction, and hypoglycemia, among others. The presence of obesity among diabetic patients compounds these complications. The nature and type of diabetes-related pregnancy complications were such that the international medical community (WHO and International Diabetes Federation) set forth the St Vincent's declaration of 1989, with one of its aims to achieve similar pregnancy outcomes in diabetic and non-diabetic women.

3.1.1.The influence of obesity on pregnancy outcome in the non-diabetic patient

As the prevalence of obesity is increasing, so is the number of women in the reproductive age who are overweight and obese. The average BMI is increasing among all age categories, and women enter pregnancy at higher weights. Women are also more likely to retain gestational weight with each pregnancy. Approximately one third of women of reproductive age in the USA are obese, with no appreciable increase from 1999.Human pregnancy is an insulin-resistant condition by itself. There is a 40-50% increase in insulin resistance during pregnancy (from pre-gravid condition). It is now universally acknowledged that maternal overweight and obesity are linked with adverse pregnancy outcome. Maternal complications include hypertension, diabetes, respiratory complications (asthma and sleep apnea), thromboembolic disease, and more frequent cesarean delivery with increased wound infection, endometritis, and anesthetic complications mainly difficulties in intubation and placement of epidural. Newborn complications include congenital malformations, large for-gestational-age infants, stillbirths, shoulder dystocia and long-term complications (obesity and diabetes). Morbidly obese women are prone to even more complications and adverse outcomes .A discussion of these complications should be the balance between the benefit/risk ratio of fetal and maternal perspectives [10].

3.1.2. Diet and obesity

Diet is one of the most important factors associated with the development of type 2 diabetes mellitus. The dietary fat more consistently associated with an increase in the risk of type 2diabetes mellitus is saturated fat. Additionally, low polyunsaturated fat intake, high trans unsaturated fat intake, and high cholesterol intake have all been associated with an increased risk of type 2 diabetes mellitus too. Several previous studies have reported an association between high intake of cholesterol and the risk of type 2 diabetes mellitus. Nevertheless, as cholesterol is only present in products from animal origin, the general view is that this association should be attributed to other components of animal products associated to cholesterol, like saturated fat [11].

Type 2 diabetes mellitus and gestational diabetes mellitus (GDM) share similar risk factors and pathophysiological mechanisms. In fact, women with GDM are at an increased risk of developing type 2 diabetes mellitus. Although diet therapy is a cornerstone of the treatment of GDM, there are few studies relating to the association between dietary intake and glycemic status during pregnancy. None of these studies reported cholesterol dietary intake during pregnancy [12].

3.1.3. Obesity and fertility

Several studies have shown an increased risk of an ovulatory infertility in obese women [odds ratio (OR)]: by mechanisms of hyper androgenism and polycystic ovarian syndrome, which share several pathophysiological characteristics, namely insulin resistance. Although some controversy still exists regarding the effect of obesity in patients who undergo in-vitro fertilization (IVF), three large population-based retrospective studies have shown lower pregnancy rates in obese patients. Linsten et al [13] reported the results of 8457 IVF patients showing significantly lower birthrate in women with BMI - 27 [OR: 0.67; 95% confidence interval (CI):

Insulin resistance is a major component of type 2 diabetes. In the past decade, the increase in the incidence of type 2 diabetes mellitus has emerged as one of the most challenging health problems in western countries. No overall strategy has been defined to reduce the epidemic [3]. However, it is recommended that all factors associated with insulin resistance should be identified and treated. Interestingly, several studies have shown that insulin sensitivity is impaired in current smokers, which led some investigators to study the relationship between cigarette smoking and diabetes mellitus. Studies in Northern Europe (United-Kingdom, Holland, Sweden), in Japan and in the United States suggest that cigarette smoking can trigger the development of diabetes. However, these populations have very different genetic backgrounds compared to the French population and the incidence of diabetes mellitus is usually higher in these countries than in France. It therefore remains to be demonstrated whether such an association exists in the French population. Moreover, most of these studies were carried out in men, and female populations were rarely studied. Confusing parameters such as weight, hip and waist measurements, alcohol consumption were not systematically evaluated, and the influence of smoking cessation is still a matter of debate [3].

In the United Kingdom Prospective Study (UKPDS) the modifiable risk factors for coronary heart disease in Type 2 diabetes were dyslipidaemia, hyperglycaemia, hypertension and smoking. The dyslipidaemia is characterized by an atherogenic lipoprotein phenotype, with increased triglyceride and low HDL-cholesterol concentrations and a preponderance of small, dense LDL particles. It has been suggested that the expression of this phenotype can be explained by increased concentrations of triglyceride rich lipoproteins promoting the cholesterol ester transfer protein (CETP) mediated reciprocal exchange of triglyceride in these lipoproteins for cholesterol esters in LDL and HDL. Thus VLDL, chylomicrons and their remnants become cholesterol ester enriched while LDL and HDL become triglyceride enriched. Hepatic lipase acts preferentially on triglyceride-enriched LDL and HDL to produce atherogenic small dense LDL, which are susceptible to oxidation and have poor receptor affinity, and small dense HDL, which have reduced anti-atherogenic potential. Thus hepatic lipase activity may facilitate the generation of an atherogenic lipoprotein phenotype in Type 2 diabetes [3].

2. Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) affects approximately2% to 4% of all pregnant women in the United States each year. Women who have had GDM are at high risk for developing non-gestational diabetes. The objective of this study was to assess the prevalence of modifiable risk factors for developing diabetes among women with previous GDM only [4].

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first detected during pregnancy. An increase in the prevalence of GDM has-been reported among pregnant women enrolled in Kaiser Permanente, Colorado (KPCO). It was estimated that the prevalence of GDM among KPCO members doubled from2.1% in 1994 to 4.1% in 2002. Women who have had GDM are at high risk for developing non-gestational diabetes. Research has shown that women with gestational diabetes have a 17% to 63% risk of developing non-gestational diabetes within 5 to 16 years after index pregnancy [4].

2.1. Gestational diabetes and cardiovascular disease

Recently, a great number of data have demonstrated that pregnancy complications, such as pregnancy-induced hypertension, delivery of pre-term or low-birth-weight babies, spontaneous pregnancy loss are all conditions associated with substantial increase in Cardio vascular Diseases (CVD) risk. It has been hypothesized that either pregnancy complications “resets” the mothers' metabolism adversely so directly increasing future CVD risk, or that unknown preexistent cardiovascular risk factors are exacerbated by the metabolic stress of pregnancy thus contributing to gestational complications. Therefore, the likelihood of pregnancy complications might have clinical implications, becoming an easy, no-cost tool to detect which women should undergo routine CVD assessment. Less attention has been focused on the relationship between gestational diabetes (GDM), a relatively frequent disease, affecting 2-5% of all pregnancies, and CVD in later years. On the other hand, the future risk of developing type2 diabetes in women with previous GDM (pGDM) is well known, ranging from 20 to 60%, depending on the severity of their insulin resistance and plasma glucose reached during pregnancy. It is not known whether women with pGDM, but who do not develop diabetes mellitus and without any other cardiovascular risk factors, show an increased CVD risk than those without gestational hyperglycemia [5].

Studies performed in small cohorts have reported sign of vascular endothelial dysfunction in vitro and in vivo during pregnancies complicated by GDM, and impaired endothelium-dependent vasodilatation, increased common carotid artery stiffness, evidence of sub-clinical inflammation and early vascular dysfunction after delivery.

Markers of endothelial dysfunction, like circulating levels of E-selectin, vascular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and inflammatory parameters, like C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be associated with CVD. Moreover, intimal medial thickness (IMT) measurement has been used as a non-invasive surrogate of CVD [6].

Few and contrasting data are available as which indicate the associations between these markers and pGDM. E-selectin and VCAM-1 concentrations were found to be elevated in a small cohort of women with pGDM. Increased levels of inflammatory parameters were associated with pGDM in non-diabetic women post-delivery, but maternal obesity was suggested as a central mediator in the inflammatory response found in gestational hyperglycemia.

3. Risk factors associated with gestational diabetes

Gestational diabetes mellitus is a heterogeneous disorder characterized by intolerance to carbohydrates and hyperglycemia in varied degrees of intensity, with onset or first diagnosis during pregnancy. The pregnancy is a physiological situation of insulin resistance; therefore, it may be the first moment in a woman's life to test her capacity to respond to a physiological stress and to detect those at greater risk of developing diabetes in the future [7]. Several risk factors for gestational diabetes mellitus such as older age, obesity and family history of diabetes are well known and discussed in the literature. Other factors are still controversial: low birth weight, short stature, smoking, multi parity, race or ethnicity, physical inactivity, gestational weight gain and socioeconomic factors [8].

Studies of pregnancy outcomes among overweight and obese mothers have been published for more than 50 years. Compared with smoking, however, the public health importance of overweight during pregnancy has received less attention. Overweight is associated with pregnancy-related diseases

0.480.94]. Fedorcsak et al [14] reviewed 5019 IVF cycles and found a lower cumulative live birth rate in the obese group 41.4%versus 50.3% in normal weight women (95% CI: 32.150.7; not significant) [15].

3.1.4. Miscarriage and obesity

Although the relationship between obesity and first trimester miscarriage has been investigated extensively, the results are far from conclusive and require further research. Whereas several Studies suggest that obesity may increase the risk of miscarriage due to adverse influences on the embryo, the endometrium or both, others found no association between miscarriage and Obesity. These studies lack consistency, however, mainly because of the use of different obesity classification systems, which disregard the WHO definition [16].

3.1.5. Thromboembolic complications and obesity

Pregnancy itself is a prothrombotic state with increases in the plasma concentration of coagulation factors I, VII, VlII and X,a decrease in protein S and inhibition of fibrinolysis, resulting in 5-fold increased risk for venous thrombosis. Other factors likely to be important in the etiology of pregnancy-associated vein thromboembolisem (VTE) are advanced maternal age, high parity, operative delivery, pre-eclampsia and obesity. Abdollahi et al [17] evaluated in a case-controlled study, the risk of thrombosis due to overweight and obesity after a first episode of objectively diagnosed thrombosis. Obesity (BMI_ 30) increased the risk of thrombosis 2-fold. Obese individuals had higher levels of factor VIII and IX, but not of fibrinogen. In addition, the combined effect of obesity and oral contraceptive pills among women aged 15-45years revealed that pill users had a 10-fold increased risk for thrombosis at BMI >25 [18].

3.1.6.Hypertension disorders and obesity

Arterial blood pressure, haemoconcentration and cardiac function are all altered by the hemodynamic changes brought about by obesity. Authors have suggested a 10-fold higher rate of chronic hypertension in obese patients compared to normal weight women. The risk of pregnancy-induced hypertension or preeclampsia is significantly greater if the mother is overweight as assessed by BMI in early pregnancy. Studies suggest a 23-fold increased risk for pre-eclampsia at BMI >30. Sattar et al [19] reported the results of the risk of hypertensive complications of pregnancy in association with waist circumference of >80 cm in data from 1142 pregnant women. The risk of pregnancy-induced hypertension was 2-fold greater (OR: 1.8; 95% CI: 1.12.9) and pre-eclampsia 3-fold greater (OR: 2.7; 95% CI: 1.16.8) in association with visceral obesity. Waist circumference was demonstrated to be a more sensitive risk marker than BMI. In a study of 287 213 pregnancies, Sebire et al [20] included 176 923 (61.6%) normal weight (BMI 2024.9), 79 014 (27.5%) overweight (BMI 2529.9) and 31 276 (10.9%)obese (BMI_30) women. Obese women were two to three times more likely to develop proteinuric pre-eclampsia. Birth weight above the 90th percentile was also increased in obese women, as was intrauterine death. Intrapartum complications included an increased rate of induction of labor and delivery by caesarean section. In the postpartum period there was an increased rate of hemorrhage, genital tract infection, urinary tract infection and wound infection. They concluded that maternal obesity carries significant risk for both mother and fetus with risk increasing with the degree of obesity and persisting after accounting for other confounding demographic factors. Bianco et al [21] performed retrospective cohort study of 613 morbidly obese (BMI >35; class II and III) and 11 313 non-obese women. A 4-fold increased risk for pre-eclampsia was reported. There was a 50% increase in frequency of fetal distress and a 2-fold increase incesarean delivery. Postpartum, obese women had a 3-fold increased incidence of endometritis. Additionally, Stone et al [22] found that the only risk factors associated with the development of severe pre-eclampsia were severe obesity in all patients (OR: 3.5; 95% CI: 1.67.4) and a history of preeclampsiain multiparous patients (OR: 7.2; 95% CI: 2.718.7) [23].

A meta-analysis showed that the risk of pre-eclampsia doubled with each 5–7 kg/m2 increase in pre-pregnancy BMI. This relationship persisted in studies that excluded women with chronic hypertension, diabetes mellitus or multiple gestations, and other confounders. Epidemiological studies have shown a relationship between pregnancies complicated by pre-eclampsia and increased risk of maternal coronary heart disease in later life. The reported increase in the relative risk of death from ischemic heart disease in association with a history of pre-eclampsia/eclampsia is 2-fold. Pre-eclampsia shares many common pathological pathways with ischemic heart disease. The metabolic syndrome explains the influence of obesity on the development of hypertensive disorders and ischemic heart disease, dyslipidemia and coagulation abnormalities.

3.1.7. Birth defects and obesity

Apart from the increase in failure to detect birth defects in obese women due to difficult interpretation of serum markers (changes in the volume of distribution) and sub optimal visualization of fetal anatomy by ultrasound examination, several studies report factual increase in birth defects among obese women. Waller et al [24] in 1994 first suggested that offspring of obese women were at increased risk of neural tube defects (OR: 1.8; 95% CI: 1.1–3.0), especially spina bifida (2.6; 1.5-4.5). These results have been confirmed in subsequent studies and have also shown increased risks of heart defects (1.18; 1.09-1.27) and omphalocele (3.3; 1.010.3). Because these types of congenital anomalies are often seen with pre-gestational diabetes, some investigators suggest that many of these obese women may have had undiagnosed type 2diabetes. Neural tube defects are associated with folic acid deficiencies, yet it is inconclusive if such a deficiency is a contributing factor to the increased risk of neural tube defect in obese women. Mojtabai suggested that women with a BMI >30 would need to increase their folate consumption by 350 mg/d to achieve the same folate levels as women with BMI <20 by contrast [25].

3.1.8. Macrosomia and obesity

Many variables have been associated with fetal overgrowth or macrosomia. Increasingly, maternal pre-gravid weight and decreased pre-gravid insulin sensitivity have been shown to strongly correlate with fetal growth, especially fat mass at birth. Increased maternal insulin resistance may be associated with altered placental function in addition to increased fetoplacental availability of nutrients in late gestation. These nutrients include glucose, but also free fatty acids and amino acids. As a result, women with GDM are at increased risk of having a macrosomic infant; those who are obese with normal glucose tolerance are almost twice as likely to have a macrosomic infant. Morbid obesity (BMI> 35) increases the risk of birth weights >4000 g (OR: 2.1; 95% CI: 1.3–3.2).

Ehrenberg et al [26] reviewed the results of 12950 pregnancies and found that obesity and pre-gestational diabetes both are independently associated with an increased

risk of macrosomia. After adjusting for confounding risk factors, these authors found that compared with normal BMI subject's obese women were at elevated risk for large-for-gestational-age newborns (LGA) delivery (16.8% vs 10.5%; P < 0.0001), as were overweight women (12.3% versus 10.5%; P ¼0.01). Baeten et al [27] found that the risk of delivering a macrosomic infant was increased (albeit not in a dose-related fashion) with each level of increasing independent of the diagnosis of diabetes [BMI> 30 (OR: 2.1; 95% CI: 1.9-2.4); BMI 25-29.9 (1.5; 1.4-1.6); BMI 20-24.9 (1.2; 1.2-1.3)]. Because the prevalence and frequency of overweight and obese women is nearly 10 times that of gestational diabetes (45% vs4.5%), abnormal maternal body habitus is likely to have the strongest influence on the prevalence of macrosomia. When studying effects of obesity on pregnancy outcome it is often uncertain if adequate screening for GDM has been carried out and therefore it is often difficult to assess if effects are caused by obesity and/or by GDM. In a study by Jensen et al [28] all women with GDM were excluded. They evaluated pregnancy outcome and BMI in glucose-tolerant non-diabetic Danish women. They concluded that the risk of hypertensive complications, cesarean section, induction of labor and macrosomia were all significantly increased in both overweight women (BMI 25.0-29.9) and obese women (BMI> 30.0) compared to women who were of normal weight (BMI18.5-24.9). The frequencies of shoulder dystocia, preterm delivery, and infant morbidity other than macrosomia were not significantly associated with maternal BMI. This population-based study clearly demonstrated that pre-pregnancy overweight and obesity are associated with adverse pregnancy outcome in glucose-tolerant women. This study was unique in that there was no single outcome measure, but rather the influence of different levels of obesity in glucose-tolerant women during pregnancy.

3.1.9. Long-term implications of obesity:

The implications of maternal obesity far surpass intrauterine life, extending into infancy and even adulthood with severe health repercussions. Both the Barker, and fetal insulin hypotheses, has proposed that impaired adult cardiovascular health is programmed in utero by poor fetal nutrition, or by genetically determined reduction of insulin-mediated fetal growth, resulting in the birth of a small infant. Low birth weight may be a significant variable for the development of the metabolic syndrome in adulthood. Obesity was an independent risk factor in the diabetic populations studied. Therefore, the emphasis today may need to address sedentary lifestyle and an issue related to obesity upon fetal programming since under nutrition is now infrequent in developed societies. Maternal obesity long has been linked with the delivery of a macrosomic infant. Now there is abundant evidence linking macrosomia to increased overweight and obesity in adolescents as well as adults. Perhaps more alarming is a recent retrospective cohort studies by Whitaker of more than 8400 children in the USA in the early 1990s. The prevalence of childhood obesity was between 2.4 and 2.7 times higher in offspring of obese women in the first trimester compared to children whose mothers' BMI was in the normal range at this early stage of pregnancy. These findings remained consistent even after controlling for additional risk factors including birth weight, parity, weight gain, and smoking during pregnancy (RR: 2.0; 95% CI: 1.7-2.3). The epidemic of obesity and subsequent risk of diabetes and components of the metabolic syndrome clearly may begin in utero with fetal overgrowth and adiposity. Fully 50-90% of adolescents with type 2 diabetes have a BMI >27,78 and 25% of obese children4-10 years of age have impaired glucose tolerance. Not surprisingly, an additional study reported evidence of a link between maternal obesity and cardiovascular disease in adult offspring, confirming Barker's hypothesis of higher adult death rates from coronary heart disease in men who were classified as low birth weight. In addition, they observed a positive association between the mother's BMI upon admission and future death rate from coronary heart disease in male offspring. They concluded that them mother's obesity may be an independent yet additional contributing factor to infant low birth weight. Fall et al [29] reported higher adult rates of type 2 diabetes in off spring of mothers who were above average weight in pregnancy. Therefore, there is an association between maternal obesity (but not paternal) and insulin resistance on the risk of offspring to develop cardiovascular disease in adulthood. In a further study, high maternal weight or BMI accounted for the association between birth weight and adult adiposity [30].

3.1.10.Maternal long-term implications of obesity

Some pregnancies are associated with excessive maternal weight gain. Mean weight retention after pregnancy ranges between 0.4 and 3.8 kg. Weight retention after pregnancy has been attributed to various causative factors, including smoking cessation, changes in activity leading to a more sedentary lifestyle, socioeconomic factors such as low income, etc. Additionally, increased weight gain during pregnancy remains the strongest factor for weight retention after pregnancy. Linne et al [31] reported that women with a weight gain of _16 kg during pregnancy were 2.5 times more likely to be a high weight retainer1 year postpartum. Of equal importance, women diagnosed with GDM have considerably higher risk of developing type 2 diabetes diagnosed with GDM in 1984-1985, and a control group of 53 women who gave birth in the same time period, Linne et al [31] performed a 2 h oral glucose tolerance test 15 years later. Ten women (35%) in the GDM group were diagnosed with type 2 diabetes mellitus vs none in the control group (P <0.001). Mean BMI in the diabetic group was 27.4 and in the non-diabetic GDM group 24.6 (P <0.05) mellitus later in life. In a casecontrol study, including 28 women.

4. Association between maternal obesity and GDM

The association between obesity, hypertension and insulin resistance in type 2 diabetes is well recognized. About 3-15% of women develop GDM during pregnancy. Although many factors are related to this risk, including ethnicity, previous occurrence of GDM, age and parity, family history of diabetes and degree of hyperglycemia in pregnancy, obesity acts as an independent risk for developing GDM, with a risk of about 20%. It has been shown that even minor degrees of carbohydrate intolerance are related to obesity and pregnancy outcome. Sebire et al [20] found a 2-fold increase in the rate of GDM (OR: 1.68; 95% CI: 1.53–1.84). Smilen et al [32] reported a 3-fold increase in GDM for obese patients. A population-based cohort study of 96 801singleton births found that not only obese women (BMI > 30.0) but also overweight women (BMI 25.0–29.9) had a markedly increased risk for GDM (OR: 5.0 and 2.4, respectively). Yogev et al [33] in a study of 6857 women, found a direct association between glucose screening categories, obesity and rate of GDM. For patients with 50 g glucose challenge test (GCT) screening results of 130-189 mg/dL, the rate of obesity was w24-30%. Thereafter, at GCT result >190 mg the rate of obesity increased 2-fold. In contrast, for non-obese women, the rate of GDM increased almost linearly for each 10 mg increment in glucose screening value. These data demonstrate that the rate of obesity and glucose tolerance are both associated with the development of GDM. Additionally, in another study, Turner et al [34] have shown that fetal size and cesarean section rate are

associated with the degree of carbohydrate intolerance as represented by screening results. Furthermore, obesity was a significant and independent contributor impacting fetal size. On-diabetic pregnant women have been the populations in the majority of studies in which the relationship between maternal-pregnancy weight and perinatal outcome have been addressed. However, there are scant data on obesity and overweight in GDM [35].

The few studies reporting obesity in gestational diabetes lack information on the effect of achieving targeted levels of glycemic control and treatment modalities on pregnancy outcome. Leiken et al [36] demonstrated an independent risk for macrosomia among obese GDM women. They found that GDM had a frequency of macrosomia no different than that of non-diabetic subjects: non obese GDM women with fasting hyperglycemia treated with diet and insulin therapy had a frequency of macrosomia no different than that of non-diabetic women. However, diet and insulin did not prevent excess macrosomia in women who were obese. These studies had small sample sizes, failed to provide information on glycemic control, and only evaluated single outcome variables [37].

Maternal age, parity, and obesity are all over represented among GDM women. These variables need to be controlled in order to draw accurate conclusions that also control confounding effects. Therefore, it is not clear if obesity, level of glycemia, or treatment modalities is independently or cumulatively responsible for fetal growth abnormalities. Studies show that obese and overweight patients achieving established levels of glucose control with insulin therapy showed no increased risk for composite outcome, macrosomia and LGA compared with normal weight GDM patients. In contrast, even when diet-treated obese patients achieved good glycemic control, there was no improvement in pregnancy outcome compared with normal weight patients [38]. Poorly controlled overweight and obese patients, regardless of treatment modality, had significantly higher rates of composite outcome, metabolic complications, and macrosomia and LGA. Although obesity in it self is related to adverse outcome in pregnancy, gestational diabetic women treated with insulin and possibly oral anti-diabetic drugs who achieve targeted levels of glycemic control will have pregnancy outcomes similar to those of normal weight women. These findings are in contrast to those of Graves et al [39]. However, the improved outcome in the insulin treated overweight and obese women may be due to an unidentified effect of insulin itself on the fetus or activation of other metabolic fuel pathway [40].

4.1. Level of obesity in GDM and pregnancy outcome

Several studies have suggested a higher rate of morbidity in morbidly obese non-diabetic pregnant women. Langer et al [41] found no significant difference between obese and morbidly obese women in pregnancy outcome compromised by diabetes when targeted levels of glycemic control were achieved. However, two thirds of the morbidly obese patients failed to achieve the desired level of glycemic control and 69% were treated with insulin. In addition to constitutional risk factors such as previous macrosomia and parity, level of glycemic control, obesity, and treatment modality were found to be independent contributors to the outcome variable. These findings support the premise that treatment with insulin and achievement of the established level of glycemic control in obese patients will result in improved pregnancy out come.

The majority of studies have found an association between hypertensive disorders and obesity. Regardless of achieving established levels of glycemic control, the rate of pre-eclampsia was not significantly different between diet-treated overweight and obese subjects. The relatively low rate of GDM severity in diettreated patients (fasting plasma glucose < 95 mg/dL) may account for this difference. In insulin-treated subjects, a w 3-fold higher risk for pre-eclampsia was found in the patients who failed to achieve established levels of glycemic control. Insulin-treated overweight/ obese patients in all BMI categories who achieved established levels of glycemic control had similar rates of pre-eclampsia. This study emphasizes that by achieving the desired level of glycemiccontrol, even in obese patients, the risk for pre-eclampsia can be attenuated [42].

4.2. Obesity, GDM and metabolic syndrome: a vicious cycle

In 1988, Reaven [43] proposed that resistance to insulin-stimulated glucose uptake (insulin resistance, IR) and secondary hyper insulinemia are involved in the etiology of three major related diseases: cardiovascular disease (CVD), type 2 diabetes and hypertension. He coined the term 'syndrome X' that has been modified later to metabolic syndrome (MS) to describe a group of abnormalities that increase the risk for CVD: resistance to insulin stimulated glucose uptake, glucose intolerance, hyper insulinemia, increased triglyceride (TG), decreased high density lipoprotein cholesterol (HDL) and hypertension. Obesity is the most important risk factor for the MS. In the NHANES study, MS was present in 4.6%, 22.4%, and 59.6% of normal weight, overweight, and obese men, respectively, and a similar distribution was observed in women. A large waist circumference identifies upto 46% of individuals who will develop the metabolic syndrome with in five years. The Kuopio Ischemic Heart Disease Risk Factor Study reported that men with the MS are about three or four times more likely to die of CVD than those without the condition. A meta-analysis of several European trials reported the MS raised the HR for CVD from 0.6 to 2.8 for women [44].

5. GDM as a predictor for subsequent development of the metabolic syndrome

Several studies have investigated the relationship between GDM and subsequent MS. Bo et al [45] reported on the development of MS in a group of 81 women with prior GDM. Prevalence of the MS and its components was 2-4-fold higher in women with prior gestational hyperglycemia and 10-fold higher if pre-pregnancy obesity coexisted when compared to normoglycemic controls, suggesting that GDM, especially in combination with prepregnancy obesity, predicts a subsequent syndrome of high cardiovascular risk. Verma et al [46] confirmed this finding. They reported that 27% of 106 patients with GDM and 8.2% of 101controls developed features of insulin resistance by 11 years after delivery. The cumulative hazard for developing MS in the next 2years was 26 times higher among GDM subjects with pre-pregnant obesity, compared with controls. It was concluded that obesity and GDM in a prior pregnancy are significant risk factors for developing MS and cardiovascular risk factors. Pallardo et al [47] in Spain studied 788 Caucasian women with GDM between three and six months postpartum. Forty-three (3.7%) were diagnosed with overt diabetes. The area under the postpartum glucose curve was positively associated with BMI, waist circumference, waist/hip ratio, triglycerides, and systolic and diastolic blood pressures. It was concluded that postpartum glucose intolerance predicts a high-risk cardiovascular profile that includes risk factors besides type 2 diabetes [48].

6. Gestational diabetes and oxidative stress

Diabetes during gestation is associated with an increased risk of fetal and maternal complications. However, the mechanisms by which diabetes lead to greater fetal abnormalities and maternal vascular complications such as preeclampsia have not been well established. The clinical manifestations of diabetes in pregnancy have been attributed to fetal hyperglycemia, hyper-lipidemia, hyper-insulinemia, or placental endothelial dysfunction. The involvement of oxidative stress was recently suggested. Oxidative stress may be increased in diabetes owing to a hyper production of reactive oxygen species (ROS) such asO_2S^-, OHS, and or a deficiency in the antioxidant defense system. The increased production of ROS has been attributed to protein glycation and glucose auto-oxidationin a hyperglycemic environment. Impaired radical scavenger function has been linked to the decreased activity of enzymatic and non-enzymatic scavengers. In particular, the action of superoxide dismutase (SOD), which catalyzes the dismutation of O_2S^- into H_2O_2 has been found to be decreased in the erythrocytes of diabetic rats and diabetic humans. Similarly, a reduction in the action of glutathioneperoxidase (GPX) and catalase (CAT), enzymes involved in the detoxification of, has been observed in chronic diabetes. Among the non-enzymatic scavengers, vitamin E, the main intra-cellular antioxidant, has-been found to be decreased in diabetic patients. Moreover, experimental studies have found evidence for free oxygen radical activity in the embryos of diabetic rats [49].

7. Risk of smoking

Cigarette smoking and overweight are leading causes of preventable diseases and deaths. In most developed countries, smoking causes more deaths by violence, accidents, alcohol, or other drugs taken together, a overweight is not only associated with Strong risks of cardiovascular diseases, but also osteoarthritis and cancers at various sites [50].

Smoking is an independent CV risk factor. According to the US Surgeon General's report of 2004, there is sufficient evidence to infer a causal relationship between smoking and sub clinical atherosclerosis, abdominal aneurysm, stroke and coronary heart disease [51]. The high proportion of both smoking and overweight in young women highlights the potential public health impact of these risk factors on adverse pregnancy outcomes. Increased rates of adverse pregnancy outcomes were reported among female tobacco workers in the 1930s, where free access to tobacco often was offered as a fringe benefit. Since then, smoking during pregnancy has been causally associated with intrauterine growth retardation, and a number of studies have shown that smoking also increases the risks of spontaneous abortion, preterm birth, placental complications, stillbirth, and sudden infant death syndrome. The hazards of smoking during pregnancy are today well known to health care providers and the general public. Smoking is also known to be associated with the atherogenic lipoprotein phenotype and insulin resistance. We have previously shown that hepatic lipase activity is related to insulin resistance in type 2diabetic subjects [52].

Cigarette smoking is associated with higher serum levels of cholesterol and lower plasma concentrations of high-density lipoprotein (HDL) cholesterol; also, smokers have higher plasma triglyceride concentrations than nonsmokers and smoking enhances platelet aggregation. Smoking impairs lipoprotein metabolism, reduces the dispensability of blood vessel walls, and induces a prothrombotic and proinflammatory state. A cross-sectional study of around 19,000 participants showed that, compared with nonsmokers, current smokers as well as former smokers have significantly higher, multivariate adjusted, clinically elevated C-reactive protein, fibrinogen and homocysteine levels. These novel risk factors for atherosclerosis all increase dose-dependently with the number of cigarettes smoked per day, the number of pack-years of cigarettes smoked and serum cotinine concentrations. Several prospective studies have demonstrated that elevated levels of C-reactive protein, fibrinogen and homocysteine are positively associated with the risk of stroke and coronary heart disease. Thus, smoking promotes the development of atherosclerosis by increasing, at the clinical level, the presence of novel cardiovascular risk factors. Moreover, smoke exposure results in tissue damage by increasing the products of lipid per oxidation and of degradation of extra cellular matrix protein endothelial dysfunction, and by apoptosis. Acute smoking increases neutrophil counts, while smoking in general is associated with increased levels of carboxyhaemoglobin, leading to hypoxaemia. Smoking also inhibits tissue repair [53].

Figure 2. A smoking directly raises cardiovascular risk

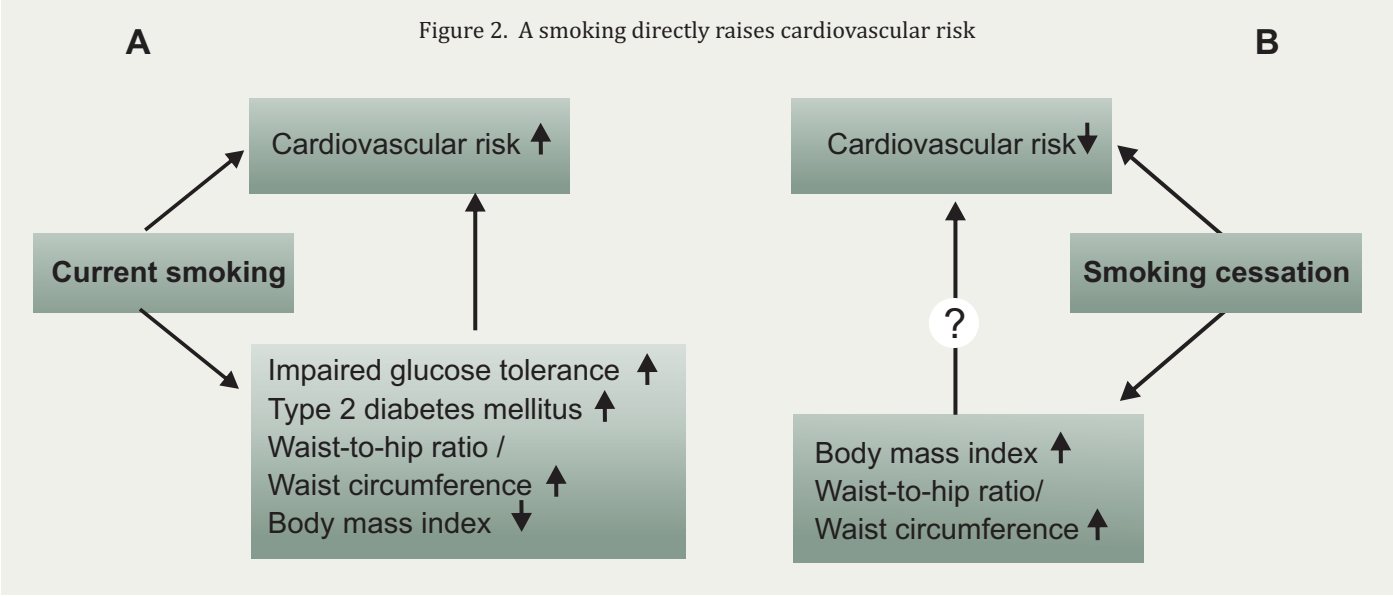

Figure. 2 A smoking directly raises cardiovascular risk, but also leads to metabolic alterations (impaired glucose tolerance, type 2 diabetes mellitus, increased waist to-hip ratio/waist circumference) that may indirectly lead to an increased cardiovascular risk. B. Smoking cessation reduces cardiovascular risk, but is accompanied by increases in body mass index and waist-to-hip ratio/waist circumference that, potentially, can compromise the cardiovascular benefits of stopping smoking [54].

Cessation of smoking leads to a 36% reduction in the relative risk (RR) of all-cause mortality for patients with coronary heart disease (CHD), regardless of age, gender; index cardiac event and country of residence, compared with those who continue to smoke (RR: 0.64, 95% CI: 0.580.71). The decline in CV morbidity and mortality is accompanied by a progressive decrease in traditional and inflammatory risk factors, although the decrease in inflammatory markers, and C-reactive protein in particular, takes longer to normalize (five to seven years) than the decline of traditional risk factors (such as total cholesterol), which are normal within one year [54] .As early as 1954, Doll and Hill [55] in the UK demonstrated that smoking greatly increases mortality due to CHD, and not only in the industrialized nations, but also in the developing countries as well. The recently published INTERHEART study, involving 52 countries, found that smokers had a greater risk of non-fatal myocardial infarction compared with those who had never smoked (OR: 2.95, 95% CI: 2.773.14). This risk increased by 5.6% for every additional cigarette smoked. Former smokers within three years of having quit still had an increased risk (OR: 1.87, 95% CI: 1.552.24). Furthermore, even smokeless tobacco (chewing tobacco) was associated with an increased risk of non-fatal myocardial infarction (OR: 2.23,95% CI: 1.413.52) [56].

Although smokers tend to have a lower BMI than nonsmokers, recent studies have shown that, in spite of this, smokers are more likely to have abdominal type obesity. Abdominal obesity reflects preferential visceral-fat accumulation; it is also a better indicator of adverse metabolic risk factors and CV disorders than BMI. The WHR shows a graded and highly significant association with acute myocardial infarction (AMI) risk, according to the INTERHEART study. The association between WHR and AMI is stronger than that between BMI and AMI. Smokers have a larger waist circumference and WHR, and a higher WHR than former smokers and never-smokers; the WHR is positively associated with the number of cigarettes smoked per day. Czernichow et al [57] demonstrated an increase in WHR in French smokers in both genders and, in a large study from Greece; tobacco smoking was positively and dose-dependently associated with a higher WHR not only in men, but also in women. WHR increases with age in both men and women, and smoking tobacco considerably potentates this age-related rise. Mizuno et al [58] studied obesity-related disorders in both non-obese and obese smoking and non-smoking Japanese subjects. They found that, among the non-obese subjects, hypertension, hyperglycaemia, dyslipidaemia and hyperuricaemia were more frequent in smokers, but with no significant differences in waist circumference. However, among those who were obese, smokers had a larger waist circumference than nonsmokers, suggesting that smoking may be a promoter of abdominal fat accumulation. The relationships between smoking and WHR, and smoking and BMI, are not similar. In a large cross-sectional study of pre- and post menopausal Dutch women, WHR increased in parallel with the number of cigarettes smoked per day, while the BMI decreased.

The most convincing evidence of a positive association between WHR and smoking comes from the study by Canoy et al [59] This study involved 21,828 men and women, aged 45 to 79 years, residing in Norfolk, UK, who had no known heart disease, stroke or cancer. Current smokers had a higher WHR compared with never-smokers in both men and women, and across all BMI categories. Among current and former smokers, those who had a greater cumulative exposure (assessed by the number of pack-years smoked) also had a higher WHR compared with never-smokers, when adjusted for potential confounders such as BMI, age, alcohol intake, physical activity, total energy intake and education. The effect of current smoking on WHR was similar in men and women. Among former smokers, the time since quitting was inversely related to WHR, but only smokers who stopped smoking more than 20 years earlier had a similar WHR to that of never-smokers, suggesting that the WHR is very slow to normalize [60].

7.1. Smoking and gestational diabetes

Tobacco use, along with obesity, is one of the most important avoidable causes of death. The number of smokers worldwide is estimated to be 1.3 billion, of which two-thirds are living in the developing countries. Among British doctors, who have high living standards, continuing to smoke reduces life expectancy by at least ten years, so the life expectancy is expected to be even shorter in developing countries. The global mortality attributable to smoking in 2000 was estimated to be 4.83 million premature deaths, with 2.41 million in developing countries and 2.43 million in industrialized countries. The leading causes of death from smoking are cardiovascular diseases (1.69 million deaths), chronic obstructive pulmonary disease (0.97 million deaths) and lung cancer (0.85 million deaths). Stopping smoking at age 60, 50, 40 or 30 years leads to a gain of about three, six, nine or ten years in life expectancy, according to the study among male British doctors followed-up for 50 years [61].

Meta-analysis of unadjusted and adjusted results of studies of the association between smoking and gestational diabetes exhibit important heterogeneity and, when taken together, do not support an association between cigarette smoking during pregnancy and the risk of gestational diabetes (Figure 3 and Figure 4)[4].

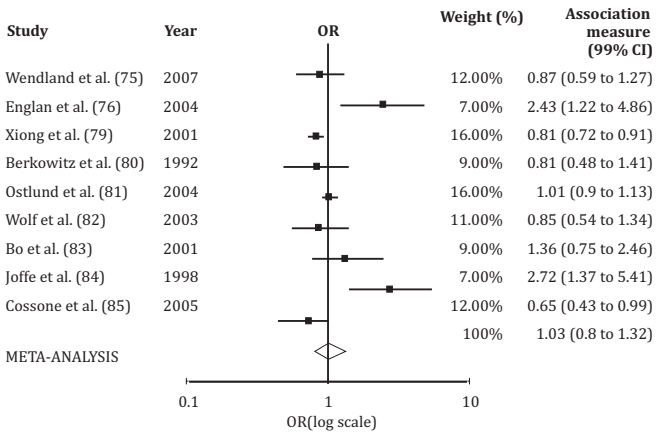

Figure 3. Meta-analysis of unadjusted results of studies of the association between smoking and gestational diabetes. Black squares indicate the odds ratio in each study and the horizontal lines represent 99% confidence intervals. Random-effects model [4,75,76,79-85].

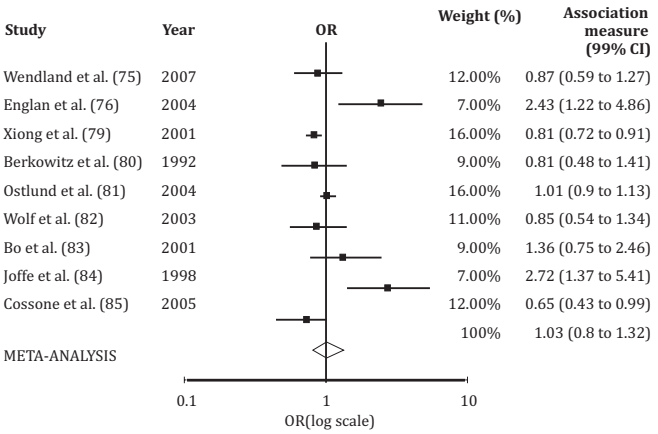

Figure 4. Meta-analysis of adjusted results of studies of the association between smoking during pregnancy and gestational diabetes. Black squares indicate the odds ratio in each study, with the square size proportional to the weight of the study in the meta-analysis and the horizontal lines represent 99% confidence intervals [4,75,76,79-85].

The first systematic review and meta-analysis evaluating the association of smoking during pregnancy and gestational diabetes found a great diversity in the assessment of outcomes and adjustment for confounding variables, sensitivity analysis did not reveal an important influence of any single study (Table 1)[4].

Table 1. Characteristics of studies of the association of cigarette smoking and gestational diabetes mellitus [4]

Author, year	Location	Data source	Description of the study population	Adjustments	Degree of Adjustments*
Terry et al., 2003 [74]	Sweden	Birth registry	First and second deliveries between January, 1987 and December, 1995.	Maternal age, living with infant's father, interpregnancy interval, maternal height, BMI during pregnancy.	++
England et al., 2004 [75]	U.S.	CPEP trial	Participants of the Calcium for Pre-eclampsia Prevention trial. 1992 to 1995.	Race/ethnicity, age, education, BMI at enrollment, pregnancy loss, private health insurance, study center, gestational age at blood collection.	++
Cnattingius et al., 2002 [76	Sweden	Birth register	Women with singleton births between1992 and 1997, in Sweden.	Age, parity, cohabitation with infant's father, maternal education, mother's country of birth, maternal height, BMI at first antenatal care visit.	++
Xiong et al., 2001[77]	Canada	Hospital register	Women from the Northern and Central Alberta Perinatal Audit and Education Program of Canada from July, 1991 to December,1997.	Parity, age, maternal weight, alcohol use, history of neonatal death, history of delivery < 37 weeks, history of cesarean section and history of major neonatal malformation.	+
Wendland et al., 2007 [79]	Brazil	Prospective study	Women using the public health clinicsin six state capitals of Brazil from 1991 to 1995.	Study center, age, skin color, pre-pregnancy BMI and weight gain during pregnancy.	+++
Berkowitz et al., 1992 [80]	U.S.	Hospital registry	Singleton pregnancies at Mount Sinai Medical Center (NY) from January, 1987 to December, 1989	None	-
Bo et al., 2001 [81]	Italy	Prospective study	Pregnant women attending the Gynecological and Obstetrical Department of the University of Turin from April, 1999 to November, 2000.	None	-
Cosson et al., 2006 [82]	France	Prospective study	Women who delivered at Jean Verdier Hospital - Bondy, from October, 2000 to December, 2002.	None	-
Wolf et al., 2003 [83]	U.S.	Prospective study	Participants of the Massachusetts General Hospital Obstetric Maternal Study (MOMS) from September, 1998 to July, 2001.	None	-
Ostlund et al., 2004 [84]	Sweden	Birth registry	All women with singleton births from 1992 to 1996,registered in the Swedish Medical Birth register.	None	-

*Degree of adjustment for potential confounders were categorized as + for age; ++ for age plus pre pregnancy BMI; +++ for these plus weight gain during pregnancy.

The impact of maternal smoking on foetal growth arises in a number of ways either directly by reducing foetal growth as environmental toxin, by shortening gestational length, thus increasing the incidence of premature births, or by altering utero placental and foetal blood flow, with consequent decrease in oxygen consumption, nutritional and energy supply to the foetus. The classic measures of foetal growth, e.g. BW, are composites of a number of components each influenced to varying degrees by a series of growth factors. Longitudinal growth in utero is insulin-like growth factor-I (IGF-I) dependent and circulating concentrations of IGF-I are reduced in pregnancy. Other factors influence the development of adipose tissue, which is an important component of weight in the last 8 weeks of pregnancy. Leptin, a 167 amino acid protein from the obese gene, is synthesized mostly in white adipose tissue but also in the placenta, and as a regulatory molecule of appetite it circulates at a concentration that is proportional to fat mass in both humans and rodents. A positive correlation between its cord concentrations, bodyweight and fat mass has been found in newborn infants suggesting that leptin may play a role in the regulation of foetal adiposity. The interaction of leptin with factors influencing foetal growth has not been determined and conflicting reports have been published on the impact of maternal smoking on cord serum leptin concentrations . In this report, we describe cord serum leptin concentrations in 1215 newborn infants born at term to Caucasian mothers and relate leptin values to BW, gestational age, gender and maternal smoking during pregnancy. This study gave clear-cut evidence on whether smoking during pregnancy, in addition to known mechanisms, also restricts foetal growth via its action on leptin metabolism [62].

Active maternal smoking during gestation induces morphological changes with consequent reduction in both volume of maternal intervillous space and surface area of foetal capillaries.These changes lead to reduced oxygen diffusion across the placenta. Metabolites of cigarette smoke cross the placenta, passing from mother to foetus, and act as vasoconstrictors that reduce uterine blood flow by up to38%. Of note is the fact that smoking hypoxia is not exclusively pre-placental in origin, but is complicated by both blood flow problems and cadmium toxicity that act at trophoblastic as well as other placental sites. Maternal smoking, therefore, places the fetus under chronic hypoxic stress, and hence contributes to restriction in weight gain, reduced length and small head circumference. Based on the model classifying the origins of hypoxia, three principal classes are recognized: pre-placental, utero-placental and post-placental hypoxia. Maternal smoking would normally lead to the pre-placental type of this classification, in which there is reduced oxygen content in maternal blood. Some studies, however, reported elevated maternal and foetal haematocrit levels in the smoking group, in addition to reduced mean BW in children. These findings suggest that fetuses of smoking mothers are under hypoxic stress that could be, in part, due to the non-adaptative morphological changes found in the placenta. Smoking-induced hypoxia could, therefore, be both pre-placental and utero-placental [63].

7.2. Smoking as modifiable risk factor for gestational diabetes

Age, obesity and family history of diabetes are well known risk factors for gestational diabetes mellitus. Most studies investigating maternal history of low birth weight, low stature, and low level of physical activity have found positive associations with gestational diabetes mellitus. Low socioeconomic levels, smoking during pregnancy, high parity, belonging to minority groups, and excessive weight gain during pregnancy presented conflicting results.

Studies show that the prevalence of smoking amongwith more likely to diabetes was significantly patients with diabetes was significantly more likely to be ever recorded in 2005 than in 2003 (98.8% v. 90.0%, $p < 0.001$). The proportion of patients whose smoking status was recorded in the 15 months before the study period was also greater in 2005 than in 2003 (86.7% v. 67.6%, $p < 0.001$). The greatest improvements in the recording of smoking status were observed among women and nonwhite ethnic groups (except Bangladeshi) after adjustment for age,sex, ethnic background and practice-level clustering (Table 2)[1].

Table2. Average of Patients with diabetes whose smoking status was recorded in the the 2003 and 2010 study periods.[1]

Characteristics	No. of patients	2003	2010	% Change	Adjusted OR
Age, yr (n = 4284)					
18-44	557 (13.0)	59.3	84.6	25.3	1.00§
45-54	676 (15.8)	66.7	87.9	21.2	0.92 (0.59 ± 1.44)
55-64	1165 (27.2)	67.0	86.4	19.5	0.80 (0.54 ± 1.17)
65-74	1212 (28.3)	68.8	86.6	17.8	0.78 (0.54 ± 1.14)
>75	674 (15.7)	74.2	88.0	13.8	1.00 (0.65 ± 1.54)
Sex (n = 4284)					
Male	2227 (52.0)	63.1	82.7	19.6	1.00§
Female	2057 (48.0)	72.4	91.1	18.7	2.01 (1.59 ± 2.54)
Ethnic background (n = 4074)†					
White British	1360 (33.4) 68.3 83.8	68.3	83.8	15.4	1.00§
Black Caribbean	813 (20.0)	73.1	90.5	17.5	1.53 (1.13 ± 2.07
Black African	365 (9.0)	73.7	95.1	21.4	3.28 (1.92 ± 5.62)
Indian	464 (11.4)	69.0	93.8	24.8	2.32 (1.47 ± 3.66)

Note: OR = odds ratio, CI = confidence interval.
*Adjusted for age, sex, ethnic background, and practice-level clustering.
**Change in percentage significant ($p < 0.001$) using McNemar test.

Abdominal obesity is associated with an atherogenic profile, and is a risk factor for T2DM, CHD, stroke and total mortality independently of weight. It can be assessed by either WHR or waist circumference, although measures of waist circumference result in less error than do those of WHR. Although smokers tend to be thinner than nonsmokers, they have a greater WHR than nonsmokers. Smokers, controlling for age and gender, are characterized by an average BMI that is at least 1 kg/m2 lower than that of nonsmokers. Continuing to smoke inhibits age-related weight gain in both men and women. The lower BMI is probably the consequence of increased energy expenditure and lower calorie intake in smokers, with the latter probably due to the appetite-suppressing action of nicotine. A large study found that smokers consumed a greater number of calories per day, both cross-sectionally and over a period of two years, than nonsmokers, while keeping their body weight unchanged. Smoking increases energy expenditure by approximately 10%. This increased energy expenditure is associated with neither increased urinary excretion of nor epinephrine, suggesting the involvement of sympathetic pathways, which is in agreement with data showing that acute smoking stimulates the sympathetic nervous system [64]. Smoking may be an independent risk factor for diabetes and also increases the risk of cardiovascular disease among people with diabetes. This study found that women with diabetes or previous GDM are equally likely to be current smokers compared with those with no diabetes. Therefore, diabetes education should include smoking cessation components.

Smoking is an important modifiable risk factor for cardiovascular disease and micro vascular complications in people with diabetes. Smoking also contributes to inequalities in diabetes outcomes and explains in part the variations in mortality between socioeconomic groups. Despite being at an increased risk of cardiovascular disease, many people with diabetes smoke, with the rate of smoking among people with diabetes approaching the rate in the general population [65].

7.3. Maternal smoking during pregnancy and risk of adiposity

Low birth weight has consistently been reported in association with adult-onset essential hypertension, CHD and stroke. Children born prematurely or at term-but small for gestational age-are at risk of reduced insulin sensitivity. A low birth weight has also been found in several studies in association with IGT or T2DM and abdominal obesity in the offspring. The main avoidable cause of a reduced birth weight is maternal smoking during pregnancy. According to a recent study, the children of women who smoked during early pregnancy, when assessed at age 3, had an elevated risk of being overweight and a higher BMI compared with the children of non-smoking mothers. Although this study did not report a significant association between maternal smoking during pregnancy and abdominal obesity, it is possible that an association of prenatal smoke exposure with abdominal obesity appears only when the children are at a later age. Another report from the same cohort described a positive relationship between gestational weight gain and the BMI of the child at age 3. In this study, excessive gestational weight gain was more frequent among pregnant women who smoked in early pregnancy (65%) than among those who were never smokers (48%). Thus, it can be hypothesized that smoking during pregnancy leads to higher gestational weight gain and potentially a higher risk of childhood obesity in the offspring. These data suggest that not only smoking in adulthood, but also intrauterine smoke exposure may be a risk factor for IGT, T2DM, obesity or abdominal-type obesity that could lead to later CV disorders. Further studies are needed to confirm this possible chain of events [66]. The distributions of maternal age, BMI, parity, household income, ethnicity, and maternal education differed between tobacco smoke exposure groups, and were treated as potential confounders (Table 3).

Table 3. Maternal characteristics by smoking status (unadjusted for sample weighting)[67]

Maternal Characteristics	Non-smoker, non ETS exposed (n = 8100)	Non-smoker, ETS exposed (n = 2259	Active smoker (n = 6397)	Excluded due to missing smoking data (n = 1541)
Maternal age at birth Mean (SD)	29.6 (5.6)	28.7 (5.5)	26.2 (6.0)	29.2 (5.8)
BMI Mean (SD)	24.0 (4.4)	24.0 (4.8)	23.2 (4.4)	23.8 (4.4)
Parity (previous live births) N (%) *				
None	3310 (42.2)	862 (40.1)	2838 (45.2)	496 (36.0)
1–2	3952 (50.4)	1083 (50.4)	2882 (45.9)	750 (54.5)
3 or more	572 (7.3)	203 (9.4)	553 (8.8)	131 (9.5)
Alcohol use in pregnancy N (%)	622 (7.7)	157 (7.0)	684 (10.7)	98 (6.6)
Ethnicity N (column %)				
White	6501 (80.4)	1701 (75.4) 6058	6058 (94.9)	1018 (68.2)
Asian	872 (10.8)	412 (18.3)	76 (1.2)	364 (24.4)
Black	438 (5.4)	43 (1.9)	117 (1.8)	64 (4.3)
Mixed or other	275 (3.4)	100 (4.4)	134 (2.1)	46 (3.1)
Education N (column %)				
Degree	1942 (24.0)	320 (14.2)	351 (5.5)	247 (16.4)
Diploma or A level	1714 (21.2)	440 (19.5)	789 (12.4)	278 (18.5)
None of the above	3090 (38.2)	938 (41.6)	3401 (53.3)	633 (42.1)

Cigarette smoking has been considered as a risk factor for diabetes outside of pregnancy and as such, could also be seen as a risk factor for gestational diabetes. However, meta-analysis of the systematic review of literature does not support the hypothesis that smoking during pregnancy increases the risk of gestational diabetes.

Environmental tobacco smoke (ETS) exposure has a clinically significant, detrimental impact on public health and so is an important issue for policy makers and clinicians. Maternal smoking during pregnancy impairs fetal growth and shortens gestation causing premature birth with significant fetal and infant mortality and morbidity. ETS contains lower doses of the same toxins that smokers inhale, so maternal ETS exposure during pregnancy should have similar but less severe effects. If ETS exposure has even a small impact on fetal growth in the womb, this could translate into significant morbidity.

Maternal smoking would normally lead to the pre-placental type of this classification, in which there is reduced oxygen content in maternal blood. Studies have shown that smoking leads to elevated maternal and foetal haematocrit levels in addition to reduced mean Birth Weight (BW) in children. Within the placentas, there will be increased cadmium levels which increases in the in the relative volumes of maternal intervillous space and in the relative surface areas of foetal capillaries, and decreases in the relative and absolute volumes of foetal capillaries.

Table 4. Association between level of tobacco smoke exposure during pregnancy and birth weight (Kg)[67]

	Mean birth Weight (SE)	Mean difference fromNon-smoker (95% CI)	Adjusted mean difference Fromnon-smoker (95% CI)	P value for trend
ETS exposure (Level of partner cigarette consumption in non-smokers)				
Non-smoker or no partner	3.448 (0.007)			
Smoker 1–10 cigs/day	3.386 (0.020)	-0.062 (-0.103, -0.021)	-0.027 (-0.067, 0.014)	0.007
Smoker 11–20 cigs/day	3.390 (0.024)	-0.058 (-0.107, -0.008)	0.053 (-0.101, -0.004)	
Smoker 20+ cigs/day	3.407 (0.042)	-0.040 (-0.124, 0.044)	-0.059 (-0.141, 0.023)	
Active Smoker (Level of Maternal cigarette consumption)				
Non-smoker				
Smoker 1–10 cigs/day		-0.104 (-0.130, -0.078)	-0.086 (-0.114, -0.059)	< 0.001
Smoker 11–20 cigs/day		-0.190 (-0.220, -0.160)	-0.190 (-0.221, -0.159)	
Smoker 20+ cigs/day		-0.277 (-0.342, -0.213)	-0.275 (-0.341, -0.209)	

Table 4 shows how birth weight varies with the reported amount smoked by maternal smokers and with different levels of ETS exposure (i.e. number of cigarettes per day smoked by partners of non-smokers). In the adjusted model, there was a significant linear trend for reduced birth weight with increasing level of exposure for both maternal smoking and ETS exposures.[67]

Studies investigating whether or not maternal ETS exposure during pregnancy affects birth outcomes have reported mixed findings. A review found significant heterogeneity between studies, but still presented synthesized findings and concluded that maternal ETS exposure during pregnancy reduced infants' adjusted mean birth weights by -24.0 g [95% CI -39.3 g to -8.6 g] and also increased the risks of babies being either "small for gestational age (SGA) or LBW at term". However, ETS exposure had no impact on the risk of either SGA or LBW at term alone and the reviewers noted that empirical studies were conducted in widely varied settings and often small and of poor quality, reporting only crude (i.e. no adjusted) birth outcomes. Although a recent Surgeon General report concluded that ETS exposure reduces birth weight, this finding was based on the same review without further literature searching or meta analyses [67].

7.4. Correlation between GDM and smoking related obesity:

Smoking cessation leads, almost inevitably, to weight gain. According to the First National Health and Nutrition Examination Survey (1971-1975 and 1982-1984), the mean weight gain attributable to the cessation of smoking, after adjustment for all potential confounders, is 2kg in men and 3.1kg in women during the first year after stopping smoking. Any further increases in weight are less over the subsequent years. Major weight gain (>13kg) occurs in around 10% of men and 13% of women. However, a higher BMI after quitting is probably not a 'true' smoking related weight increase because the BMI of sustained quitters is similar to that of never-smokers of corresponding ages. Thus, because smokers have a lower BMI than nonsmokers, the BMI increase after quitting has a tendency to return to the level of those who have never smoked. The mean weight gain over a ten-year period is about 4.4kg in men and 5kg in women. In the Lung Health Study, participants who quit smoking had a mean weight gain of 2.95kg/year among men and 3.09kg/year among women, corresponding to an increase of 3.61% and 4.69%, respectively, over their initial body weight. Over five years, one-third of sustained quitters gained more than or equal to 10kg. The mechanisms of smoking-cessation-induced weight gain include increased caloric intake, decreased resting metabolic rate, less physical activity, increased appetite and higher lipoprotein lipase activity [68].

The risk of major weight gain after stopping smoking is higher in those who smoked more than 15cigarettes/day, are aged less than 55 years, have low levels of physical activity or, in women, have had children. Smokers with the highest cigarette consumption before quitting have the greatest risk of becoming overweight. Inflammatory markers also predict weight gain after smoking cessation. During a three-year follow-up, the baseline

leucocyte count and fibrinogen levels predicted weight gain, suggesting a close relationship between inflammatory mediators and regulation of energy balance [69].

The weight increase is less if smokers do not stop smoking completely. Compared with those who stopped totally, those who alternated smoking and non-smoking periods gained only 2.82kg at six months after quitting compared with an average of 5.45kg in those who stopped completely. Post cessation weight gain may be moderated by genetic factors that, as yet, have not been elucidated. Concordance in twins for weight change after smoking cessation was higher in mono zygotic (53%) than in di zygotic (38%) pairs in the only study that, to the present author's current knowledge, assessed post-quitting weight increases in terms of genetics.

Smoking during pregnancy has long been recognized as the most important preventable risk factor for an unsuccessful pregnancy outcome in developed countries. Overweight has also repeatedly been associated with a number of adverse pregnancy outcomes, as well as maternal complications during pregnancy or delivery. There is an ever-growing body of epidemiological data to support the profound deleterious effects maternal smoking during pregnancy have on intrauterine well-being and on fetal growth [70].

Nevertheless, tobacco use persists as the leading preventable cause of intrauterine growth restriction (IUGR) and small-for-gestational age (SGA) infants in the developed world. Although some data suggest a moderate decline in self-reported and validated smoking during pregnancy, prevalence rates are currently estimated at 12–20% in industrialized countries. Although birth weight is modified by a number of genetic and socio-environmental factors, a causal relationship between tobacco exposure and delivery of SGA infants has been established. In 1957 Simpson and Linda [71] reported that mean birth weight of infants born to mothers who smoked _10 cigarettes/day was 200 g less than of those delivered by reported non-smokers. Since then, this association has been repeatedly demonstrated with relative risk estimates ranging from 1.5 to 2.9. Moreover, repeated observations of a dose–response relationship as well as a positive effect of smoking cessation on fetal weight is indicative of a causal relation between smoking and IUGR/SGA infants. Furthermore, several population-based analyses have attempted to characterise the effect of smoking on the incidence of various pregnancy complications [72].

8. Discussion

Smoking during pregnancy has long been recognized as the most important preventable risk factor for an unsuccessful pregnancy outcome in developed countries. The causal association between smoking and fetal growth restriction, together with concern over maternal long-term health, represent the main reasons for the effort to reduce smoking prevalence during pregnancy.

Studies show that smoking may be an independent risk factor for gestational diabetes and also increases the risk of cardiovascular disease among people with diabetes. Women with diabetes or previous GDM are equally likely to be current smokers compared with those with no diabetes. Therefore, diabetes education should include smoking cessation components [73].

Although studies show a great diversity in the assessment of outcomes and adjustment for confounding variables, sensitivity analysis did not reveal an important influence of any single study. The evidence published so far for the association between smoking and, gestational diabetes is inconsistent [74-77]. It is possible that differences between the study settings such as screening procedures for GDM, or due to variations in the content of cigarettes [78] or in the frequency of stopping smoking during pregnancy may explain this inconsistency. Lumping ex-smokers with never smokers could raise the risk in this comparison group, producing an apparent lower risk in smokers.

Moreover, the degree of information in the reports is frequently less than desirable. Aspects such as characteristics of the population, definitions of exposures and of diagnostic procedures and thus outcomes, statistical analysis routines and measures of association are not systematically described in the reports, limiting the comparability of the studies and utility of some of the extracted data.

Half of the studies showed a significant association between dose dependent smoking and gestational diabetes, Other half showed little association, The difference in the results may be due to heterogeneity in different smoking exposure measurements, difference in research design, difference in exposure definitions etc. Change in smoking habits as a result of pregnancy or wrong information about pregnancy status may be the source of bias, Large sample size with less heterogeneity is required to establish the association between smoking and gestational diabetes.

9. Conclusion

Current data suggest that dose dependent smoking may be a risk factor in gestational diabetes but the present study do not give a clear cut evidence on the direct relation between smoking and gestational diabetes. Increased smoking during pregnancy may lead to glucose intolerance, increasing the risk for gestational diabetes. Further research studies with more specific and less heterogeneous research design is required to evaluate the association between smoking and gestational diabetes.

10. Reference

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