Non classical risk factors for gestational diabetes mellitus: a systematic review of the literature

Fatores de risco não clássicos para diabetes mellitus gestacional: uma revisão sistemática da literatura

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Abstract

Age, obesity and family history of diabetes are well known risk factors for gestational diabetes mellitus. Others are more controversial. The objective of this review is to find evidence in the literature that justifies the inclusion of these other conditions among risk factors. The MEDLINE, Cochrane, LILACS and Pan American Health Organization databases were searched, covering articles dating from between 1992 and 2006. Keywords were used in combination (AND) with gestational diabetes mellitus separately and with each one of the risk factors studied. The methodological quality of the studies included was assessed, resulting in the selection of 41 papers. 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. Publication bias cannot be ruled out. Standardization of techniques, cutoff points for screening and diagnosis, as well as studies involving larger sample sizes would allow future meta-analyses.

Gestational Diabetes; Diabetes Mellitus; Risk Factors

Introduction

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 [1]. 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.

Several international guidelines [2,3,4,5,6] recommend selective screening for pregnant women older than 29 or for younger women with risk factors. Others advise universal screening [7]. In Brazil, the Ministry of Health and the Work Group in Diabetes and Pregnancy (*Grupo de Trabalho em Diabetes e Gravidez* – GTDG) recommend that all pregnant women should be screened for gestational diabetes mellitus (through fasting glucose in the 20th week of gestation) and, in the presence of risk factors and regardless of the first result, that screening should be repeated in the third trimester [7,8].

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, multiparity, race or ethnicity, physical inactivity, gestational weight gain and socioeconomic factors.

The goal of this review is to evaluate the recent literature in order to establish whether all women presenting these conditions should be screened for gestational diabetes mellitus.

Methods

The search was made in the MEDLINE database and studies from between 1992 and 2006 were included. The keywords used in the search were the combination (AND) of gestational diabetes or pregnancy diabetes with each one of the following terms (in parenthesis are, respectively, the number of titles found with each one of the association, before eliminating the duplicates): birth weight (1,868; 2,847); low birth weight (798; 519); low birth size (45; 85); small birth size (53; 63); small for gestational age (525; 376); age (1,154; 2,860); obesity (335; 923); cigarette smoking (17; 45); weight increase (291; 451); weight gain (271; 374); body mass index (560; 738); height (165; 232); short stature (28; 25); anthropometry (437; 584); race (268; 380); ethnics (308; 404); family history of diabetes (199; 272); education (217; 426); economic level (12; 21); social and economic factors (14; 15); physical activity (97; 150); exercise (135; 226); and risk factors (1,365; 2,319) . The terms age, obesity and family history of diabetes mellitus were included in an attempt to identify other risk factors of interest for the current review.

After searching, 5,759 titles were indentified. The first selection was made through the reading of the titles. Criteria for article inclusion were: English, Portuguese, Spanish or French language; studies involving humans; and papers that evaluated gestational diabetes mellitus as an outcome and risk factors for its development. From the remaining 357 abstracts, 41 papers were selected. These selected papers studied one or more of the chosen risk factors and included gestational diabetes mellitus as outcome. Studies with animals and those that evaluated treatments for gestational diabetes mellitus were excluded.

The methodological quality of the selected papers was evaluated using the criteria suggested by Downs & Black [9]. This is a checklist developed to assess the methodological quality not only of randomized controlled trials but also non-randomized studies. Using the criteria, it was possible to construct a profile of the paper, highlighting its methodological strengths and weaknesses. This checklist consisted of 27 items distributed across five sub-scales:

(1) Reporting (10 items): which assess whether the information provided in the paper was sufficient to allow a reader to make an unbiased assessment of the findings of the study;

(2) External validity (3 items): which reviews the extent to which the findings from the study could be generalized to the population from which the study subjects were derived;

(3) Bias (7 items): which address biases in the measurement of the intervention/exposition and the outcome;

(4) Confounding (6 items): which address bias in the selection of study subjects;

(5) Power (1 item): which attempts to assess if negative findings from a study could be due to chance.

In items 4, 14, and 15, "intervention" was interpreted as "exposure," and in nº. 19 "compliance with the intervention" was replaced by "avoidance of misclassification error of the exposure". Items 8, 13, 23, and 24 were not considered, since these are specific to clinical trials. Answers were scored 0 or 1, therefore, the highest score could be 23. The scores given to each paper and commentaries are shown in the Table 1. For each of the exposures, a funnel plot was drawn to evaluate publication bias. Because of the limited number of available studies in the literature for some of the exposures, it was only possible to plot the following: weight of the mother at birth, height and Asian ethnicity and Indian/Pakistani ethnicity.

Results and discussion

Table 1 presents alphabetically (by author) a summary of the studies included in the review. The methodological quality of studies ranged from 10 to 22 (median 18; SD = 2.9). The quality of reporting was good. Most of the studies (80%), however, lack information on representativeness. With regard to internal validity (items 14 to 27) the main weaknesses identified were lack of information on the methodology used for defining the outcome and adjustment for confounding. In addition, none of the studies presented information if the power was enough to detect the association between exposure and gestational diabetes mellitus; and characteristics of losses and refusals were neither presented nor discussed. The sections below present a summary of the publications on each of the potential risk factors and a discussion on methodological issues.

Birth weight

Since the fetal origin theory began to be discussed [10], stating that susceptibility to chronic diseases could be programmed in the uterus, studies have demonstrated an inverse associa-

Table 1

Review table: risk factors for gestational diabetes mellitus.

Authors (place/year)	Design n Data source	Gestational time Gram glucose/ time diagnostic criteria	Risk factors investigated	Main results Prevalence/Association with gestational diabetes mellitus	Score/Comments
Anastasiou et al. [26] (Greece/1998)	Cross-sectional 2,772 Primary	24-32 weeks 100g/3hs NDDG	Age, education, weight; prior and current BMI, height, born before/after 1960 (war)	Prevalence: 24.7% Average height inversely associated to increased glucose intolerance; adjustment for weight, education separately	Score: 13 Study center reference. Regression used height as outcome; gestational diabetes mellitus as predictor
Berkowitz et al. [35] (USA/1992)	Cohort 10,187 Secondary	26-32 weeks 100g/3hs NDDG	Age, race/ethnicity, birth place, marital status, health insurance, hospital, parity, prior preterm birth, stillbirth, prior BMI, family history of diabetes mellitus, smoking habits, drugs	Prevalence: 3.2% Adjusted association: > age, eastern race, first generation Hispanic, other race/ethnic groups, public service, > prior weight, family history of diabetes mellitus > gestational diabetes mellitus risk	Score: 19 Public hospital screened more than private hospital
Bo et al. [75] (Italy/2002)	Case-control 700 Primary	24-28 weeks 100g/3hs Carpenter & Coustan	Age, education, job, prior and current BMI, height, parity, family history of gestational diabetes mellitus, previous pregnancy	Adjusted association: < education, manual worker, owner primary home + education > gestational diabetes mellitus risk	Letter to editor without evaluation
Bo et al. [24] (Italy/2003)	Case-control 300 Primary/Secondary	24-28 weeks 100g/3hs Carpenter & Coustan	Birth weight, gestational age, family history of diabetes mellitus, age, prior, current weight, height, BMI, weight gain, smoking habits	Adjusted association: < birth weight > gestational diabetes mellitus risk	Score: 18 Weight in quartiles and means differences evaluated
Branchtein et al. [27] (Brazil/2000)	Cross-sectional 4,973 Primary	21-28 weeks 75g/2hs WHO	Age, color, education, weight, prior BMI, height, skin-fold, waist circumference, family history of diabetes mellitus, parity, clinic, gestational age, gestational diabetes mellitus prior, room temperature	Adjusted association: height ≤ 151cm > gestational diabetes mellitus risk (after stratification for global adiposity, association significant only for obese)	Score: 17 Interaction height vs. weight non evaluated
Corrado et al. [62] (Italy/2006)	Cohort 2,922 Secondary	Oral test of glucose tolerance Carpenter & Coustan	Age, BMI, family history of diabetes mellitus, weight gain	Prevalence: 2.9% Adjusted association: > age, > BMI, family history of diabetes mellitus > gestational diabetes mellitus risk	Letter to editor without evaluation
Deruelle et al. [63] (France/2004)	Case-control 348 Primary	50g/1h DIAGEST O'Sullivan	Age, height, weight, smoking habits, socioeconomic level, hypertension	Weight gain > 18kg not associated with > gestational diabetes mellitus risk	Score: 11 Cases and controls selected by exposition; weight gain measured at the end of pregnancy; no adjustments
Dempsey et al. [71] (USA/2004)	Case-control 541 Primary/secondary	24-28 weeks 100g/3hs NDDG	Age, parity, education, social-economic level, prior BMI, physical activity	Physical activity previous year: 55% reduction in gestational diabetes mellitus risk; physical activity first 20 weeks compared with inactive: 48% reduction in gestational diabetes mellitus risk	Score: 21 Physical activity self reported

(continues)

Table 1 (continued)

Authors (place/year)	Design n Data source	Gestational time Gram glucose/ time diagnostic criteria	Risk factors investigated	Main results Prevalence/Association with gestational diabetes mellitus	Score/Comments
Dempsey et al. [72] (USA/2004)	Cohort 909 Primary	24-28 weeks 100g/3hs NDDG	Age, education, income, job, smoking habits, alcohol, height, prior weight, medical history, parity, physical activity year before and previous week	Incidence: 4.6% Adjusted association: reduced risk any physical activity, previous year and during pregnancy < gestational diabetes mellitus risk	Score: 19 Sample selected two clinics
Di Cianni et al. [33] (Italy/2003)	Cohort 3,806 Primary	24-28 weeks 100g/3hs Carpenter & Coustan	Age, weight; prior BMI, weight gain, height, family history of diabetes mellitus, obstetric history	Prevalence: 8.74% Association:> age, > BMI prior, < height, > weight gain, family history of diabetes mellitus < gestational diabetes mellitus risk	Score: 19 Risk not shown
Dye et al. [70] (USA/1997)	Cohort 12,799 Primary/secondary	Medical record	Age, race, parity, prior BMI, weight gain, health insurance	Prevalence: 2.9% Stratification by BMI: BMI > 33kg/m^2 > physical activity < gestational diabetes mellitus risk; BMI > 33kg/m^2 + private insurance + reduced physical activity: > gestational diabetes mellitus risk	Score: 17 Self-reported physical activity; interaction insurance vs. physical activity not evaluated
England et al. [43] (USA/2004)	Cohort 3,774 Primary	13-21 weeks 100g/3hs O'Sullivan	Smoking habits	Adjusted association: > smoking at study enrollment (13-21 weeks) > gestational diabetes mellitus risk	Score: 17 The design of the study was not for this evaluation
Egeland et al. [20] (Norway/2000)	Cohort 138,714 Secondary	Self-reported	Birth weight, ponderal index, weight/gestational age, grandmother characteristics during her pregnancy (age, parity)	Prevalence: 0.36% Adjusted association: > age, > parity, low birth weight, < weight/gestational age > gestational diabetes mellitus	Score: 21 Self-reported gestational diabetes mellitus
Innes et al. [21] (USA/2002)	Cohort 23,395 Secondary	Medical record ICD 9th revision	Uterus experiences (multi fetal, birth order, parents education, age, illnesses and childbirth mother); birth weight, gestational age, race/ ethnic, age, marital status, job, education, insurance, programs welfare, prenatal, alcohol, smoking habits, height, BMI, weight gain	Prevalence: 1.9% Adjusted association: > age, < education, > BMI,< height, low birth weight, family history of diabetes mellitus > gestational diabetes mellitus risk	Score: 22 Data from 2 big datasets of New York state (USA)
Jang et al. [25] (Korea/1998)	Cross-sectional 9,005 Primary	24-28 weeks universal 100g/3hs NDDG	Age, weight, BMI, height; family history of diabetes mellitus, parity, weight gain	Prevalence: 1.9% Adjusted association: > age, > BMI, family history of diabetes mellitus, < height, weight gain > gestational diabetes mellitus risk	Score: 20 Universal screening
Keshavarz et al. [30] (Iran/2005)	Cohort 1,310 Primary	24-28 weeks universal 100g/3hs Carpenter & Coustan	Age, social economic level, job, height, BMI, parity, family history of diabetes mellitus	Incidence: 4.8% Association: > age, > parity, < height, family history of diabetes mellitus, BMI, lower economic status > gestational diabetes mellitus risk	Score: 14 One hospital/no adjustments
Kieffer et al. [48] (USA/1999)	Cross-sectional 10,854,224 Secondary	Self-reported	Age, education, parity, marital status, prenatal, race/ethnic	Prevalence: 2.5% Adjusted association: Asian-Indians, black people, Philippine, Puerto Ricans, South and Center American born outside USA > gestational diabetes mellitus risk compared to white	Score: 18 Self-reported gestational diabetes mellitus

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Table 1 (continued)

Authors (place/year)	Design n Data source	Gestational time Gram glucose/ time diagnostic criteria	Risk factors investigated	Main results Prevalence/Association with gestational diabetes mellitus	Score/Comments
Khine et al. [52] (USA/1999)	Case-control/Cohort 632/11,486 Secondary	Medical record ICD 9th revision	Age, race/ethnicity, weight, height, BMI, family history of diabetes mellitus, medical disorders (gestational diabetes mellitus, macrossomy, stillbirth, anomalous embryo), health insurance	Teenage pregnancy: incidence: 1.7% (> BMI total > gestational diabetes mellitus risk) Total population: incidence: 4.8% (> Asiatic, > age, > BMI, > gestational diabetes mellitus risk)	Score: 19 Case-control/Cohort
Kousta et al. [32] (UK/2000)	Case-control 816 Primary/secondary	Medical record Oral test of glucose tolerance/WHO	Height, ethnicity, age	Average height for European, South Asians, Afro-Caribbean with gestational diabetes mellitus < controls	Score: 16 Cases: 10 hospitals in London and neighborhood/ Controls: 1 hospital No adjustments
Kumari et al. [45] (Arab Emirates/2002)	Case-control 4,721 Secondary	Medical record	Age, previous morbid (anemia, hypertension, eclampsy)	> Parity > Incidence gestational diabetes mellitus ($p < 0.001$) ≥ 10; Prevalence: 23.2% Parity 2-4; Prevalence: 1.2%	Score: 15 Selected at high level hospital; no adjustments
Lauszus et al. [46] (Denmark/1999)	Cohort 383 Secondary	75g/3hs	Age; weight; prior BMI; height, parity; gestational age	Incidence: 14% Association: > age, > BMI > parity, < weight gain > gestational diabetes mellitus risk	Score: 17 Screening for risk factors; no adjustments
Moses et al. [18] (Australia/1999)	Case-control 276 Secondary	Third trimester 75g/2hs ADIPS	Mother's pregnant age at birth, gestational age, birth weight; length	No association for birth weight	Score: 10 Cases: referred to treat gestational diabetes mellitus, born in hospital that attended 50% of births. Controls: next baby born same hospital same gestational age, mother's age (± 2 years) to the pregnant mother case; only collected birth weight; no adjustments
Pettitt et al. [17] (USA/1998)	Cohort 831 Primary	75g/2hs WHO	Birth weight, age, weight, height, BMI, family history of diabetes mellitus	Adjusted association: < birth weight > gestational diabetes mellitus risk	Score: 16 Do not shows analysis
Plante et al. [15] (USA/1998)	Cohort 6,550 Secondary	Medical record	Birth weight, gestational age, race (white, black)	Prevalence: 1.5% Association: whites with small for gestational age > gestational diabetes mellitus risk	Score: 17 No differentiation among previous diabetes mellitus or gestational diabetes mellitus; did not separate large for gestational age from adequate for gestational age; no adjustments
Plante et al. [16] (USA/2002)	Cohort 7,802 Secondary	Medical record	Birth weight, gestational age, race (white, black)	Prevalence: 2.9% No association for birth weight	Score: 17 Same population of the previous study < prevalence of small for gestational age

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Table 1 (continued)

Authors (place/year)	Design n Data source	Gestational time Gram glucose/ time diagnostic criteria	Risk factors investigated	Main results Prevalence/Association with gestational diabetes mellitus	Score/Comments
Rao et al. [49] (USA/2006)	Cohort 3,779 Secondary	No information	Age, education, parity, prenatal, insurance, hypertension	Adjusted association: Indian-Pakistanis > gestational diabetes mellitus risk	Score: 18 Comparisons between seven self-referred ethnic groups: American-Asians, Islands of the Pacific, against the total prevalence of this sample; European white was not included; data of one hospital
Rao et al. [49] (USA/2006)	Cohort 6,511 Secondary	No information	Age, education, parity, obesity, insurance, hypertension, multiple pregnancy, gestational diabetes mellitus	Adjusted association: Chinese and Philippines > gestational diabetes mellitus risk regarding Japanese	Score: 16 Ethnicity designated and gestational diabetes mellitus self-referred; comparison between ethnicities
Rodrigues et al. [53] (Canada/1999)	Cohort 402/7,718 Secondary	24-30 weeks 100g/3hs NDDG	Age, ethnicity, weight gain, height, parity, smoking habits, physical activity	Prevalence of Canadian natives: 11.4%; Adjusted association: > age, prior weight Prevalence of non natives: 5.3%; adjusted association: > age,> parity, > weight, smoking habits, < height Grouped regression: interaction ethnicity vs. weight: obese natives 2x > risk of gestational diabetes mellitus compared to obese non natives	Score: 19 Comparison risk factors gestational diabetes mellitus in native-Canadians cohort vs. risk factor gestational diabetes mellitus non-native Canadians; lack of information for height
Rudra et al. [28] (USA/2006)	Cohort 1,644 Primary	24-28 weeks 100g/3hs NDDG	Age, race/ethnicity, family history of diabetes mellitus, education, job, income, physical activity, smoking habits, weight change, height, prior BMI, parity	Adjusted association: < height, > prior BMI, weight increase after 18 years > gestational diabetes mellitus risk	Score: 20 One hospital
Rudra et al. [73] (USA/2006)	Case control; cohort 216 cases; 472 control; cohort: 897 Primary/Secondary	24-28 weeks 100g/3hs NDDG	Age, race/ethnicity, hypertension; prior BMI, parity, physical activity (type, frequency, duration year before)	Adjusted association: < insertion physical activity; < metabolic equivalent hours/weeks physical activity > gestational diabetes mellitus risk	Score: 18 (case-control)/Score: 19 (cohort) Recreational physical activity self-referred year before; refuse: 83% (cases)/58% (controls)
Saldana et al. [60] (USA/2006)	Cohort 952 Primary	24-29 weeks 100g/3hs Carpenter & Coustan	Age, height, weight; prior BMI, weight gain	Adjusted association: > weight gain, > prior BMI > gestational diabetes mellitus risk	Score: 20 Sample: 57% eligible pregnant
Savona-Ventura & Chircop [23] (Malta/2003)	Case-control 162/250 Primary/Secondary	75g/2h > 155mg/dL	Birth weight; family history of diabetes mellitus	Association: low and high birth weight, motherhood history of diabetes mellitus > gestational diabetes mellitus risk	Score: 17 Cases: gestational diabetes mellitus; control general population same period No reference regarding diagnosis of gestational diabetes mellitus; non adjustments
Seghieri et al. [22] (Italy/2002)	Cohort 604 Primary/Secondary	24-28 weeks 100g/3hs ADA	Birth weight, age, parity, family history of diabetes mellitus, weight; BMI (prior; current)	Adjusted association: > age, family history of diabetes mellitus, low birth weight > gestational diabetes mellitus risk	Score: 17 Pregnant with risk factors, weight and birth self-referred

(continues)

Table 1 (continued)

Authors (place/year)	Design n Data source	Gestational time Gram glucose/ time diagnostic criteria	Risk factors investigated	Main results Prevalence/Association with gestational diabetes mellitus	Score/Comments
Solomon et al. [42] (USA/1997)	Cohort 14,613 primary	Self-referred	Age, race/ethnicity, family history of diabetes mellitus, height, prior BMI; BMI at 18 years, weight increase, smoking habits, physical activity	Incidence: 4.9% Adjusted association: > age, non whites, family history of diabetes mellitus, > prior BMI, BMI at 18 years, weight gain, smoking habits, > vigorous physical activity > gestational diabetes mellitus risk	Score: 20 Self-referred gestational diabetes mellitus, weight, height
Tabak et al. [31] (Hungary/2002)	Cohort 1,635 Primary	75g WHO	Weight, height, BMI, age, education, family history of diabetes mellitus	Prevalence: 5.7% Association: > BMI, > age, > family history of diabetes mellitus > gestational diabetes mellitus risk	Letter to editor without evaluation
Terry et al. [44] (Sweden/2003)	Cohort 212,190 Secondary	Handbook register ICD 9th revision	Age, weight, height, BMI, smoking habits, living with father	Prevalence: 0.4% Association: > age, < height > BMI, stop smoking between gestations > gestational diabetes mellitus risk Adjusted association: > BMI, < education, > age	Score: 13 Different criteria for diagnosis of gestational diabetes mellitus
Thorsdottir et al. [64] (Iceland/2002)	Cohort 615 Primary	75g/2hs WHO	Age, height, marital status, smoking habits, parity, weight gain, prior weight, hypertension, prior eclampsia	Association: < weight gain > gestational diabetes mellitus risk	Score: 20 Sample size to other variables, not to gestational diabetes mellitus. Gestational diabetes mellitus. Weight gain at the end of pregnancy
Williams et al. [19] (USA/1999)	Cohort 41,839 Secondary	Self-referred/ Medical record ICD 9th revision	Age, marital status, education, health system, parity, prior weight , weight gain, smoking habits, prenatal, hypertension	Non-Hispanic whites = 2.8%; Afro-Americans: 2.6%; Native-Americans: 2.7%; Hispanics: 3.0% Adjusted association: low birth weight for all ethnic > gestational diabetes mellitus risk	Score: 19 Secondary data; with self-referred gestational diabetes mellitus; links between data banks 88.8% of pregnant women
Yang et al. [29] (China/2002)	Cohort 9,471 Primary	26-30 weeks 75g/2hs WHO	Age, home income, education, height, weight gain, prior BMI, family history of diabetes mellitus, abortion, smoking habits, previous illnesses, alcohol	Prevalence: 2.31% Adjusted association: > age, < height, > prior BMI, smoking habits, family history of diabetes mellitus, weight gain > gestational diabetes mellitus risk	Score: 17 Weight gain was associated only at adjusted analysis
Yue et al. [47] (Australia/1996)	Cohort, 3,807 Primary	24-28 weeks 75g/2hs ADIPS	Age, ethnicity, BMI, parity	Prevalence: 6.7% Adjusted analysis for age and BMI: Chinese OR 5.6; Vietnams OR 3.6; Indians OR 6.4; Arabs OR 2.5, Aborigines OR 3.7 regarding the Anglo-Celtics	Score: 18 Data collected at a prenatal clinic. Exclusion of 24% of data because belonging to 30 different races
Zhang et al. [74] (USA/2006)	Cohort 21,765 Primary	Self referred	Age, race, family history of diabetes mellitus, weight, BMI, smoking habits, parity, prior physical activity, diet, alcohol	Incidence: 6.5% Adjusted association: > physical activity, > metabolic equivalent hours/weeks; walking fast or very fast, to go up stairs (≥ 15 steps/ day); less time watching TV < gestational diabetes mellitus risk	Score: 20 Physical activity measured questionnaire vs. one record week , correlation: 0.79

ADA: American Diabetes Association; ADIPS: Australasian Diabetes in Pregnancy Society; BMI: Body Mass Index; DIAGEST: Study Group on Gestational Diabetes; ICD: International Classification Diseases; NDDG: National Diabetes Data Group; WHO: World Health Organization.

tion between birth weight and delayed risk of type 2 diabetes mellitus [11,12,13], insulin resistance [12,14] and other factors of metabolic syndrome [11,12,14].

Ten studies that evaluated such an association were identified. Plante [15], in 1998, found that women who were born "small for the gestational age" presented a fourfold risk of gestational diabetes mellitus. However, when analyzing the same cohort four years later (at the ages of 24 to 26), using the same methodology, they did not find statistical significance, although they did identify an inverse trend in the relationship between birth weight and gestational diabetes mellitus. In the second sample, there was a smaller number of pregnant women that had been born small for the gestational age [16]. In both analyses, the authors had not adjusted for family history of diabetes mellitus, nor had separated the mothers who had been born with adequate weight from the ones that had been born large for gestational age. Large babies at birth, children of mothers with diabetes mellitus or gestational diabetes mellitus that were part of the comparison group, could dilute the effect of the association between low birth weight and gestational diabetes mellitus. Studies carried out with the Pima Indians from Arizona, United States [17], had shown a "U-shaped" association, small for the gestational age and large for gestational age women presented an increased risk of diabetes mellitus, but after controlling for family history of diabetes mellitus the association was no longer significant.

In 1999, a small Australian study by Moses et al. [18], examining pregnant women referred for medical management of their gestational diabetes mellitus, found that the mean 2-h glucose concentration at diagnosis of gestational diabetes mellitus presented a U-shaped association when women with gestational diabetes mellitus had been analyzed apart as three groups – small for gestational age, adequate for gestational age and large for gestational age. Among women diagnosed with gestational diabetes mellitus, the 2-h glucose level was higher among the small for gestational age group than in the adequate for gestational age group, which could suggest a higher insulin resistance between the small for gestational age women, however the association was not statistically significant. In the same year, Williams et al. [19], in a large study of pregnant women divided into four racial groups, (white non-Hispanic, Afro-American, Hispanic and Native-American) found twofold risks in the association between < 2,000g birth weight and gestational diabetes mellitus, for all groups, compared to 3,000-3,999g, even after adjustment for age, parity, marital status, health insurance, cigarette smoking and arterial hypertension, although in some categories, because of the small number of gestational diabetes mellitus, the association was not significant.

In 2000, Egeland et al. [20] studied a large retrospective cohort in Norway (138,714 pregnant women) and identified an inverse trend of gestational diabetes mellitus with birth weight and weight for gestational age (OR: 1.8; 95%CI: 1.1-3.0; and OR: 1.7; 95%CI: 1.2-2.5, respectively). The comparison was done between women with birth weight < 2,500g, compared to those weighing 4,000-4,500g as a reference group. The analyses were controlled for age, parity and history of diabetes mellitus of the mother of the pregnant woman.

Later in 2002, Innes et al. [21] carried out a study enrolling 23,395 pregnant women that were born in New York State in the Unites States. The adjusted analyses had strengthened the inverse dose-response relationship and the magnitude of the association between low birth weight and the risk of gestational diabetes mellitus between women born weighing less than 2,000g (OR: 4.23; 95%CI: 1.55-11.51) in relation to those born with 3,500-3,999g. The inverse association between birth weight and gestational diabetes mellitus was strong for women that were born preterm and those born at term. The adjusted analyses included age, primiparity, twins, and maternal complications of pregnancy during her own intrauterine life, such as preeclampsia/eclampsia and diabetes mellitus of her mother. Regarding the current pregnancy, the authors adjusted for socioeconomic and demographic variables (age, race, education, and occupation), height, prepregnancy body mass index (BMI) and weight gain.

In 2002, in Italy, Seghieri et al. [22] found a significant association between birth weight < 2,600g and gestational diabetes mellitus after adjustment for age, parity, family history of diabetes mellitus and pre-pregnancy BMI. The odds ratio to present gestational diabetes mellitus was nearly two times higher among women with birth weight < 2,600g, when compared to higher birth weights (OR: 1.89; 95%CI: 1.09-3.29).

A small study on the island of Malta [23], with 162 pregnant women diagnosed with gestational diabetes mellitus, from 1996 to 2001 that had information for birth weight and family history of diabetes mellitus, compared the characteristics of these mothers with population data through studies made between 1965 and 1981. Birth weights < 2,000g and > 4,500g had presented, respectively, crude OR of 2.79 and 2.73, compared to normal weight. As in previous studies [17], the association found between large for gestational age and gestational diabetes mellitus occurred particularly between women with a family history of diabetes mellitus and, especially, among those with maternal history of diabetes mellitus.

In Italy in 2003, Bo et al. [24], found that glucose tolerance decreases according to weight quartiles: 3,389±644; 3,184±583 and 3,077±661 respectively for normoglycemic, glucose intolerant and gestational diabetes mellitus pregnant women. When the analysis excluded pregnant women born to gestational diabetes mellitus mothers, a mean weight decrease was observed in all categories and among the gestational diabetes mellitus women the birth weight was 2,992±581 on average. When controlling for age, gestational age, maternal diabetes, pre-pregnancy BMI and weight gain, the OR were 3.7 (95%CI: 1.72-8.00).

The funnel plot (Figure 1) does not show evidence of publication bias. Conclusions from the available studies point out the importance of adjusting birth weight for family history of diabetes mellitus and especially for maternal diabetes mellitus, since the daughters of women who present gestational diabetes mellitus have greater risk to present high birth weights and strong genetic and/or environmental characteristics that increase the chance for gestational diabetes mellitus in their pregnancy. In this way, when comparing mean birth weight of mothers with and without gestational diabetes mellitus, those who were heavier at birth are probably born from mothers who also had gestational diabetes mellitus. This fact will increase the mean birth weight among mothers at increased risk from genetic basis. On the other hand, when birth weight is analyzed as a dichotomous variable (low birth weight – yes/no), the normal weight category would include macrossomic babies. In these two situations if there is no control for maternal diabetes, the potential association between low birth weight and gestational diabetes mellitus may not be detected.

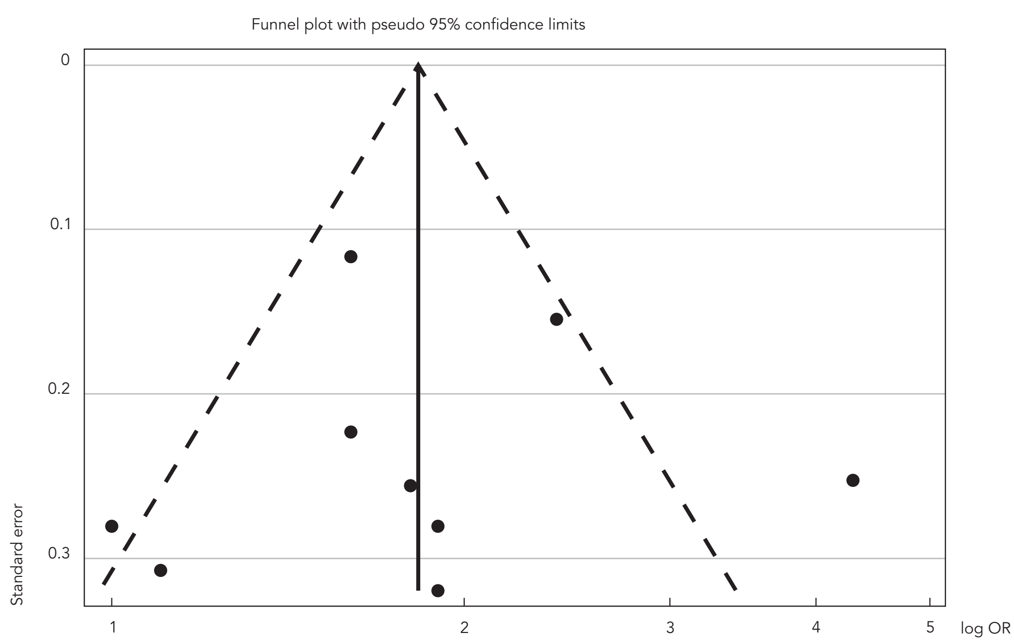
As for the control of birth weight for gestational age, although it does not seem to change the association [20,21], there is still no strong evidence to simply ignore such an adjustment.

Height

Four studies evaluated height as a major risk factor for gestational diabetes mellitus, controlling for confounders. Jang et al. [25], in 1998, studying

Figure 1

Low birth weight Funnel plot.



a cohort of Korean women, found that the height of pregnant women, divided into quartiles, was inversely associated with the gestational diabetes mellitus diagnosis. The association remained regardless of age, weight and pre-pregnancy BMI, family history of diabetes mellitus, parity and weight gain during pregnancy. Anastasiou et al. [26], evaluating a cohort of pregnant Greek women referred to a service for screening of diabetes, found that the mean height among pregnant women with gestational diabetes mellitus was significantly lower than among those without gestational diabetes mellitus. Such findings remained true even after stratification by weight, maternal schooling and cohort effect. Branchtein et al. [27], in 2000 in Brazil, found an inverse association between mean glycemic values one and two hours after glucose load and height. Logistic regression showed that shorter women (≤ 151cm) had a 60% greater increase (OR) of gestational diabetes mellitus, when compared with the ones from the highest quartile, independently of the prenatal clinic of origin, age, obesity, family history of diabetes mellitus, education, skin color, waist circumference, parity, previous gestational diabetes mellitus, environment temperature and gestational age. Rudra et al. [28], in 2006, studying an American cohort found significant association between height (in quartiles) and gestational diabetes mellitus. Adjusted analyses for age, race/ethnics, education and BMI had shown that heights above 160cm were protective (30-60% risk reduction) for the development of the disease.

Other studies evaluating the association between height and gestational diabetes mellitus presented conflicting results: Yang et al. [29] in 2002, investigated height averages of diabetic and non diabetic pregnant Chinese women; Iranians were studied by Keshavarz et al. [30] in 2005; and Tabak et al. [31] assessed pregnant Hungarians in 2003 but did not find significant differences in a comparison of mean values. Only the first study controlled for confounders [29]. The findings among different ethnicities was discussed by Kousta et al. [32], in 2000, studying mean differences, comparing pregnant women with and without gestational diabetes mellitus, categorized by origin as European, South Asian and Afro-Caribbean. Short stature associated to gestational diabetes mellitus had been found for all the groups in the crude analysis, although the association between Afro-Caribbean was not statistically significant [32]. On the other hand, studying several risks for the development of gestational diabetes mellitus, Di Cianni et al. [33] and Innes et al. [21], respectively, in Italian and American populations, had also found a significant inverse association between height and gestational diabetes mellitus, even after adjustments for confounders.

Genetic and hormonal factors apart, fetal and infant nutrition are important determinants of height in adulthood [34]. Therefore, the association between short stature and gestational diabetes mellitus could in fact be a result of confounders such as low socioeconomic level, and to be mediated by obesity. That could also be explained by the fetal origin theory. Considering that insulin is an important factor for normal growth, directly or indirectly (through GH/IGF1 axis), short stature would only be a marker of insulin resistance. It is important to point out that for this potential risk factor publication bias cannot be ruled out as shown in the funnel plot (Figure 2).

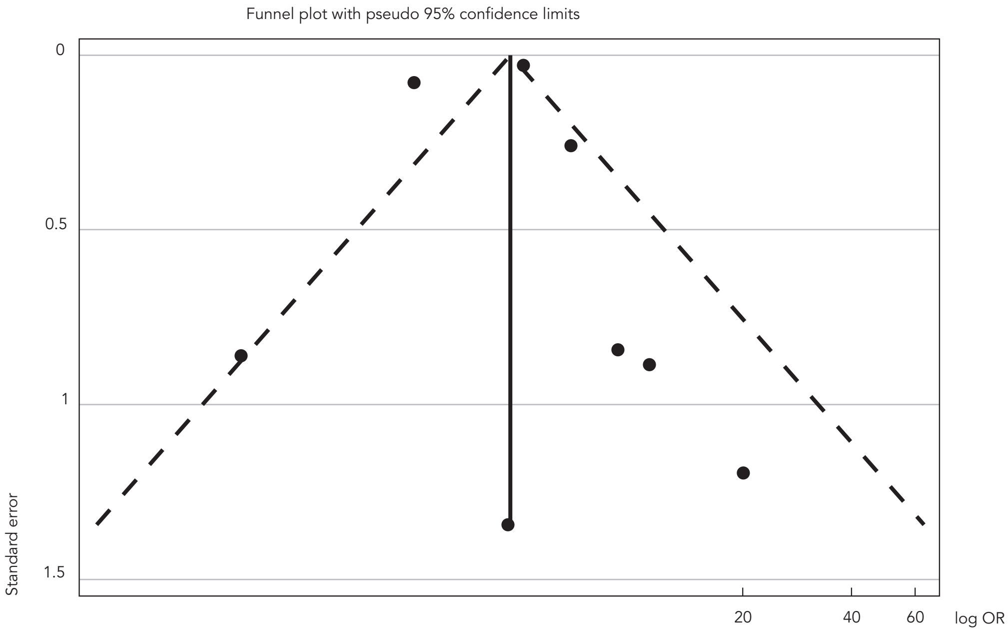
Socioeconomic level/education

Considering socioeconomic levels, Innes et al. [21] did not find an association between gestational diabetes mellitus development and private or public insurance, occupation during pregnancy, or education of the parents of the pregnant woman at the time of her birth. However, they found an inverse association between the educational level of the pregnant woman and gestational diabetes mellitus, after adjustment for other social, economic and demographic factors. Berkowitz et al. [35], studying a hospital sample composed of all socioeconomic categories, found greater prevalence of gestational diabetes mellitus among women in a public health service, compared with those coming from private clinics [35]. A study carried out in Italy [24] found that high levels of maternal education were associated with reduced risks of gestational diabetes mellitus (OR: 0.61; 95%CI: 0.4-0.9), compared to less educated women. When categorized by occupation, non-employed women with a primary level of education presented an OR of 1.87 (95%CI: 1.1-3.2) and the blue-collar workers, an OR of 1.73 (95%CI: 1.1-2.9), compared to white-collar women, even after controlling for age, BMI, height, family history of diabetes mellitus and previous pregnancy [24]. On the other hand, Yang et al. [29], when studying Chinese pregnant women, did not find an association between gestational diabetes mellitus and education or average household income. Keshavarz et al. [30], studying pregnant Iranian women, did not find an association between gestational diabetes mellitus and education or occupation; however, they did find an association with low socioeconomic level. Both studies did not control for confounders.

An inverse association between socioeconomic status and type 2 diabetes mellitus was found in some studies [36,37]. Despite the fact that

Figure 2

Height Funnel plot.



the epidemiologies of these two conditions are similar, it is not clear if the socioeconomic situation can be a risk factor for gestational diabetes mellitus. It is possible that the low maternal socioeconomic level is a proxy for the socioeconomic level of the parents, and the latter is potentially acting as a confounding factor for being born with low weight, short stature and greater weight in adulthood, characteristics that, in previous studies, had been detected as more frequent in poor populations and with smaller education levels and described as independent factors of type 2 diabetes mellitus risk. Thus, a careful hierarchical analysis taking into account the income of the parents could elucidate the relationship between current socioeconomic factors and gestational diabetes mellitus [38].

Cigarette smoking

Although cigarette smoking is positively associated with hyperinsulinism and insulin resistance in some studies [39,40], the association between tobacco and gestational diabetes mellitus has been little investigated. A cross-sectional study carried out in Scandinavia [41] showed that to smoke more than ten cigarettes per day during pregnancy affects the homeostasis of the glucose towards gestational diabetes mellitus, which was confirmed by others [42]. In the Nurse Cohort study [42], in the study by England et al. [43], and in another cohort of Chinese pregnant women [29], an increased risk for gestational diabetes mellitus was found among smokers compared to non smokers. In the first cohort, the gestational diabetes mellitus diagnosis was self-reported and the definition of smoking habits consisted of pre-gravid current smokers. In the others, the gestational diabetes mellitus diagnosis was made by means of an oral glucose tolerance test and cigarette smoking during pregnancy in the first was categorized as never smoked, quit before, quit during and smoke at enrollment and in the Yang et al. [29] study as non smoker (none or occasional) or smoker (to smoke one or more cigarettes per day). Although adjustments were carried out for the same confounders, Yang et al. [29] found higher OR (7.82; 95%CI: 1.73-35.28) associated to smoking than the others. The fact that the Chinese cohort was composed of lean, young women, with low prevalence of family history of diabetes, without multiparity and in a context of greater bicycle usage could explain these differences. The wide confidence interval in the study by Yang et al. suggests a lack of precision in the estimate, since only two of the diabetic pregnant women were smokers [29,42].

Other studies have not found this association [21,35,44]. Berkowitz et al. [35] did not include cigarette smoking in the multivariate analysis and, therefore, had not adjusted its effect for the effects of other variables; and Innes et al. [21] and Terry et al. [44] carried out studies with young pregnant women, with average ages of 21 and 24 respectively, probably with less time of exposure to smoking. One methodological problem of the studies was that some studies [21,29,35] classified women as smokers (at least one cigarette per day) or non-smokers, without considering the exposure period.

Parity

In the study by Egeland et al. [20] 2000, after controlling for age, they found an OR for women with two, three and four or more childbirths, compared to those with only one childbirth, of respectively, 1.5 (95%CI: 1.2-1.9), 1.9 (95%CI: 1.4-2.5) and 3.3 (95%CI: 2.1-5.1). Kumari et al. [45] 2002, studying grand multiparity, in a uniformly high socioeconomic population (United Arab Emirates), found that women with parity ≥ 10 had greater gestational diabetes mellitus incidence. When stratified by age, these pregnant women belonged to the oldest category.

Jang et al. [25] 1998 and Di Cianni et al. [33] 2003 found greater ratio of women with gestational diabetes mellitus in the group with parity ≥ 2, in comparison to primiparas. After controlling for age, pre-pregnancy BMI, height, family history of diabetes mellitus and weight gain during pregnancy, both results were non statistically significant.

For Berkowitz et al. [35] 1992, in the crude analysis, the prevalence of gestational diabetes mellitus increased with parity, relative risks for two, three and more than four children, in relation to the first pregnancy, respectively 1.14 (95%CI: 0.88-1.50), 1.71 (95%CI: 1.25-2.34) and 2.17 (95%CI: 1.57-3.00). Lauszus et al. [46] 1999 and Keshavarz et al. [30], in a descriptive analysis, found that women with more children were more likely to present gestational diabetes mellitus.

The association between parity and diabetes is strongly linked to obesity and age. Women with higher parity frequently are older and more obese. Obesity is an intermediate outcome in the causal pathway between parity and gestational diabetes mellitus, probably a mediating factor. However, age is a potential confounder in the association between parity and gestational diabetes mellitus. Therefore, no study evaluating parity could ignore to control for age. Adjustments for BMI, on the other hand could diminish the strength of this association. To study this association through a hierarchical model could provide a better estimate of the association between greatest parity and the risk of developing gestational diabetes mellitus.

Race, ethnicity

The observation that some racial and ethnic groups presented higher gestational diabetes mellitus frequencies have stimulated studies to evaluate the role of racial or ethnic factors. A study carried out by Berkowitz et al. [35], in 1992, raises a controversy in relation to the risk of gestational diabetes mellitus based on habits and behavior changes of immigrant populations. In a cohort of pregnant women from different socioeconomic and ethnics backgrounds in New York, the authors found a higher adjusted risk of gestational diabetes mellitus for Orientals, women from India, the Middle East and among Hispanics (only those born outside the USA). A study carried out in Australia, in 1996, strengthens these findings, showing that gestational diabetes mellitus is more common among immigrant populaces, especially among minorities (racial groups), even after adjustment for age and BMI [47].

Another study [48], in the USA, investigated the impact of the birth on the prevalence of gestational diabetes mellitus, between 15 ethnic and racial groups (among them native, Hispanic, non Hispanic whites, Afro-descendants and Asians). Having been born outside the USA and having immigrated increased the probability of having gestational diabetes mellitus. In part, this association was explained by the age of the mother, as the oldest pregnant women were immigrants. The significant association between several racial and ethnic groups remained the same even after controlling for age. The authors, however, had not adjusted for important confounders such as socioeconomic and obesity variables. This study also demonstrated that Japanese women born outside the USA have the lowest prevalence of gestational diabetes mellitus with adjusted OR (0.74; 95%CI: 0.69-0.81) compared to non Hispanic white women born in the USA. This finding was confirmed by Rao et al. [49], suggesting that Japanese women do not modify their habits after immigration. On the other hand, the percentage of gestational diabetes mellitus among those born in the USA is well above the American average. Studies of type 2 diabetes mellitus show that the first and the second generation of Japanese born in the USA present a gradually higher prevalence when compared to Japanese born in Japan and even greater than those who are residents of Japan [50].

Dornhorst et al. [51], in London, found ethnic origin to be a stronger predictor of gestational diabetes mellitus than age, BMI or parity, and a similar result was also found by Khine et al. [52] among pregnant American women, when they evaluated prevalence of gestational diabetes mellitus stratified by race and age. Clear racial differences had also been found in the study of nurses, in which women who were Afro-American, Hispanic or that had Asian ethnicity had a significantly increased risk of gestational diabetes mellitus, when compared with whites, even after adjustment for BMI, age, family history of diabetes mellitus, level of physical activity and parity. Being this study made in cohort of women of same professional category, there was, in a certain way, an adjustment for restriction, to social and economic factors [42].

On the other hand, Innes et al. [21], when studying pregnant women in the state of New York in 2002, did not find an association between gestational diabetes mellitus and race when the sample was divided into groups of "non-Hispanic whites", "black people" "Hispanic" and "other non-whites".

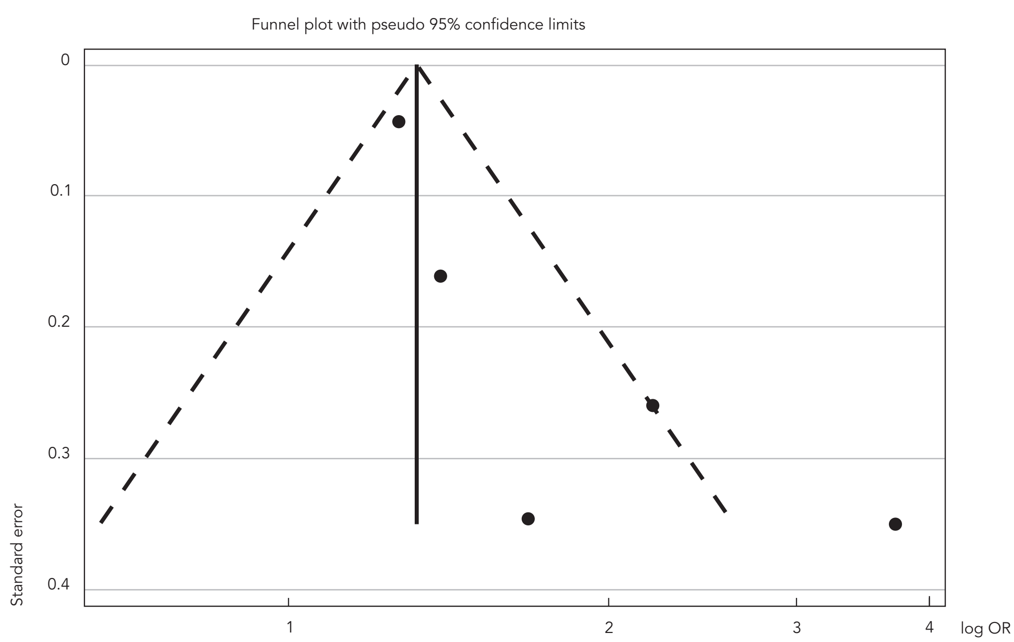
Studies have also been carried out with native populations (Cree) from Canada. The increased risk was only found among obese natives in comparison to non native Canadians [53].

Funnel plots suggest that the risks found for Asians are not a result of publication bias (Figure 3), while those associated with Indians/Pakistanis may be biased. It is interesting to note that the highest prevalence of gestational diabetes mellitus found among ethnic groups was observed in studies carried out with populations of immigrants in Western countries. In studies made in the original populations, the prevalence is lower than in Western countries [29,54,55]. It is important to point out that more recent studies show that the prevalence of diabetes mellitus is increasing in China and in other Eastern countries, due to adaptations to modern lifestyles, brought about by the economic developments of the last decade [56].

Far beyond genetic questions and change in lifestyle, aspects linked to prejudice must also be considered. Emotional stress can influence metabolic functions, because it increases the production of cortisol and other hyperglycemic hormones, besides activating the pro-inflammatory elements of the innate immune system and modifying the sympathetic nervous system [57].

Figure 3

Asian ethnic Funnel plot.



Thus, in developed countries, the highest risk of diabetes mellitus and gestational diabetes mellitus, between different ethnic groups, could be justified by genetics, age of pregnant immigrant, by lifestyle changes, socioeconomic factors and, possibly, as a result of suffering prejudice.

Weight gain

The Brazilian Society of Diabetes (SBD) considers as a risk factor for gestational diabetes mellitus excessive weight gain [58], however few studies evaluated this variable as an independent risk factor.

One of the first studies was published by Scholl et al. [59], in 1995, among low income pregnant and racial minorities from New Jersey, USA. The authors showed that high concentrations of insulin were associated with a greater increase and retention of weight post-partum. Later, studies by Jang et al. [25], in 1998, Yang et al. [29], 2002 and Saldana et al. [60], 2006 controlling for age, weight and pre-pregnancy BMI, height, family history of diabetes mellitus and parity, have shown a significant association between weight gain and gestational diabetes mellitus, some studies have also adjusted for smoking habits and alcohol use.

Saldana et al. [60], also evaluated the association between weight gain at the end of the second semester (and the US Institute of Medicine weight gain recommendation [61]) and the risk of glucose intolerance and gestational diabetes mellitus, finding higher risks than in the previous analyses. A high statistical significance (< 0.0001) was also found in an adjusted analysis in the difference between weight gain among pregnant women with gestational diabetes mellitus or not, at the moment of the diagnosis, in the study of Di Cianni et al. [33].

On the other hand, in a Letter to the Editor, Corrado et al. [62] stated that in a retrospective study in Italy they did not find an association between gestational diabetes mellitus and weight increase. This was also true for Deruelle et al. [63], in 2004, who compared weight gains above 18kg to lower gains. And in another study, women with BMI ranging from 19.5 to 25.5kg/m^2 gaining less than 11kg during pregnancy were more likely to present gestational diabetes mellitus in comparison to those gaining more than 20kg (p = 0,02) in the crude analysis of the study by Thorsdottir et al. [64], however the sample was too small to study the outcome. These findings were confirmed by Innes et al. [21], analyzing weight gain in quartiles (< 11.35; 11.35-15.8; 15.9-20.4 and 20.5kg), and observing a crude OR for gestational diabetes mellitus that was smaller for pregnant women in the highest quartile of weight gain, without statistical significance after adjustments (also for pre-pregnancy weight); and by Lauszus et al. [46], comparing average weight gain in women with a normal oral glucose tolerance test and diabetic women. As obesity is a known risk factor for gestational diabetes mellitus, it is possible that the effect of this variable was biased by reverse causality, since high-weight pregnant women with other risk factors for gestational diabetes mellitus are oriented not to gain weight during pregnancy. The differences in the results might also be explained by the time interval in which weight gain was measured: in the four first studies, weight gain was measured up until the gestational diabetes mellitus diagnostic test, while other studies measured up until the end of the pregnancy. Behavioral changes, indicated for the treatment of gestational diabetes mellitus could have an influence on weight increase after the diagnosis.

Physical activity

Physical activity has been associated to a reduced risk for excessive weight gain, insulin resistance and type 2 diabetes mellitus [65,66,67]. Few studies evaluated the association between physical activity and gestational diabetes mellitus, however it has been stated that increasing physical activity could decrease the glucose intolerance in diabetic pregnant women [68].

The lack of studies can be attributed, in part, to the difficulty in measuring this variable, the potential reverse causality and recall biases, as well as poor prenatal care counseling towards physical activity.

In 1997, Solomon et al. [42] measured pre-pregnancy physical activity, in terms of mean metabolic equivalent expenditures [69]. This study found a non significant reduction of gestational diabetes mellitus risk for women who were vigorously physical active or did brisk walking before pregnancy. Dye et al. [70], also in 1997, found that inactive women presented OR: 1.9 (95%CI: 1.2-3.1) for gestational diabetes mellitus, compared to active women, only among those with BMI pre-pregnancy > 33. This study considered as physical activity those activities performed during leisure time.

Dempsey et al. [71,72], in a case-control study (2004) and in a cohort study (2004), observed an approximately 50% reduction in gestational diabetes mellitus risk associated to several types of recreational physical activities, performed in the previous year and/or during the first 20 weeks of pregnancy, adjusted for age, race, parity and pre-pregnancy BMI. The same population using the same adjustments was analyzed by Rudra et al. [28,73] in a case-control study and as a cohort, assessing the relation between perceived exertion during pre-pregnancy recreational physical activity, divided in weak, moderate, strenuous and very strenuous and gestational diabetes mellitus. The reduced risk for gestational diabetes mellitus was 59% for moderate, up to 81% for very strenuous, in relation to weak, in the case-control study, and 37% and 43%, respectively, in the cohort study.

A recent study with the population from the *Nurse's Health Study II,* observed an adjusted risk ratio of the comparison between the highest and the lowest quintile of vigorous activity, equal to 0.77 (95%CI: 0.69-0.94). Still, among women who have not performed vigorous activities, brisk walking and climbing stairs (up to 15 steps daily) were associated with risk reduction [74]. In spite of different ways of measuring physical activity, studies highlight the importance of this variable as an independent protective factor for gestational diabetes mellitus.

Conclusions

The systematic review of the literature allows us to draw the following conclusions:

(a) Well designed studies [20,21], found increased risks in the association between low birth weight and gestational diabetes mellitus. Some studies found there to be a statistical significance although with no control for family history of diabetes mellitus and BMI [19] and with no weight categorization [15], which guaranteed significance for others [23]. According to the literature, maternal history of low birth weight must be included as a risk factor for gestational diabetes mellitus. New studies must either consider controlling for familiar history of gestational diabetes mellitus (mainly the mother of the pregnant woman) or always separate birth weight categories that contemplate the highest weights separately in order to investigate this association;

(b) In relation to height, all but one of the studies found an association. Although publication bias cannot be ruled out, the challenge in including short stature as a risk factor for gestational diabetes mellitus seems to be the definition of the cut-off point for this variable. In Brazil, based on the Brazilian Gestational Diabetes Study (EBDG), the study of Branchtein et al. [27] defined it as ≤ 151cm, however studies in other countries observed associations using different height categories [21,25,26,29,33].

(c) Socioeconomic levels are investigated mostly in studies carried out in developed countries. The existing social inequities in developing countries hinder comparison with developed countries. Due to controversial results, it could be more elucidative to study this association in countries where differences between high and low socioeconomic levels are huge, and therefore, the potential association would be more easily proven;

(d) Regarding smoking habits, half of the studies found there to be a statistically significant association. These differences in the results may result from a lack of power, different smoking exposure measurements, differences in the diagnostic methods, different definitions of the exposure, besides different confounders' control. Changes in smoking habit as a result of the pregnancy or wrong information about smoking status (since risks associated to tobacco exposure in pregnancy are well known), also could be sources of bias. The heterogeneity of the studied populations, the lack of control, in some cases, for known potential confounding factors and the effect of others, still not described, may also have led to different results. In order to clarify this association, more studies are necessary, with sample sizes large enough to contemplate the possible confounding factors and standardization of exposure;

(e) The association between parity and diabetes seems consistent in the different studies investigated and is marked by a dose-response fashion. However, women with highest parity are frequently older and heavier. Therefore, no study that evaluates parity could ignore a proper age adjustment. In the evaluated studies, only two had adjusted for age, presenting conflicting results. To identify the mediating effect of obesity, hierarchical analyses could show the real association between high parity and the risk of developing gestational diabetes mellitus;

(f) The racial question has not yet been well elucidated. Differences in the metabolic susceptibility to diabetes mellitus can exist, but ambient factors, due to behavioral changes (such as physical activity or nutritional patterns), or factors linked to emotional stress, associated to the immigrant situation, to the socioeconomic condition, must be more investigated in future studies, especially in developed countries;

(g) The results found for weight gain during pregnancy are controversial since well designed studies presented conflicting results. Maternal pre-pregnancy weight influences the weight gain in the course of pregnancy [60]. Studies evaluating the weight gain until the moment of the diagnosis, adjusting for gestational age, besides other potential confounders such as age, obesity, parity and smoking habits, could elucidate this question; and

(h) There are indications, through three cross-sectional studies and one cohort study, that physical activity performed right before and during pregnancy could modify the risk of gestational diabetes mellitus. Studies would have to be carried out in women before the gestational diabetes mellitus diagnosis, with the objective to prevent the reverse causality associated to behavior changes after the diagnosis of gestational diabetes mellitus. All domains of physical activity should be assessed (leisure time, commuting and occupational).

Different methodologies used by the researchers to define the exposures and outcome did not allow for a meta-analysis to be carried out. Although the literature reviewed suggests that the investigated characteristics are risk factors for gestational diabetes mellitus, the presence of publication bias i.e. the preferential publication of researches that present positive results cannot be discarded for the majority of risk factors. This finding prevents the recommendation of including these factors among those that point out women in higher risk of gestational diabetes mellitus. The standardization of the techniques and cutoff points for screening and diagnosis, besides adequate sample sizes, will allow future meta-analyses, which make possible the confirmation or the removal of these new criteria from the list of the risk factors for gestational diabetes mellitus.

Resumo

Idade, obesidade e história familiar de diabetes são fatores de risco bem conhecidos para diabetes mellitus gestacional. Outros são controversos. O objetivo desta revisão é encontrar evidências na literatura que justifiquem a inclusão dessas condições entre os fatores de risco. Bases de dados MEDLINE, Cochrane, LILACS e Organização Pan-Americana da Saúde foram procuradas. A revisão incluiu artigos de 1992 a 2006. Palavras-chave foram usadas em combinação com diabetes mellitus gestacional separadamente e com cada um dos fatores de risco estudados. A qualidade metodológica dos estudos incluídos foi medida, totalizando 41 estudos. A maioria dos trabalhos que investigaram história materna de baixo peso, baixa estatura e baixa atividade física encontrou associação positiva com diabetes mellitus gestacional. Baixo nível sócio-econômico, fumo durante a gestação, alta paridade, pertencer a minorias e excessivo ganho de peso apresentam resultados conflitantes. Padronização de técnicas, pontos de corte para rastreamento e diagnóstico, assim como estudos envolvendo maiores amostras podem permitir futuras metanálises.

Diabetes Gestacional; Diabetes Mellitus; Fatores de Risco

Contributors

M. A. S. O. Dode contributed to the conception and design; acquisition of data; analysis and interpretation of data; drafting the article and critically revising it for important intellectual content; and final approval of the version to be published. I. S. Santos reviewed all steps of the process and reviewed the article for the final approval of the version to be published.

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