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Review Article

Biomarkers of oxidative stress in maternal plasma, umbilical cord and placenta of patients with gestational diabetes: a systematic review and meta-analysis⋆

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ABSTRACT

Objective: To determine the association between Gestational Diabetes Mellitus (GDM) and oxidative stress biomarkers in the mother, placenta, and newborn.
Methods: We conducted a systematic review and meta-analysis following the PRISMA guidelines. We searched PubMed/MEDLINE and the Web of Science database without language restrictions. The search was updated on December 28, 2023, and included reports published between 1998 and 2021. Two independent reviewers performed article selection and data extraction.
Results: Our findings show a significant increase in malondialdehyde and 8-isoprostane levels in the maternal plasma and placenta of women with GDM compared to those without GDM (SMD [95 % CI] = 1.99 [1.51, 2.48], $Tau^2 = 1.51$, $I^2 = 94$ %, $p < 0.00001$; SMD [95 % CI] = 1.90 [0.08, 2.72], $Tau^2 = 1.14$, $I^2 = 93$ %, $p < 0.00001$, respectively). Additionally, there was a decrease in superoxide dismutase (SOD) levels in maternal plasma (SMD [95 % CI] = −2.80 [-5.23, −0.36], $Tau^2 = 7.56$, $I^2 = 98$ %, $p < 0.00001$). However, no significant changes in SOD were observed in the placenta or the umbilical cord blood of offspring from women with GDM (SMD [95 % CI] = −1.79 [-4.66, 1.07], $Tau^2 = 6.23$, $I^2 = 97$ %, $p < 0.00001$; SMD [95 % CI] = −1.07 [-3.37, 1.24], $Tau^2 = 5.31$, $I^2 = 97$ %, $p < 0.00001$, respectively).
Conclusion: These results suggest an association between GDM and increased oxidative stress levels in both maternal and fetal circulation, as well as the placenta. The high heterogeneity in the results of the meta-analysis, which could be due to clinical and methodological factors, is a limitation of this study.

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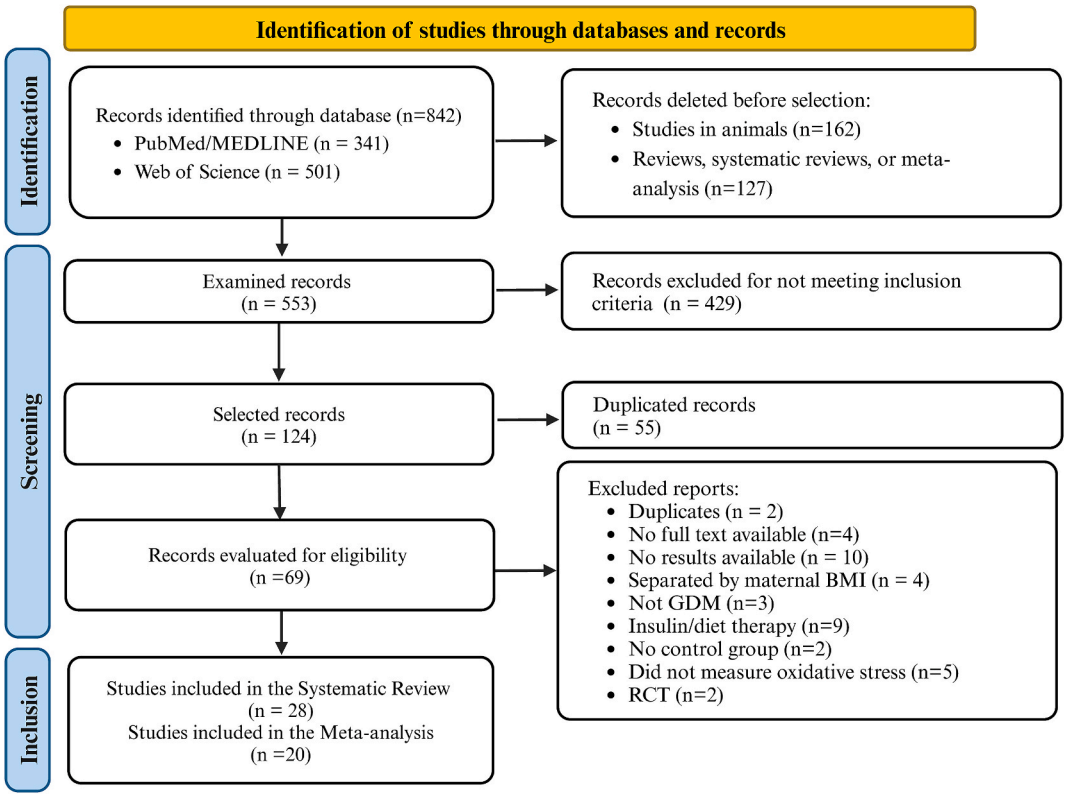

Fig. 1. PRISMA flowchart.

1. Introduction

Gestational diabetes mellitus (GDM) is a metabolic endocrine disorder defined as glucose intolerance, with onset during pregnancy and ending after delivery [1]. It is a significant public health concern due to its adverse maternal and neonatal outcomes [2]. GDM is the most frequent pregnancy complication, affecting approximately 14 % of pregnancies worldwide, representing 20 million births annually, according to estimations of the International Diabetes Federation (IDF) [3]. In the last few years, increasing evidence has shown a higher occurrence of this condition in occidental populations, partly explained by the increase in maternal age and the rate of overweight and obesity during reproductive age [4,5]. This situation has positioned GDM as a significant public health problem with immediate adverse effects on the pregnant woman and the newborn and a high risk for developing type 2 diabetes mellitus in infancy or adulthood [6]. In terms of the risk to the offspring's health, maternal hyperglycemia has been correlated with increased fetal morbidity and mortality [7]. Furthermore, an increased risk of preeclampsia, spontaneous abortion, prematurity, fetal death, intrauterine growth restriction or macrosomia, neonatal malformations, and hypoglycemia has been widely documented as complications of GDM [7–10].

Considering the high prevalence of GDM and the detrimental effects on the health of the mother and the newborn, developing tools for early diagnosis and treatments to improve maternal and infant prognosis is necessary [11,12]. Previous studies have demonstrated that genetic, epigenetic, and environmental factors contribute to the development of GDM, reflecting the complexity of the mechanisms behind its genesis and evolution [7]. Regarding the mechanisms, clinical evidence has shown an association between maternal hyperglycemia and increased oxidative stress [13,14]. The latter condition, defined as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and molecular damage [15,16]could contribute to the pathophysiology of GDM and the related maternal and fetal complications [7,14,17–21]. Nevertheless, despite the strong correspondence between oxidative stress and the etiology and complications of GDM, an analysis linking clinical data of oxidative stress biomarkers and GDM has not been systematically carried out [13,19,21,22].

High levels of oxidative damage, as those reached under oxidative distress [15], lead to disruption of redox signaling and nonspecific oxidation of lipids, proteins, and DNA [15,16,23]. The peroxidation of lipids has been widely studied and ascribed to the damage inflicted by oxygen free radicals to polyunsaturated fatty acids of cell membranes [20]. 8-isoprostanes (8-isop) and malondialdehyde (MDA) are sensitive indicators of these processes and traditionally used as biomarkers to assess oxidative damage [24]. In the case of oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is the biomarker mainly employed [25]. At the same time, the production of carbonyl groups is widely used to evaluate the injury of proteins, which are principal targets of oxidants in biological environments [26].

To prevent, counteract, or repair the damage inflicted by biologically relevant oxidants, cells have developed sophisticated antioxidant systems involving enzymes and low-weight molecules; both addressed for clinical purposes [27]. Among the antioxidant enzymes, the activity of superoxide dismutase (SOD), which catalyzes the dismutation of superoxide to hydrogen peroxide (H_2O_2), and catalase (CAT) and glutathione peroxidase (GPX), which catalyze the decomposition of H_2O_2 to H_2O and O_2 [23,28], are commonly determined. The levels of low molecular weight antioxidants (non-enzymatic antioxidants), such as reduced glutathione (GSH) [29], or exogenous molecules, such as vitamins, minerals, and phenolic compounds, have been assessed in human plasma, serum, and urine [30]. An interesting example of the latter is the determination of ascorbic (vitamin C, Vit C), a water-soluble antioxidant able to neutralize tocopheryl radicals, repairing vitamin E (Vit E), an important chain-breaking antioxidant of cell membranes [31].

Clinical studies have indicated that under physiological conditions, pregnancy is associated with a slight increase in the levels of biomarkers

Table 1
Search strategy.

#one	("Fetal Blood"[MeSH] OR "Fetal Blood*"[Tiab] OR "Cord Blood*"[Tiab] OR "Fetal Erythrocytes"[Tiab] OR "Fetal Serum"[Tiab] OR "Fetal Plasma"[Tiab] OR "Fetoplacental Circulation"[Tiab])
#two	("placenta"[MeSH] OR "maternal fetal exchange"[MeSH] OR "placental extracts"[MeSH] OR "placental tissue"[Tiab] OR "placenta"[Tiab])
#3	("Blood"[MeSH] OR "maternal blood*"[Tiab] OR "Maternal Erythrocytes"[Tiab] OR "Maternal Serum"[Tiab] OR "Maternal Plasma"[Tiab])
#4	("Reactive Oxygen Species"[MeSH] OR "Reactive Oxygen Species"[Tiab] OR "ROS"[Tiab] OR "Singlet Oxygen"[MeSH] OR "Singlet Oxygen"[Tiab] OR "Superoxides "[MeSH] OR "Superoxide*"[Tiab] OR "Peroxides"[MeSH] OR "Peroxide*"[Tiab] OR "Hydroxyl Radical"[MeSH] OR "Hydroxyl Radical*"[Tiab] OR "Hypochlorous Acid"[MeSH] OR "Hypochlorous Acid *"[Tiab] OR "Peroxynitrous Acid"[MeSH] OR "Peroxynitrous Acid*"[Tiab] OR "Peroxynitrite "[Tiab] OR "Nitric Oxide Synthase"[MeSH] OR "Nitric Oxide Synthase*"[Tiab] OR "NOS "[Tiab] OR "eNOS "[Tiab] OR "iNOS "[Tiab] OR "Homocysteine"[MeSH] OR "Homocysteine"[Tiab] OR "Hcy "[Tiab] OR "Adenosine Deaminase"[MeSH] OR "Adenosine Deaminase"[Tiab] OR "ADA "[Tiab] OR "Nitrites"[MeSH] OR "Nitrite*"[Tiab] OR "Superoxide Dismutase"[MeSH] OR "Superoxide Dismutase"[Tiab] OR "SOD "[Tiab] OR "Glutathione Peroxidase"[MeSH] OR "GSH-PX"[Tiab] OR "GPX"[Tiab] OR "Glutathione"[MeSH] OR "Glutathione"[Tiab] OR "GSH"[Tiab] OR "Catalase"[MeSH] OR "Catalase"[Tiab] OR "CAT "[Tiab] OR "Heme Oxygenase-1"[MeSH] OR "Heme Oxygenase*"[Tiab] OR "HO-1"[Tiab] OR "Heme Oxygenase-2"[Supplementary Concept] OR "HO-2"[Tiab] OR "Heme Oxygenase-3 protein, human"[Supplementary Concept] OR "HO-3"[Tiab] OR "Sulfhydryl Compounds"[MeSH] OR "Sulfhydryl"[Tiab] OR "Thiol*"[Tiab] OR "FT"[Tiab] OR "Alpha-1-microglobulin"[Supplementary Concept] OR "Alpha-1-Microglobulin" [Tiab] OR "Alpha(1)- microglobulin "[Tiab] OR "Alpha1-microglobulin"[Tiab] OR "Alpha-1microglobulin"[Tiab] OR "Alpha1microglobulin"[Tiab] OR "Alpha-1-M"[Tiab] OR "Alpha1-M"[Tiab] OR "Alpha(1)M"[Tiab] OR "Alpha1M"[Tiab] OR "Alpha1-MG"[Tiab] OR "Alpha1MG"[Tiab] OR "A1MG"[Tiab] OR "Alpha-1-microglobulin"[Tiab] OR "Alpha1microglobulin"[Tiab] OR "A1M"[Tiab] OR "Thioredoxins"[MeSH] OR "Thioredoxin*"[Tiab] OR "NADH"[Tiab] OR "NADPH"[Tiab] OR "Antioxidant Potential*"[Tiab] OR "AOP "[Tiab] OR "Total Antioxidant Capacity"[Tiab] OR "TAC "[Tiab] OR "Paraoxonase-1"[Tiab] OR "PON1"[Tiab] OR "Hemopexin"[Tiab] OR "Hpx "[Tiab] OR "Myeloperoxidase"[Tiab] OR "MPO "[Tiab] OR "Xanthine Oxidase"[MeSH] OR "Xanthine Oxidase"[Tiab] OR "XO "[Tiab] OR "8-Hydroxy-2′-Deoxyguanosine"[MeSH] OR "Deoxyguanosine" [Tiab] OR "8-OhdG"[Tiab] OR "Malondialdehyde"[MeSH] OR "Malondialdehyde"[Tiab] OR "MDA"[tiab] OR "Thiobarbituric Acid Reactive Substances"[MeSH] OR "Thiobarbituric Acid Reactive Substance* "[Tiab] OR "TBAR*"[Tiab] OR "Oxidized Low Density Lipoprotein"[Supplementary Concept] OR "Oxidized Low Density Lipoprotein*"[Tiab] OR "oxLDL "[Tiab] OR "F2-Isoprostanes"[MeSH] OR "F2-Isoprostane*"[Tiab] OR "F2 Isoprostane "[Tiab] OR "Ischemia-Modified Albumin"[Supplementary Concept] OR "Ischemia-Modified Albumin"[Tiab] OR "Ischemia-Modified Albumin "[Tiab] OR "Ischemia Modified Albumin"[Tiab] OR "Ischemia Modified Albumin"[Tiab] OR "Isch emia-modified albumin"[tiab] OR "IMA"[Tiab] OR "IMAR"[Tiab] OR "Protein Carbonyl Level*"[Tiab] OR "Tyrosine"[MeSH] OR "Tyrosine"[Tiab] OR "Nitrotyrosine" [Tiab] OR "Nucleated Red Blood Cell*"[Tiab] OR "NRBC"[tiab] OR "Oxidative Stress Biomarker*"[Tiab] OR "Oxidative Stress Marker*"[Tiab] OR "Oxidative Stress"[Tiab] OR "OS "[Tiab] OR "Oxidative Stress"[MeSH] OR "Antioxidant Status"[Tiab] OR "Antioxidant Balance"[Tiab] OR "Antioxidant Defense Marker*"[Tiab] OR "Antioxidants"[MeSH] OR "Antioxidant *"[Tiab] OR "Redox Status"[Tiab] OR "Lipid Peroxidation"[Tiab] OR "Lipid Peroxidation"[MeSH] OR "Methemoglobin"[MeSH] OR "Methemoglobin"[Tiab] OR "Methaemoglobin "[Tiab])
#5	("Diabetes, Gestational"[MeSH] OR "Diabetes, Gestational"[MeSH] OR "Gestational Diabetes Mellitus"[Tiab] OR "Gestational Diabetes"[Tiab])
#4	#1 AND #4 AND #5
#5	#2 AND #4 AND #5
#6	#3 AND #4 AND #5
#7	#1 OR #2 OR #3 AND #4 AND #5

of oxidative stress [32]. This has been partially explained by the high energy demand and oxygen utilization, two characteristics of pregnancy [32]. Nevertheless, in GDM, the balance between oxidant production and the antioxidant system is impaired, resulting in increased levels of oxidative stress and its subsequent damage [33]. Experimental and clinical studies in women with GDM have shown increased extents of biomarkers of oxidative damage in maternal plasma, placental tissue, and the fetal compartment, the latter measured in the blood of the umbilical cord [33,34]. However, currently, it is not clear which biomarkers represent a suitable alternative to evaluate the damage inflicted by oxidative stress and its association with GDM.

2. Objective

This study aims to determine the association between GDM and oxidative stress markers in the mother, the placenta, and the newborn.

3. Methods

The systematic review and meta-analysis were conducted following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) submission format and guidelines [35,36] (Fig. 1). The study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a unique ID: CRD42024498846.

3.1. Eligibility criteria, information sources, search strategy

The selection criteria were observational studies (longitudinal cohort, case-control, cross-sectional). The characteristics and inclusion criteria were as follows: mothers with GDM diagnosed by any of the existing diagnostic criteria, measurement of biomarkers of oxidative stress (lipids, proteins, and DNA) and/or enzymatic and non-enzymatic antioxidants in maternal plasma and/or umbilical cord and/or the placenta during the third trimester or delivery, all types of delivery, pregnant control group healthy. Studies carried out in women with type 1 or type 2 pregestational diabetes, measurements of oxidative stress biomarkers and antioxidant enzymes before the first trimester of pregnancy, without a control group, were excluded. Randomized clinical trials (RCTs), supplementation intervention studies, and studies without results were also ignored.

We searched PubMed/MEDLINE and Web of Science databases. The search was extended to December 28, 2023. No language or geographic location restrictions were applied.

The PECO (population, exposure, comparison, outcome) approach was followed for the formulation of our research question.

Population: pregnant women.

Exposure: gestational diabetes mellitus.

Comparison: healthy pregnant women without gestational diabetes mellitus.

Outcome: maternal or neonatal or placental biomarkers of oxidative stress and antioxidant enzymes.

Our research question was: Are pregnant women with gestational diabetes, the placenta, and their offspring at higher risk of presenting elevated biomarkers of oxidative stress and decrease in antioxidant enzymes, compared with healthy pregnant women? The strategy to address this question included the keywords listed in Table 1. The search strategy was conducted by an independent reviewer, and two independent reviewers carried out the study selection, data extraction and verification.

3.2. Study selection

The search results were exported to Microsoft Excel for abstract screening. Two reviewers performed the eligibility assessment of studies in an independent and standardized manner. Studies meeting initial screening criteria were selected for full assessment. Statistical analysis with Cohen's Kappa test was performed to assess the degree of agreement between the researchers in the study selection process. There was considerable agreement [37] (Kappa Cohen = 0.784). Disagreements between reviewers were resolved by consensus.

Table 2
Newcastle-Ottawa Scale (NOS).

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES								
Studies	Selection				Comparability	Exposure		
	Case definition	Case representativeness	Control selection	Definition of controls	Comparability of cases and controls	Exposure Check	Same verification	Non-response rate
Kamath et al., 1998 [61]	*	*		*	*	*	*	*
Pustovrh et al., 2000 [50]	*	*		*	*	*	*	
Dey et al., 2008 [66]	*	*		*	*	*	*	
Shang et al., 2015 [20]	*	*			*	*	*	*
Li et al., 2014 [56]	*	*	*		*	*	*	
Coughlan et al., 2004 [59]	*	*		*	*	*	*	
Ramírez-Emiliano et al., 2017 [49]	*	*	*	*	*	*	*	*
Qiu et al., 2013 [51]	*	*		*	*	*	*	*
Kinalski et al., 2001 [62]	*			*	*	*	*	*
Rodrigues et al., 2018 [17]	*			*	*	*	*	*
Toljic et al., 2017 [42]	*	*		*	*	*	*	*
Peuchant et al., 2004 [41]	*	*	*	*	*	*	*	*
Bulut et al., 2021 [44]	*	*			*	*	*	
Karacay et al., 2010 [18]	*	*		*	*	*	*	*
Krishnasamy et al., 2020 [43]	*	*	*		*	*	*	*
Ma et al., 2021 [67]	*	*		*	*	*	*	
Usluoğullari et al., 2017 [47]	*	*	*	*	*	*	*	*
Xin et al., 2014 [57]	*	*		*	*	*	*	*
Manoharan et al., 2019 [64]	*			*	*	*	*	*
Ozler et al., 2020 [48]	*	*	*		*	*	*	
Jatavan et al., 2020 [34]	*	*	*	*	*	*	*	*
Erbağcı et al., 2021 [46]	*	*		*	*	*	*	*
Madazli et al., 2008 [58]	*	*		*	*	*	*	
Topcouglu et al., 2015 [63]	*	*		*	*	*	*	*
Gilfillan et al., 2016 [65]	*	*			*	*	*	*
Lewandowski et al., 2014 [45]	*	*			*	*	*	

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES								
Studies	Selection				Comparability	Exposure		
	Cohort Representativeness	Unexposed cohort selection	Exposure determination	Demonstration result was not at the beginning	Cohort Comparability	Evaluation of the result	Long follow-up	Adequate follow-up
Rueangdetnarong et al., 2018 [22]	*	*	*		*	*		*
Durga et al., 2018 [32]	*	*	*			*	*	*

3.3. Data extraction

An Excel table was used for data registry and extraction. The information included in the table was data related to the authors, year of publication, study design, sample size, time and place of measurement, type of biomarker and determination method, mean and standard deviation or median and interquartile range for the BMI, biomarkers of oxidative stress and antioxidant enzymes.

3.4. Assessment of risk of bias and study quality

Possible publication bias was assessed using Egger's regression test and Funnel Plot symmetry visualization [38]. The quality of the evidence was evaluated using the Newcastle-Ottawa Scale (NOS) [39,40]. For each study, low-quality (<5 stars), moderate-quality (5–7 stars), and high-quality (>9 stars) labels were assigned (Table 2).

3.5. Data synthesis and statistical analysis

The studies that provided the number of control and GDM individuals, the mean and standard deviation of the biomarkers and an adequate description of the methods performed were included in the meta-analysis. When possible, the units of measurement were standardized, and data from the pregnant woman, umbilical cord and

Table 3
Biomarkers of oxidative stress and antioxidants in women with GDM.

Oxidative stress biomarkers											
Reference	Year of publication	Study design	#case/ control	Time of measurement	Measurement location	BMI (Kg/m^2)		Biomarkers	Results		Determination
						GDM	Control		GDM	Control	
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Plasma	27.1 ± 1.4	27.1 ± 1.4	MDA μmol/L	1400 ± 100	1300 ± 90	HPLC-FL (515/532 nm). Calibration curve, TEP method.
Madazli et al. [58]	2008	Cohort	22/22	Before childbirth	Plasma	24.7 ± 1.9	23.5 ± 1.6[a]	MDA μmol/L	5.8 ± 0.6	3.2 ± 0.4[a]	Absorbance (wavelength; n.a.). Calibration curve, TEP method.
Karacay et al. [18]	2010	Case control	27/29	2nd and 3rd trimester	Plasma	32.4 [8.4]	29.2 [5.2]	MDA μmol/L	7.8[2.3]	6.5[1.9][a]	Vis (535 nm). FL (532/550 nm). Calibration curve, TEP method.
Xin et al. [57]	2014	Case control	131/107	2nd and 3rd trimester	Plasma	24.1 ± 3.5	22.1 ± 5.2[a]	MDA μmol/L	39.8 ± 13.2	31.6 ± 14.4[a]	Commercial kit (Zhongshan Golden Bridge Biotech, China) Absorbance (wavelength; n.a.). Calibration curve, TEP method.
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	MDA μmol/L	6.9 ± 0.7	4.8 ± 0.6[a]	Commercial kit (colorimetric method, Nanjing Jiancheng bioengineering institute, China)
Gilfillan et al. [65]	2016	Case control	20/18	At delivery	Plasma	30.4 ± 10.4	28.2 ± 7.1	TBARS/ MDAμmol/L	22 ± 8	22 ± 10	Vis (530–540 nm). Commercial kit (Cayman).
Rodriguez et al. [17]	2018	Case control	48/30	3rd trimester	Plasma	31.5 ± 4.4	29.45 ± 4.3	TBARS/MDA μmol/L	5.8 ± 2.0	3.9 ± 1.6[a]	Not specified.
Toljic et al. [42]	2017	Case control	37/28	2nd and 3rd trimester	Plasma	NR	NR	TBARS/MDA μmol/L	28.5 ± 6.3	18.2 ± 2.6[a]	Vis (532 nm). Calibration curve, TEP method.
Krishnasamy et al. [43]	2020	Case control	50/50	3rd trimester	Plasma	25.7 ± 5.5	24.2 ± 4.7	MDA μmol/L	0.64 ± 0.08	0.55 ± 0.06[a]	Vis (532 nm). Commercial kit (Sigma Aldrich, USA).
Manoharan et al. [64]	2019	Cross-sectional	40/40	3rd trimester	Plasma	22.1 ± 2.6	22.2 ± 1.0	MDA μmol/L	148.3 ± 24.9	113.3 ± 37.3[a]	Visible (535 nm). Calibration curve, TEP method.
Bulut et al. [44]	2021	Case control	22/29	2nd and 3rd trimester	Plasma	25.7 ± 2.5	24.2 ± 2.9	MDA μmol/L	10.5 ± 0.5	8.4 ± 2.6	Visible (532 nm).
Ma et al. [67]	2021	Case control	104/126	2nd and 3rd trimester	Plasma	NR	NR	MDA μmol/L	23.8 ± 2.1	12.8 ± 1.9[a]	Colorimetric method.
Kamath et al. [61]	1998	Case control	20/15	At delivery	Erythrocyte	NR	NR	MDA nmol/g Hb	12.7 ± 2.5	8.1 ± 3,2	Vis (532 nm). Extinction coefficient of the MDA-TBA complex (1.56×10^5 $M^{-1}cm^{-1}$).
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Erythrocyte	27.1 ± 1.4	27.1 ± 1.4	MDA nmol/g Hb	12.1 ± 0.8	9.7 ± 0.7	HPLC-FL (515/532 nm). Calibration curve, TEP method.
Dey et al. [66]	2008	Case control	18/18	3rd trimester	Erythrocyte	NR	NR	TBARS/MDA nmol/g Hb	6.7 ± 1.0	5.2 ± 0.7	Vis 532 and 600 nm. Extinction coefficient of the MDA-TBA complex (1.56×10^5 $M^{-1}cm^{-1}$).
Rodriguez et al. [17]	2018	Case control	48/30	3rd trimester	Erythrocyte	31.5 ± 4.4	29.45 ± 4.3	TBARS/MDA nmol/g Hb	25.1 ± 5.9	16.7 ± 7.7[a]	Not specified.
Li et al. [56]	2014	Case control	26/47	3rd trimester	Plasma	21.6 ± 3.1	20.3 ± 2.1[a]	8-isop ng/mL	9.3 ± 2.9	7.4 ± 2.2[a]	Commercial kit (Enzo life Sciences, Farmingdale, USA).
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	8-isop ng/mL	7.8 ± 1.2	3.8 ± 1.0[a]	Commercial kit (BlueGene Biotech, Shanghai, China).
Rueangdetnarong et al. [22]	2018	Cohort	30/32	2nd and 3rd trimester	Plasma	21.5 ± 3.9	22.7 ± 3.1	8-isop	737.5 [584.9–1811.5]	249.1 [47.7–997.2][a]	Commercial kit ELISA Kit (Cell Biolabs, Inc. San Diego, CA, USA).
Jatavan et al. [34]	2020	Cross-sectional	43/37	2nd and 3rd trimester	Plasma	21.3 ± 3.7	22.4 ± 3.0	8-isop ng/mg protein	1.2 ± 1.0	0.7 ± 1.0[a]	NS.
Lewandowski et al. [45]	2014	Cross-sectional	16/20	3rd trimester	Plasma	27.7 ± 3.6	26.4 ± 4.2	LPO nmol/mg	64.1 ± 24.3	47.0 ± 18.1[a]	LPO-586 kit purchased from Calbiochem (La Jolla, CA, USA).
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	LPO ng/ml	14.1 ± 2.1	14.6 ± 2.8	Commercial kit (BlueGene Biotech, Shanghai, China).

(*continued on next page*)

Table 3 (*continued*)

Oxidative stress biomarkers

Reference	Year of publication	Study design	#case/ control	Time of measurement	Measurement location	BMI (Kg/m^2)		Biomarkers	Results		Determination
						GDM	Control		GDM	Control	
Karacay et al. [18]	2010	Case control	27/29	2nd and 3rd trimester	Plasma	32.4 [8.4]	29.2 [5.2]	LHP uM HPE	0.1[0.1]	0.1[0.1]	HPLC-CL.
Toljic et al. [42]	2017	Case control	37/28	2nd and 3rd trimester	Plasma	NR	NR	8-OHdG nmol/L	56.6 ± 32.2	42.9 ± 10.5[a]	ELISA Kit II (Trevigen). Absorbance at 450 nm. Calibration curve with 8-OHdG standard.
Erbağ cı et al. [46]	2021	Case control	33/84	2nd trimester	Urine	25.6 ± 3.5	25.4 ± 4.6	8-OH-dG nmol/ nmol creatinine	1.5 ± 0.8	1.3 ± 0.6	LC-MS. Internal standard.
Karacay et al. [18]	2010	Case control	27/29	2nd and 3rd trimester	Plasma	32.4 [8.4]	29.2 [5.2]	AOPPs µmol/L	0.3[0.3]	0.1[0.1][a]	Spectrophotometric method. Presence of potassium iodide and acetic acid at 340 nm.
Usluogullari et al. [47]	2017	Case control	48/46	2nd and 3rd trimester	Plasma	25.3 ± 2.5	25.1 ± 3.0	OSI AU	0.2 ± 0.1	0.2 ± 0.1[a]	Spectramax M5 Microplate Reader (MV05047, Molecular Devices, Sunnyvale, CA).
Ozler et al. [48]	2019	Case control	57/29	2nd and 3rd trimester	Plasma	30.3 ± 5.0	30.0 ± 4.8	OSI AU	5.1 ± 3.2	3.4 ± 1.3[a]	Automated colorimetric method.
Usluogullari et al. [47]	2017	Case control	48/46	2nd and 3rd trimester	Plasma	25.3 ± 2.5	25.1 ± 3.0	TOS µmol H_2O_2 equiv./L	3.3 ± 1.5	2.8 ± 1.8[a]	Vis absorbance. Oxidation of ferrous ion. Titrating of ferric ions with xylenol orange.
Ozler et al. [48]	2020	Case control	57/29	2nd and 3rd trimester	Plasma	30.3 ± 5.0	30.0 ± 4.8	TOS nmol 2HO Eq/mg	9.2 ± 6.4	5.5 ± 2.1[a]	Vis absorbance. Oxidation of ferrous ion. Titrating of ferric ions with xylenol orange.

Antioxidant biomarkers

Reference	Year of publication	Study design	#case/ control	Time of measurement	Measurement location	BMI (Kg/m^2)		Biomarkers	Results		Determination
						GDM	Control		GDM	Control	
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	SOD U/mL	72.3 ± 18.8	117.1 ± 15.6[a]	Colorimetry. Commercial kit (Nanjing Jiancheng bioengineering institute, China).
Gilfillan et al. [65]	2016	Case control	20/18	At delivery	Plasma	30.4 ± 10.4	28.2 ± 7.1	SOD	333 ± 136	258 ± 53	Commercial kit (Randox Laboratories, UK). X/XO, Red Formazan assay.
Ma et al. [67]	2021	Case and control	104/126	2nd and 3rd trimester _	Plasma	NR	NR	SOD U/mL	0.006 ± 0.003	0.022 ± 0.003	Colorimetry. Pyrogalol auto-oxidation.
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	erythrocyte	27.1 ± 1.4	27.1 ± 1.4	SOD U/gHb	807.8 ± 45.2	901.6 ± 69.4	Randox test (Randox, Crumlin, UK). X/X.
Dey et al. [66]	2008	Case control	18/18	3rd trimester	erythrocyte	NR	NR	SOD U/gHb	1005.2 ± 115.9	2267.8 ± 363.6[a]	Colorimetry. X/XO, NBT assay.
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	GPX U/mL	775.0 ± 129.9	1084.9 ± 284.6[a]	Colorimetry. Commercial kit (Nanjing Jiancheng bioengineering institute, China).
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	erythrocyte	27.1 ± 1.4	27.1 ± 1.4	GPX U/gHb	70.0 ± 3.2	81.9 ± 4.2[a]	Randox test (Randox, Crumlin, UK). Decrease of NADPH.
Rodriguez et al. [17]	2018	Case control	48/30	3rd trimester	Erythrocyte	31.5 ± 4.4	29.45 ± 4.3	CAT K/mg-Hb	45.2 ± 8.5	50.9 ± 11.3[a]	Determination of H_2O_2 . Vis absorbance.
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Plasma	27.1 ± 1.4	27.1 ± 1.4	Vit A mg/L	0.7 ± 0.1	0.5 ± 0.1	HPLC
Ma et al. [67]	2021	Case control	104/126	2nd and 3rd trimester _	Plasma	NR	NR	Vit A mg/L	0.2 ± 0.1	0.6 ± 0.1[a]	HPLC
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Erythrocyte	27.1 ± 1.4	27.1 ± 1.4	Vit A mg/L	0.9 ± 0.1	1.7 ± 0.3	HPLC

(*continued on next page*)

Table 3 (*continued*)

Antioxidant biomarkers											
Reference	Year of publication	Study design	#case/ control	Time of measurement	Measurement location	BMI (Kg/m^2)		Biomarkers	Results		Determination
						GDM	Control		GDM	Control	
Dey et al. [66]	2008	Case control	18/18	3rd trimester	Plasma	NR	NR	Vit C mg/L	0.3 ± 0.04	0.3 ± 0.07	Colorimetry DNPH assay
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	Vit C mg/L	12.4 ± 1.4	14.3 ± 1.7[a]	Colorimetry Commercial kit (Nanjing Jiancheng bioengineering institute, China).
Rodriguez et al. [17]	2018	Case control	48/30	3rd trimester	Plasma	31.5 ± 4.4	29.45 ± 4.3	Vit C mg/L	10.8 ± 2.9	14.0 ± 5.3[a]	Colorimetry DNPH assay
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Plasma	27.1 ± 1.4	27.1 ± 1.4	Vit E mg/L	9.2 ± 0.6	10.2 ± 0.5	HPLC
Dey et al. [66]	2008	Case control	18/18	3rd trimester	Plasma	NR	NR	Vit E mg/L	21.9 ± 3.9	10.9 ± 2.2	Colorimetry
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	Vit E ug/L	9.6 ± 0.4	9.7 ± 0.6	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China).
Ma et al. [67]	2021	Case control	104/126	2nd and 3rd trimester	Plasma	NR	NR	Vit E mg/L	24.3 ± 2.8	8.4 ± 2.1[a]	HPLC
Peuchant et al. [41]	2004	Case control	16/26	3rd trimester	Erythrocyte	27.1 ± 1.4	27.1 ± 1.4	Vit E nmol/g Hb	9.7 ± 0.6	10.5 ± 0.5	HPLC
Krishnasamy et al. [43]	2020	Case control	50/50	3rd trimester	Plasma	25.7 ± 5.5	24.2 ± 4.7	GSH pmol/mL	0.2 ± 0.1	0.3 ± 0.1[a]	Colorimetry DNTB assay
Dey et al. [66]	2008	Case control	18/18	3rd trimester	Erythrocyte	NR	NR	GSH mg/g Hb	23.6 ± 2.6	17.3 ± 1.1[a]	Colorimetry
Ma et al. [67]	2021	Case and control	104/126	2nd and 3rd trimester _	Erythrocyte	NR	NR	GSH mg/gHB	59.7 ± 5.4	79.4 ± 5.6[a]	Colorimetry DNTB assay
Dey et al. [66]	2008	Case control	18/18	3rd trimester	Plasma	NR	NR	GST IU/L	3.2 ± 0.4	1.2 ± 0.2[a]	Spectrophotometrically
Karacay et al. [18]	2010	Case control	27/29	2nd and 3rd trimester	Plasma	32.4 [8.4]	29.2[5.2]	TAS	1.1[0.3]	1.6[0.3][a]	Bleaching of cation radical ABTS Randox commercial kit (Crumlin,UK)
Usluogullari et al. [47]	2017	Case control	48/46	2nd and 3rd trimester	Plasma	25.3 ± 2.5	25.1 ± 3.0	TAS µmol Trolox equiv/L	1.7 ± 0.4	2.0 ± 0.6	Bleaching of cation radical ABTS Colorimetry
Ozler et al. [48]	2019	Case control	57/29	2nd and 3rd trimester	Plasma	30.3 ± 5.0	30.0 ± 4.8	TAS µmol Trolox equiv/L	1.8 ± 0.3	1.7 ± 0.4	Colorimetry
Manoharan et al. [64]	2019	Cross-sectional	40/40	3rd trimester	Plasma	22.1 ± 2.6	22.2 ± 1.0	TAS umol/L	174.8 ± 34.2	256.9 ± 38.9[a]	Commercial kit (Bioassay Systems, Hayward, CA). Reduction of Cu^{2+}
Shang et al. [20]	2015	Case control	28/40	Before childbirth	Plasma	28.5 ± 2.6	27.64 ± 2.8	TAC U/mL	6.3 ± 1.0	10.6 ± 1.9[a]	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Ma et al. [67]	2021	Case control	104/126	2nd and 3rd trimester _	Plasma	NR	NR	TAC U/mL	9.3 ± 1.6	12.5 ± 5.4[a]	Automatic biochemical analyzer Fe^{3+} reduction

[a] Statistical significance $p > 0.05$; Values are Mean ± SD or Mean[95 %CI]. Abbreviations: NS: Not Specified; NR: Not Registered; NS: Not Significant; BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; MDA: malondialdehyde; 8-isop: 8-isoprostanes; PC: Carbonylated Proteins; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; LPO: lipid peroxides; TBARS: Thiobarbituric acid reactive substances; SOD: Superoxide Dismutase; GSH: glutathione; GPX: glutathione peroxidase, Vit A: Vitamin A, Vit C: Vitamin C, Vit E: Vitamin E; TAC: Total Antioxidant Capacity; HPLC-FL: High liquid chromatography coupled to fluorescence detector. In parenthesis are indicated excitation and emission wavelengths, TEP: 1,1,3,3-tetraethoxypropane, TBA: Thiobarbituric acid, FL: Fluorescence spectrophotometry, Vis: Visible spectrophotometry, RBC: Red blood cells, PBS: Phosphate buffer saline.

Table 4
Biomarkers of oxidative damage and antioxidants in the umbilical cord of the offspring of women with GDM.

Oxidative stress biomarkers in the umbilical cord blood

Reference	Year of publication	Study design	#case/ control	Measurement location	BMI (Kg/m^2)[a]		Biomarkers	Results[a]		Determination
					GDM	Control		GDM	Control	
Kinalski et al. [62]	2001	Case control	13/17	Plasma	NR	NR	MDA µmol/L	4.7 ± 1.5	1.1 ± 0.4[a]	Commercial kit (Bioxytech, France)
Madazli et al. [58]	2008	Cohort	22/22	Plasma	24.7 ± 1.9	23.5 ± 1.6[a]	MDA µmol/L	3.4 ± 0.4	2.1 ± 0.3[a]	Vis (wavelength; n.a.) Calibration curve, TEP method
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	MDA µmol/L	8.7 ± 1.1	4.8 ± 1.1[a]	Commercial kit (colorimetric method)
Gilfillan et al. [65]	2016	Case control	20/18	Plasma	30.4 ± 10.4	28.2 ± 7.1	TBARS/ MDAµmol/ L	25 ± 11	22 ± 8	Vis (530–540 nm) Commercial kit (Cayman)
Durga et al. [32]	2018	Cohort	24/24	Plasma	NR	NR	MDA µmol/L	8.8 ± 0.9	6.9 ± 1.1[a]	Commercial kit (colorimetric method, BioAssay Systems, Hayward, CA)
Manoharan et al. [64]	2019	Cross-sectional	40/40	Plasma	22.1 ± 2.6	22.2 ± 1.0	MDA µmol/L	48.5 ± 11.5	30.7 ± 14.6[a]	Vis (535 nm) Calibration curve, TEP method
Kamath et al. [61]	1998	Case control	20/15	Erythrocyte	NR	NR	MDA nmol/ g Hb	10.1 ± 2.2	6.8 ± 3.8[a]	Visible (532 nm) Extinction coefficient of the MDA-TBA complex (1.56×10^5 $M^{-1}cm^{-1}$)
Li et al. [56]	2014	Case control	26/47	Plasma	21.6 ± 3.1	20.3 ± 2.1[a]	8-isop ng/ mL	5.8 ± 1.1	4.4 ± 0.9[a]	ELISA kit (Enzo Life Sciences, Farmingdale, USA)
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	8-isop ng/ mL	6.9 ± 0.9	3.9 ± 0.9[a]	Commercial kit (BlueGene Biotech, Shanghai, China)
Rueangdetnarong et al. [22]	2018	Cohort	30/32	Plasma	21.5 ± 3.9	22.7 ± 3.1	8-isop	82.1 [30.9–233.8]	74.3 [44.1–109.2]	Commercial kit ELISA Kit (Cell Biolabs, Inc. San Diego, CA, USA)
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	LPO ng/mL	14.9 ± 1.9	15.4 ± 1.9	Commercial kit (BlueGene Biotech, Shanghai, China)
Topcouglu et al. [63]	2015	Case control	45/51	Plasma	NR	NR	TOS µmol H2O2/L	3 ± 1.2	2.6 ± 0.7[a]	Bleaching of cation radical ABTS Colorimetry
Topcouglu et al. [63]	2015	Case control	45/51	Plasma	NR	NR	OSI UA	1.5 ± 0.5	1.3 ± 0.3[a]	Automated colorimetric method
Durga et al. [32]	2018	Cohort	24/24	Plasma	NR	NR	Comet Assay µmol/ L	68.9 ± 7.9	30.3 ± 4.8[a]	Single Cell Gel Electrophoresis technique)

Antioxidant biomarkers in umbilical cord blood

Reference	Year of publication	Study design	#case/ control	Measurement location	BMI (Kg/m^2)[a]		Biomarkers	Results[a]		Determination
					GDM	Control		GDM	Control	
Kinalski et al. [62]	2001	Case control	13/17	Plasma	NR	NR	SOD U/mL	5.0 ± 0.6	8.5 ± 1.6[a]	Commercial kit ((Bioxytech, France)
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	SOD U/mL	45.4 ± 21.6	101.4 ± 9.9[a]	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Gilfillan et al. [65]	2016	Case control	20/18	Plasma	30.4 ± 10.4	28.2 ± 7.1	SOD	346 ± 133	262 ± 64[a]	Commercial kit (Randox Laboratories, UK) X/XO, Red Formazan assay
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	GPX U/mL	948.8 ± 205.9	1373.3 ± 188.1[a]	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	Vit C µg/mL	13.2 ± 1.6	13.9 ± 1.8	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	Vit E µg/mL	9.6 ± 0.6	9.5 ± 0.6	Colorimetry Commercial kit (Nanjing Jiancheng

(continued on next page)

Table 4 (*continued*)

Antioxidant biomarkers in umbilical cord blood									
Reference	Year of publication	Study design	#case/ control	Measurement location	BMI (Kg/m^2)[a]		Biomarkers	Results[a]		Determination
					GDM	Control		GDM	Control	
										Bioengineering Institute, China)
Kinalski et al. [62]	2001	Case control	13/17	Plasma	NR	NR	GSH µmol/L	19.6 ± 3.4	14.4 ± 3.6[a]	Colorimetry (Bioxytech LPO-586 and Bioxytech GSH-400; Oxis International, France).
Dey et al. [66]	2008	Case control	18/18	Plasma	NR	NR	GST IU/L	4.5 ± 0.6	2.4 ± 0.4	Spectrophotometrically
Manoharan et al. [64]	2019	Cross-sectional	40/40	Plasma	22.1 ± 2.6	22.2 ± 1.0	TAS µmol/L	174.3 ± 52.3	209.5[a]	Commercial kit (Bioassay Systems, Hayward, CA) Reduction of Cu^{2+}
Shang et al. [20]	2015	Case control	28/40	Plasma	28.5 ± 2.6	27.6 ± 2.8	TAC U/mL	6.4 ± 1.5	11.4 ± 2.7[a]	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Topcouglu et al. [63]	2015	Case control	45/51	Plasma	NR	NR	TAC mmol Trolox equiv/L	2.1 ± 0.1	2.0 ± 0.1[a]	Bleaching of cation radical ABTS Colorimetry
Durga et al. [32]	2018	Cohort	24/24	Plasma	NR	NR	TAC µmol Trolox equiv/L	223.3 ± 32.5	244.9 ± 45.2	Commercial kit (QuantiChromTM (DTAC-100))

[a] Statistical significance $p > 0.05$; Values are Mean ± SD or Mean[95 %CI]. Abbreviations: NS: Not Specified; NR: Not Registered; NS: Not Significant; BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; MDA: malondialdehyde; 8-isop: 8-isoprostanes; PC: Carbonylated Proteins; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; LPO: lipid peroxides; TBARS: Thiobarbituric acid reactive substances; SOD: Superoxide Dismutase; GSH: glutathione; GPX: glutathione peroxidase, Vit A: Vitamin A; Vit C: Vitamin C; Vit E: Vitamin E; TAC: Total Antioxidant Capacity; HPLC-FL: High liquid chromatography coupled to fluorescence detector. In parenthesis are indicated excitation and emission wavelengths; TEP: 1,1,3,3-tetraethoxypropane; TBA: Thiobarbituric acid; FL: Fluorescence spectrophotometry; Vis: Visible spectrophotometry; RBC: Red blood cells; PBS: Phosphate buffer saline.

placenta were included in the meta-analysis. In addition, the authors of the studies that did not have results or did not have the units of measurement were contacted by email. The studies for which we did not have access to the above data were not included in the meta-analysis.

Statistical analyses were performed in Review Manager 5.4 and STATA 15.1. All statistical analyses were performed using the standardized mean difference (SMD) methodology. The random-effects model meta-analyses were considered due to the diversity of methods, differences in the biological samples used, and the status of the patients. The heterogeneity between studies was assessed using the I^2 statistic. Variation in effect sizes across studies was evaluated using Tau^2. Sensitivity analysis was performed by eliminating each study one by one and all the combinations of studies grouping the studies of each biomarker (MDA, 8-isop and SOD) in maternal plasma, placenta and umbilical cord according to 1) type of study, 2) quality of the studies, 3) method of biomarker analysis, 4) timing of maternal plasma sampling (the same was done for heterogeneity analysis). Significance was defined as $p < 0.10$ in Egger's test, and the significance of the other statistical tests was defined as $p < 0.05$. All comparisons were bilateral, and, when applicable, 95 % confidence intervals (CI) are described.

4. Results

4.1. Study selection

A total of 842 studies were retrieved (341 PubMed/MEDLINE and 501 Web of Science). Studies with incomplete texts, those that did not meet the inclusion criteria, or that were duplicated, were excluded. Applying these restrictions resulted in 69 articles that were analyzed for full-text eligibility, leading to the exclusion of 41 for not meeting the above criteria. With this search strategy, 28 articles were included in the systematic review. However, for the meta-analysis, only 20 of these 28 articles were included, as the remaining 8 did not provide values for oxidative stress markers or did not measure MDA or 8-isop (Fig. 1).

4.2. Study characteristics

Clinical data of oxidative stress and antioxidant enzyme biomarkers (reported in the selected 28 articles) were classified according to the origin of the samples: the blood of pregnant women and umbilical cord and placental tissue; Tables 3–5, respectively. The selected studies were published between 1998 and 2021. Of them, 21 were case-controls, 3 were cross-sectional, and 4 were cohort design. The body mass index (BMI) of pregnant women was shown to be highly variable, and 4 studies did not report the nutritional status of pregnant women. The sample was collected between the second and third trimesters of pregnancy or at delivery.

4.3. Risk of bias and quality of included studies

The Analysis of publication bias was carried out using funnel symmetry plot for MDA, 8-isoprostanes, and SOD (Fig. 2), accompanied by Egger's regression test, which highlights that there is a type of publication bias; MDA ([95 % CI] = [2.48, −10.08], p = 0.002); 8-isop ([95 % CI] = [12.16–22.24], p = 0.000). However, the Egger test was positive for SOD ([95 % CI] = [−23.32–15.77, p = 0.674), and no publication bias was observed. The quality of the evidence was evaluated using the NOS scale. All studies were considered of moderate quality and retained for the final systematic review and meta-analysis.

4.4. Synthesis of results

After analyzing the methodology of the selected papers, specifically the analytical methods used for the biomarkers, 20 articles were included in the meta-analysis. For analysis purposes, when possible, the units of measurement for biomarkers were standardized for the meta-analysis. However, when standardization was not possible, those data were excluded from the meta-analysis. Fifteen studies included in the meta-analysis reported values of MDA, four of 8-isop, and eight presented data of SOD activity.

Pregnant women with GDM had higher levels of MDA in plasma and

Table 5
Oxidative stress biomarkers and antioxidant enzymes in the placenta of GDM.

Oxidative stress biomarkers in placental tissue

References	Year of publication	Study design	#case/ control	BMI (Kg/m^2)[a]		Biomarkers	Results[a]		Determination
				GDM	Control		GDM	Control	
Kinalski et al. [62]	2001	Case control	13/17	NR	NR	MDA nmol/mg	1.7 ± 0.3	0.6 ± 0.2[a]	Commercial kit (Bioxytech, France)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	MDA nmol/mg	7.8 ± 1.7	5.4 ± 1.7[a]	Commercial kit (colorimetric method)
Ramirez -Emiliano et al. [49]	2017	Case and control	12/12	32.7 ± 5.3	32.7 ± 5.2	TBARS/MDA nmol/mg)	1.6 ± 0.3	3.8 ± 0.4[a]	Not specified
Manoharan et al. [64]	2019	Cross-sectional	40/40	22.1 ± 2.6	22.2 ± 1.0	MDA µmol/mg of protein	1.1 ± 0.3	0.6 ± 0.1[a]	Visible (535 nm) Calibration curve, TEP method
Coughlan et al. [59]	2004	Case and control	24/25	29.9 ± 9.1	24.4 ± 4.1[a]	8-isop ng/mg prot.	1.7 ± 0.7	0.7 ± 0.2[a]	Immunoassay kit (Cayman Chemical Company, Ann Arbor, MI, USA)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	8-isop ng/mg prot.	5.1 ± 1.7	2.5 ± 1.0[a]	Commercial kit (BlueGene Biotech, Shanghai, China)
Pustovrh et al. [50]	2000	Case and control	10/10	NR	NR	Lipid peroxidation (nmol/mg)	1.8 ± 0.3	1.0 ± 0.1	Spectrophotometry
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	LPO (ng/mg)	12.5 ± 3.4	12.4 ± 3.9	Commercial kit (BlueGene Biotech, Shanghai, China)
Qiu et al. [51]	2013	Case and control	19/21	28.7 ± 6.8	25.9 ± 7.2	8-OHdG (ng/µg DNA	0.3 ± 0.1	0.3 ± 0.1	New 8-OHdG Check Enzyme-Linked Immunosorbent Assay Kit.
Coughlan et al. [59]	2004	Case and control	24/25	29.9 ± 9.1	24.4 ± 4.1[a]	CP nmol/mg prot	0.2 ± 0.2	0.1 ± 0.01[a]	Immunoassay (Zenith Technology, Dunedin, New Zealand)
Ramirez-Emiliano et al. [49]	2017	Case and control	12/12	32.7 ± 5.3	32.7 ± 5.2	CP ng/mg prot.	586.4 ± 8	1119.0 ± 249.5[a]	Absrobance of the carbonyl-DNPH adduct Calibration curve with carbonyl-DNPH mix (SUPELCO, Bellefonte, PA, USA)

Antioxidant biomarkers in placental tissue

Authors	Years of publication	studio design	#case/ control	BMI (Kg/m^2)[a]		Biomarkers	Result[a]		Determination
				DMG	Control		DMG	Control	
Pustovrh et al. [50]	2000	Case and control	10/10	NR	NR	SOD U/mg	11.6 ± 0.3	11.8 ± 0.3	Colorimetry X/XO, NBT-Formazan assay
Kinalski et al. [62]	2001	Case and control	13/17	NR	NR	SOD U/mg	1.6 ± 0.5	3.1 ± 0.3[a]	Commercial kit ((Bioxytech, France)
Coughlan et al. [59]	2004	Case and control	24/25	29.9 ± 9.1	24.4 ± 4.1[a]	SOD U/mg	1.8 ± 0.1	1.6 ± 0.1[a]	Commercial kit (Randox,(Crumlin, Northern Ireland, UK)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	SOD U/mg	42.2 ± 14.5	72.8 ± 15.1[a]	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Coughlan et al. [59]	2004	Case and control	24/25	29.9 ± 9.1	24.4 ± 4.1[a]	GPX	NE	NE	Commercial kit (Randox Laboratories)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	GPX U/mg	475.5 ± 126.9	520.7 ± 157.5	Colorimetry Commercial kit (Nanjing Jiancheng bioengineering institute, China)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	Vit C µg/mg	4.3 ± 0.8	4.4 ± 0.8	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	Vit E µg/mg	10.3 ± 1.9	10.5 ± 1.5	Colorimetry Commercial kit (Nanjing Jiancheng Bioengineering Institute, China)
Kinalski et al. [62]	2001	Case and control	13/17	NR	NR	GSH µmol/l/mg	16.1 ± 1.9	16.3 ± 1.2	Colorimetry (Bioxytech LPO-586 and Bioxytech GSH-400; Oxis International, France).
Shang et al. [20]	2015	Case control	28/40	28.5 ± 2.6	27.6 ± 2.8	TAC U/mg	3.8 ± 0.6	4.7 ± 0.8[a]	Commercial kit (BlueGene Biotech, Shanghai, China)
Manoharan et al. [64]	2019	Cross-sectional	40/40	22.1 ± 2.6	22.2 ± 1.0	TAC µmol/mg	5.5 ± 1.9	10.6 ± 3.2[a]	Commercial kit (Bioassay Systems, Hayward, CA) Reduction of Cu^{2+}

[a] Statistical significance $p > 0.05$; Values are Mean ± SD or Mean[95 %CI]. Abbreviations: NS: Not Specified; NR: Not Registered; NS: Not Significant; BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; MDA: Malondialdehyde; 8-isop: 8-isoprostanes; PC: Carbonylated Proteins; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; LPO: Lipid peroxides; TBARS: Thiobarbituric acid reactive substances; SOD: Superoxide Dismutase; GSH: Glutathione; GPX: Glutathione peroxidase, Vit A: Vitamin A, Vit C: Vitamin C, Vit E: Vitamin E; TAC: Total Antioxidant Capacity; HPLC-FL: High liquid chromatography coupled to fluorescence detector. In parenthesis are indicated excitation and emission wavelengths; TEP: 1,1,3,3-tetraethoxypropane; TBA: Thiobarbituric acid, FL: Fluorescence spectrophotometry; Vis: Visible spectrophotometry; RBC: Red blood cells; PBS: Phosphate buffer saline.

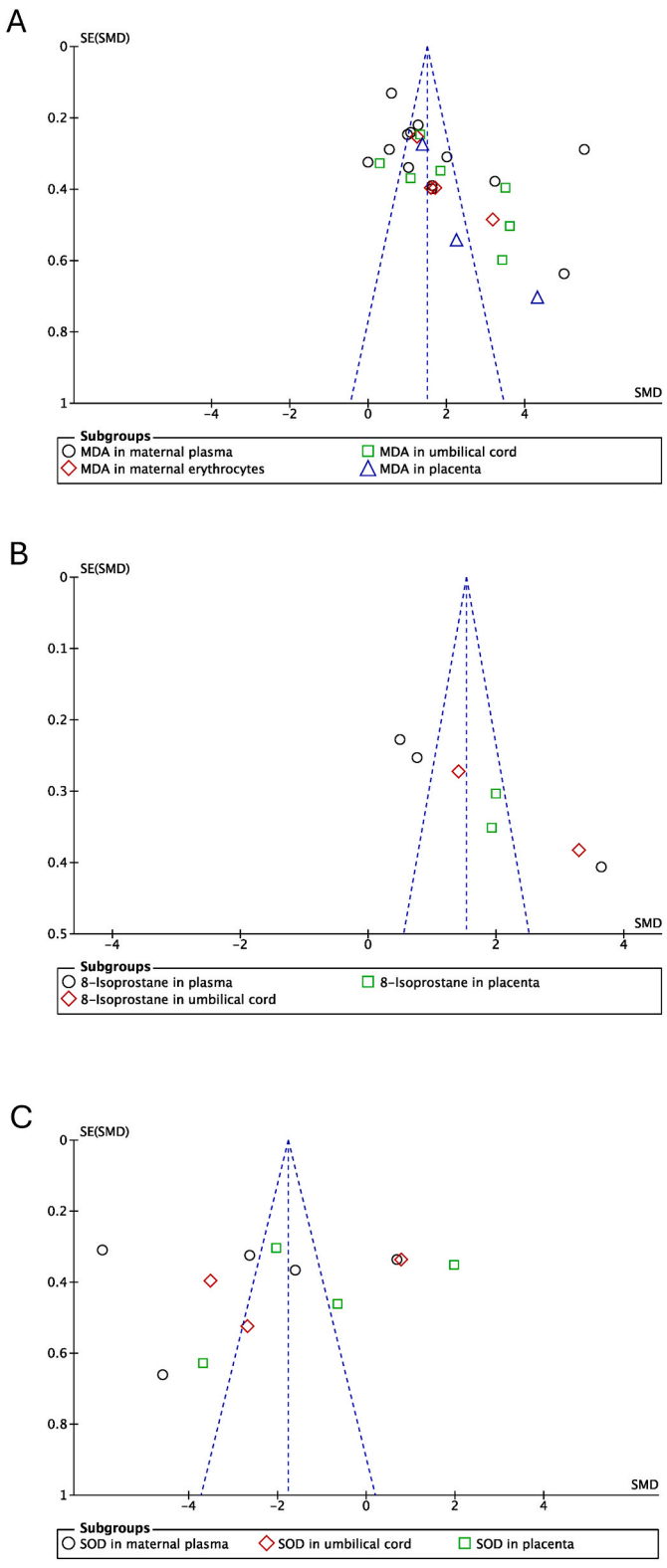

Fig. 2. Funnel plot showing the publication bias of studies. **A**, MDA. **B**, 8-isop. **C**, SOD. Small studies with larger effect sizes are shown on the lower right side of the plot.

erythrocytes, and also where higher in the umbilical cord and placenta (SMD [95 % CI] = 1.85 [1.06, 2.64], Z = 4.60, p < 0.00001; Tau^2 = 1.99, I^2 = 96 %, p < 0.00001); SMD [95 % CI] = 1.87 [1.12, 2.61], Z = 4.90, p < 0.00001; Tau^2 = 0.43, I^2 = 76 %, p = 0.006; SMD [95 % CI] = 2.10 [1.19, 3.02], Z = 4.50, p < 0.00001; Tau^2 = 1.37, I^2 = 91 %, p < 0.00001; SMD [95 % CI] = 2.55 [0.99, 4.10], Z = 3.22, p = 0.001; Tau^2 = 1.61, I^2 = 87 %, p = 0.0004, respectively) compared to non-GDM women (Fig. 3). At a global level in the maternal and fetoplacental unit, a significant increase in MDA was also observed (SMD [95 % CI] = 1.99 [1.51, 2.48], Z = 8.04, p < 0.00001; Tau^2 = 1.51, I^2 = 94 %, p < 0.00001) (Fig. 3). Despite showing higher levels in pregnant women with GDM, 8-isop did not show a significant difference when compared with controls (SMD [95 % CI] = 1.60 [0.02, 3.17], Z = 1.99, p = 0.05; Tau^2 = 1.84, I^2 = 96 %, p < 0.00001). Similarly, increased levels of 8-isop were observed in umbilical cord blood (SMD [95 % CI] = 2.34 [0.05, 4.18], Z = 2.50, p = 0.01; Tau^2 = 1.65, I^2 = 94 %, p < 0.0001), and placenta tissue (SMD [95 % CI] = 1.97 [1.52, 2.42], Z = 8.58, p < 0.00001; Tau^2 = 0.00, I^2 = 0 %, p = 0.89) of women with GDM. A similar pattern was evidenced globally in the maternal-fetoplacental unit (SMD [95 % CI] = 1.90 [0.08, 2.72], Z = 4.52, p < 0.00001; Tau^2 = 1.14, I^2 = 93 %, p < 0.00001) (Fig. 4).

In maternal plasma, meta-analysis showed a significant decrease in SOD activity (SMD [95 %CI] = −2.80 [−5.23, −0.36], Z = 2.25, p = 0.02; Tau^2 = 7.56, I^2 = 98 %, p < 0.00001) (Fig. 5). Nevertheless, compared with control groups, such decrease was not observed in umbilical cord blood, SOD (SMD [95 % CI] = −1.79 [−4.66, 1.07], Z = 1.23, p = 0.22; Tau^2 = 6.23, I^2 = 97 %, p < 0.00001) and placenta tissue (SMD [95 % CI] = −1.07 [−3.37, 1.24], Z = 0.91, p = 0.36; Tau^2 = 5.31, I^2 = 97 %, p < 0.00001) of GDM women. Contrarily, a significant global decrease of SOD levels was observed in the fetoplacental maternal unit (SMD [95 %CI] = −1.97 [−3.38, 0.55], Z = 2.73, p = 0.006; Tau^2 = 6.07, I^2 = 98 %, p < 0.00001).

4.4.1. *Sensitivity analysis*

The sensitivity analysis was performed by grouping the studies of each biomarker (MDA, 8-isop and SOD) in maternal plasma, placenta, and umbilical cord according to 1) type of study, 2) quality of the studies, 3) biomarker analysis method. The effects and heterogeneity remained stable with the omission of different studies according to each grouping. However, when grouped by time of maternal plasma sampling (second trimester, third trimester, both or at the time of delivery), it was observed that MDA in maternal plasma had a greater significant effect and low heterogeneity (SMD [95 % CI] = 1.17 [0.93, 1.40], Z = 9.76, p=<0.00001; Tau2 = 0.00, I2 = 0 %, p = 0.70) when grouped into those who took the sample in the third trimester. But the overall effect remained stable.

4.4.2. *Heterogeneity analysis*

High heterogeneity was determined for the reported levels of MDA in samples of maternal plasma and erythrocytes, umbilical cord blood, and placental tissue; I^2 = 96 %, I^2 = 76 %, I^2 = 91 % and I^2 = 87 %, respectively. Levels of 8-isop and SOD activity also showed high heterogenicity; for 8-isop in maternal plasma and umbilical cord blood, I2 = 96 % and I2 = 94 %, respectively, and for SOD in maternal plasma, umbilical cord, and placenta; I^2 = 98 %, I^2 = 97 % and I^2 = 97 %, respectively. The high heterogeneity in these analyses could be due to differences in the samples, variations between patients, or their nutritional status. Additionally, variability derived from the pre-analytical and analytical conditions, methods and experimental procedures employed can also contribute to the heterogeneity in the data.

5. Discussion

5.1. *Main findings*

This systematic review and meta-analysis investigated the association between GDM and the levels of various biomarkers of oxidative stress, as well as the activity of antioxidant enzymes in maternal plasma, blood of the umbilical cord, and placental tissue. Meta-analysis of published data evidenced a significant increase in MDA and 8-isop in the feto-placental and maternal compartment, suggesting increased levels of

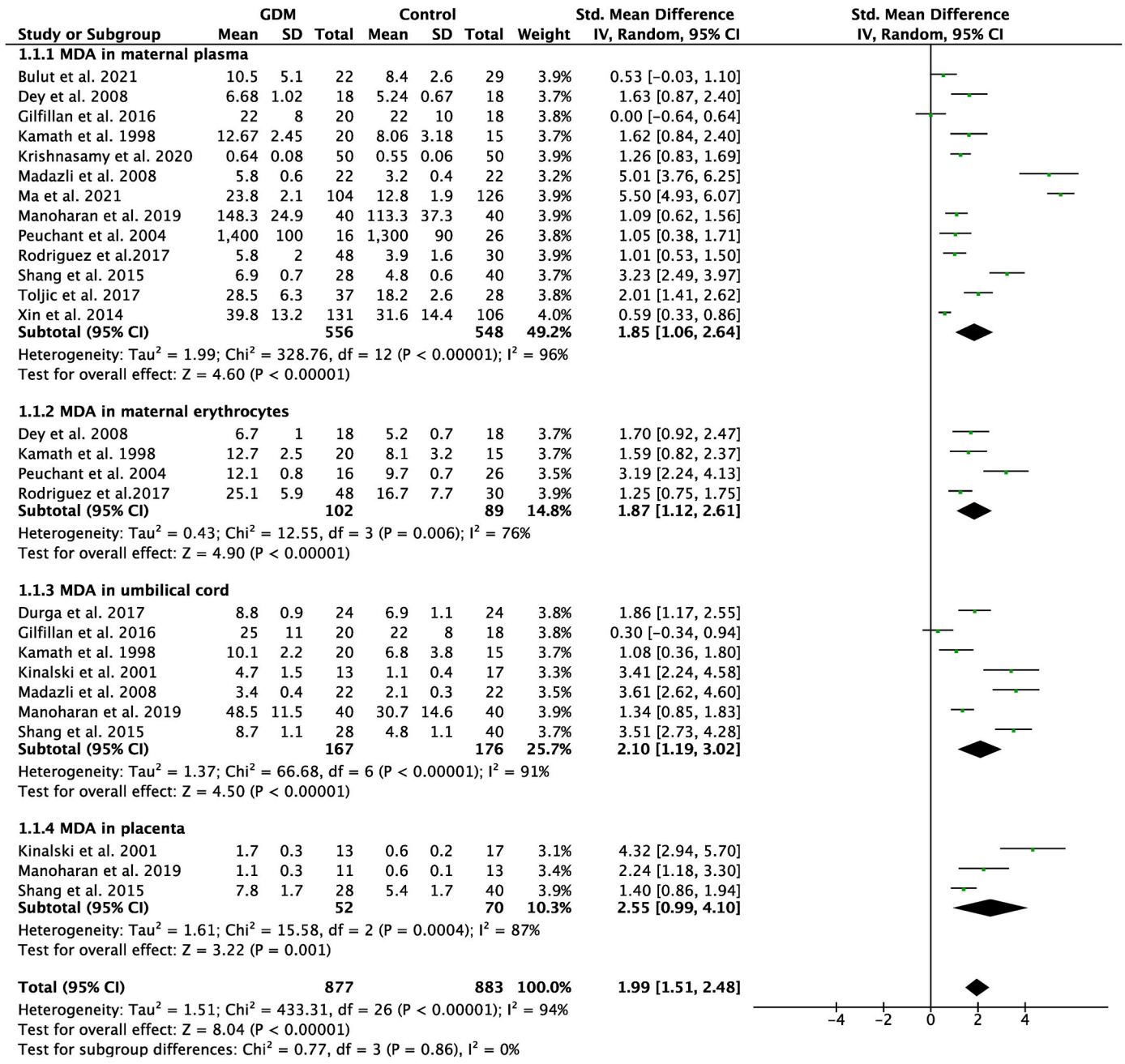

Fig. 3. Forest plot of the standardized mean difference in MDA concentration (mol/L) by measurement site in pregnant women, umbilical cord, and placenta of women with GDM and healthy controls. Random-effects model results are plotted in the black diamonds. Solid lines represent a 95 % confidence interval.

oxidative stress in pregnant women with GDM. Also, compared to controls, a significant decrease in SOD activity was observed in maternal plasma. However, in the placental tissue and umbilical cord blood of pregnant women with GDM, this enzyme's activity did not differ significantly from that of controls. However, these conclusions are limited by the high heterogeneity of the meta-analysis, which may be of clinical and methodological origin.

5.2. *Comparison with existing literature*

Pregnancy is a condition where a physiological increase of oxidative stress is observed, playing an essential role in implantation, embryo development, placental function, and fetal growth [52,53]. Nonetheless, under GDM conditions (and other pathologies unrelated to pregnancy), an excessive increase in the production of oxidants is induced, which could be accompanied by decreased levels of the antioxidant defense [7,19]. This scenario results in exacerbated oxidative stress and nonspecific damage to biomacromolecules [33]. In this context, this meta-analysis evidenced an increase in maternal oxidative stress during the second and third trimesters of pregnancy, as evidenced by measurements of MDA, which significantly increased in women with GDM. The latter may be due to impaired glucose tolerance and insulin resistance in patients with GDM, leading to maternal hyperglycemia. The latter condition could be directly involved in forming oxidants, leading to increased levels of oxidative stress in GDM [17,18,33], and the related pathological complications in the mother and newborn, affecting the placental function. Elevated glucose and lipid levels in overweight pregnant women with GDM modulate oxidative stress, suggesting that these markers could be potential biomarkers for the early diagnosis of GDM; however, further evidence is needed [54]. Additionally, high maternal

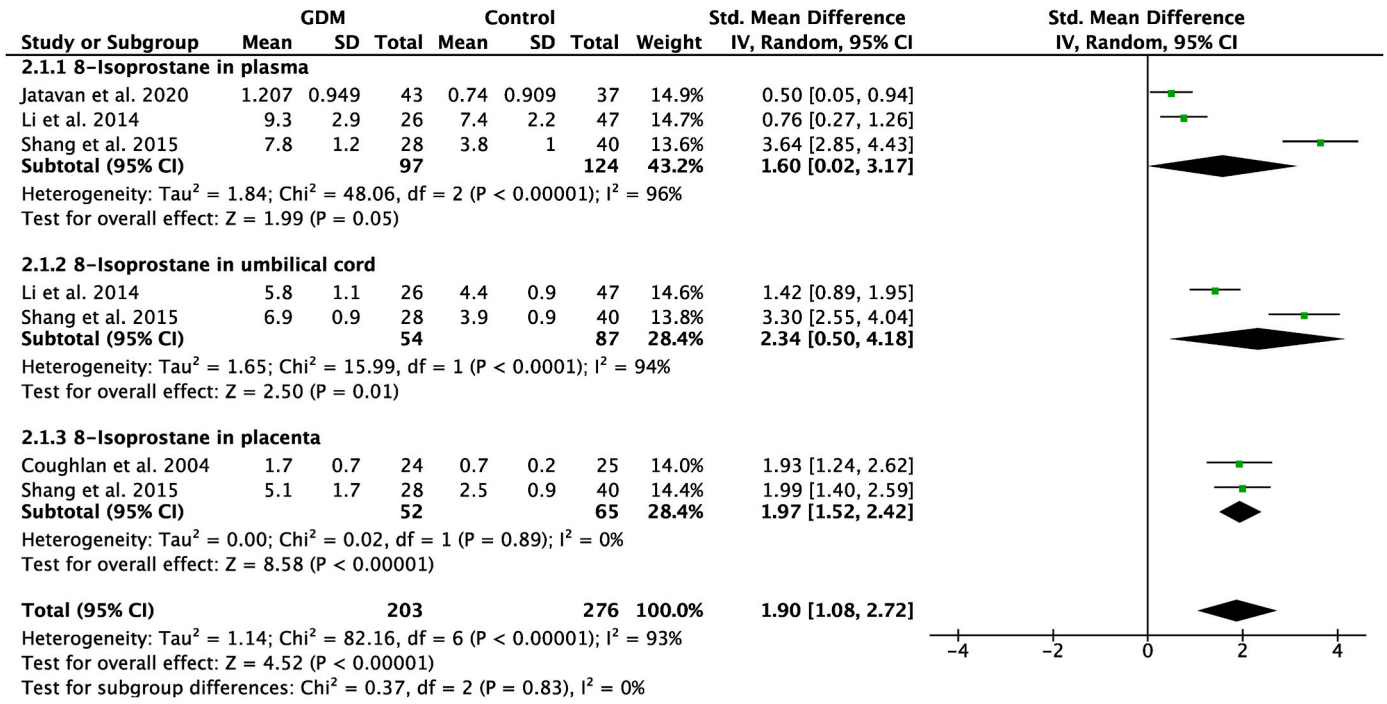

Fig. 4. Forest plot of standardized mean difference in the concentration of 8-isoprostane (ng/mL or ng/mg prot) subdivided by measurement in pregnant women, umbilical cord, and placenta of women with GDM and healthy controls. Random-effects model results are plotted in the black diamonds. Solid lines represent a 95 % confidence interval.

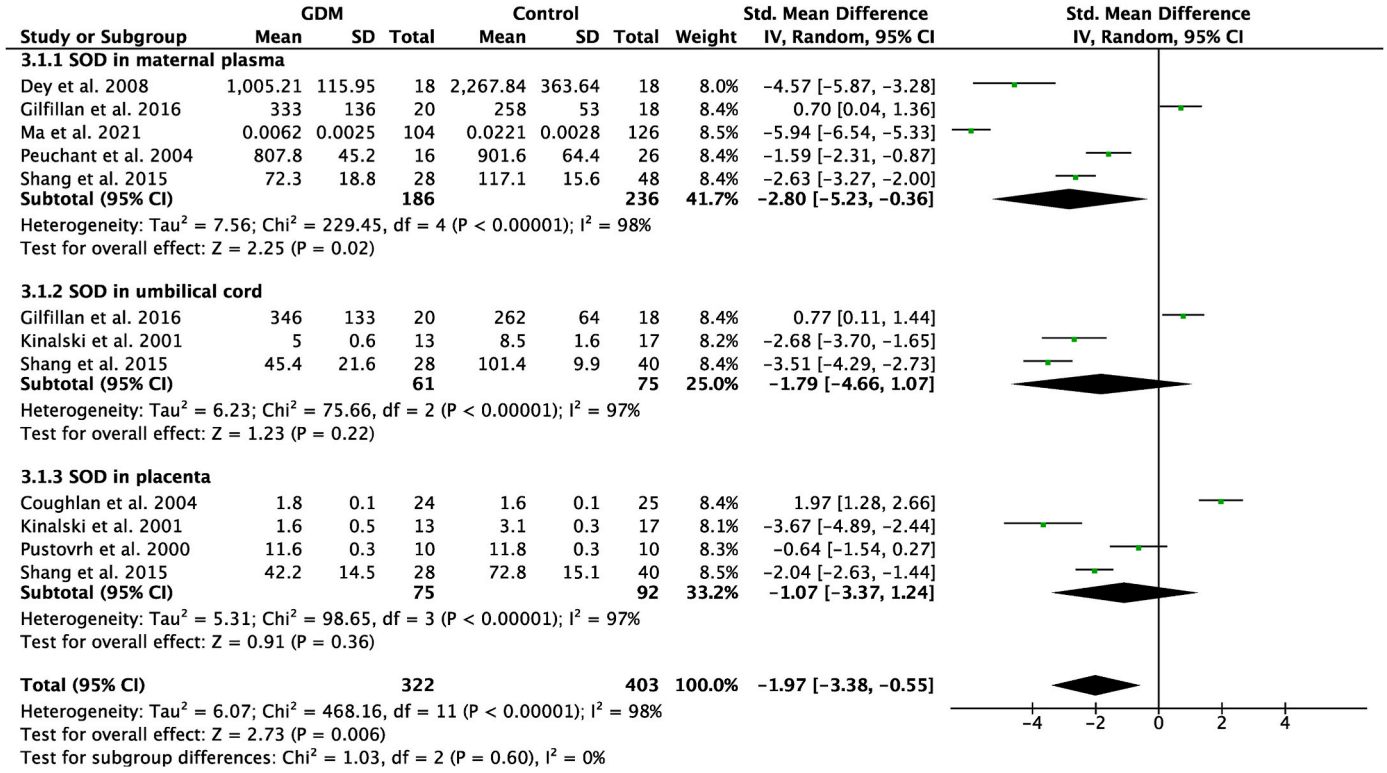

Fig. 5. Forest plot of standardized mean difference in the concentration of SOD (U/mL o U/g Hb) subdivided by measurement in pregnant women, umbilical cord, and placenta of women with GDM and healthy controls. Random-effects model results are plotted in the black diamonds. Solid lines represent a 95 % confidence interval.

glucose levels lead to increased placental glucose transport and elevated fetal insulin levels. These fetal metabolic adaptations are associated with increased fetal adiposity and the early programming of cardiovascular and metabolic diseases in the offspring of women with GDM [55]. It should be noted that the increased levels of oxidative stress in pregnant women with GDM are unrelated to their BMI, since studies including

women with different BMI evidence a significant increase in biomarkers of oxidative stress in maternal plasma, umbilical cord blood and placental tissue [56–59]. These results suggest that there is no correlation between increased levels of oxidative stress, which are consistently observed in the circulation of women with GDM, and maternal BMI.

It is well established that GDM is associated with increased fetal growth, implying increased cell proliferation and metabolism [7,8]. During pregnancy higher levels of biomarkers of oxidative stress are generated [60] concomitantly with the high fetal growth rate in GDM, could explain (at least partially) the higher levels of oxidative stress detected in the umbilical cord blood of GDM pregnancies, as evidenced by elevated MDA, 8-isop, Total Oxidative State (TOS), Oxidative Stress Index (OSI) and comet assay indexes [20,32,56,57,61–64]. In parallel with the latter, decreased levels of the activity of SOD, GPX and TAC [20,62,64,65], suggest that the fetuses of GDM women are exposed to high levels of oxidative stress, with important implications for fetal well-being, probably involving biochemical alterations in the fetus, especially in the metabolic complications of diabetes [20].

An increase in oxidative stress biomarkers was also evidenced in the placental tissue of women with GDM. Although oxidative stress plays an essential immunoregulatory role during pregnancy and is required for placental development, excessive production can hamper normal placental functions [60]. Additionally, it has been shown that the placentas of pregnant women with GDM are characterized by a higher expression of antioxidant genes [64]. In the placenta of GDM women, oxidants can activate the Nrf2 pathway resulting in increased expression of SOD and CAT enzymes [20]. These data suggest that the GDM placenta may be better adapted to the excess of maternal oxidants and the consequent oxidative challenge, protecting the nutritional function of the placenta and, eventually, the fetus from the excess of maternally-derived oxidants. Studies show conflicting results regarding the levels of antioxidant enzymes in GDM placentas; while several studies reported decreased SOD activity [20,62,66,67], others reported increased values [59,65]. These contradictory results could be related to the metabolic severity of GDM and other anthropometric or metabolic variables in the study populations [64].

As presented in Tables 1–3, MDA was the most measured biomarker, followed by 8-isop [20]. Both biomarkers were significantly increased in maternal plasma, umbilical cord blood and placental tissue of pregnant women with GDM, as reported by Shang et al. [20] Surprisingly, only two studies have reported biomarkers of oxidative damage and antioxidant defense in the triad mother-placenta-newborn, with these showing an interesting positive correlation between MDA and blood glucose concentration [20,64].

In summary, the above-described analyses suggest that new studies are needed to fill the knowledge gap regarding redox status biomarkers in pregnant women with an accurate diagnosis of GDM. Furthermore, new advances in the field are necessary to understand the fundamental mechanisms underlying the relationship between GDM and oxidative stress.

5.3. Strengths and limitations

Comparison of the herein-studied clinical data is a challenging task. This is likely related to the observed differences in studies regarding clinical and analytical issues. In the former case, clinical matters such as different diagnostic criteria for GDM, incomplete (or non-existent) clinical data, various sites of sample collection (e.g., different locations in the placenta), and differences in the trimester of pregnancy were observed. On the other hand, analytical differences in the biomarkers employed, including analytical methodologies, sample treatments, and the units used to express the results, were detected. These differences limit the inclusion of studies in the meta-analysis and would explain the high heterogeneity observed in the included studies. Notably, studies employing MDA as a biomarker would be strongly affected by several shortcomings of the assay. As mentioned above, the production of MDA has been linked to the oxidation and peroxidation of lipids. However, this product is also generated from protein oxidative damage, suggesting a low specificity [68]. In addition, MDA reacts with nucleophiles, has low stability in aqueous media and lacks a chromophore in the visible region, making its analytical determination difficult in biological samples. For these reasons, the derivatization of MDA using tiobarbituric acid (TBA) to form an MDA-TBA_2 adduct is one of the most commonly employed strategies [68,69]. Under acidic media, this adduct exhibits high absorptivity at 432 nm and fluorescence, enabling its determination using appropriate standards by visible spectrophotometry or liquid chromatography coupled to UV–vis or fluorescence detection. Unfortunately, in biological samples, other products also react with TBA, resulting in false-positive results in this assay. In addition, the analytical methodology includes several steps, some of which correspond to drastic experimental conditions (e.g., incubation at high temperatures), which may mediate the oxidation of samples and explain the high heterogeneity of results [24,68]. There are oxidative stress biomarkers that were not included in this meta-analysis due to a lack of clinical studies in GDM where they were used.

6. Conclusions and implications

Clinical studies evidenced a strong link between GDM and the level of MDA, 8-isop and SOD in samples of plasma of pregnant women with GDM. These results reflect a significant increase in the levels of oxidative damage in the maternal unit and a decrease in the antioxidant capacity of pregnant women; however, such a connection was not evidenced in the placental tissue and umbilical cord. The increased biomarkers of oxidative stress in women with GDM could be associated with adverse perinatal outcomes such as fetal mortality, preeclampsia and intrauterine growth restriction, macrosomia, neonatal malformations, and hypoglycemia [17,70]. Elevated glucose levels in overweight pregnant women with GDM modulate oxidative stress, this suggests that these markers could be potential biomarkers for the early diagnosis of GDM, although further evidence is needed. Several factors related to the design of the clinical studies, such as characteristics of the patients, type of samples and biomarkers, as well as shortcomings of the analytical methodologies employed, limited a more comprehensive covering of clinical studies and probably led to the high heterogenicity of data, as supported by the meta-analysis. Therefore, new strategies for better standardization of this kind of intervention are needed. Considering the association between oxidative stress and the complications and consequences of GDM, studies to get new insights about the regulation of the systemic redox status in pregnant women with GDM are an essential objective in treating this high-risk and prevalent perinatal condition.

CRediT authorship contribution statement

Karina Etchegaray-Armijo: Writing – original draft, Formal analysis, Data curation. **Edson Bustos-Arriagada:** Data curation. **Deborah Navarro-Rosenblatt:** Methodology. **Claudio Vera:** Methodology. **María Luisa Garmendia:** Writing – review & editing, Formal analysis, Conceptualization. **Luis Sobrevia:** Writing – review & editing, Writing – original draft, Validation. **Camilo López-Alarcón:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Paola Casanello:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Registration

PROSPERO registration number CRD42024498846.

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Declaration of competing interest

None.

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