OBSTETRICS

Celiac disease and obstetric complications: a systematic review and metaanalysis

Gabriele Saccone, MD; Vincenzo Berghella, MD; Laura Sarno, MD; Giuseppe M. Maruotti, MD, PhD; Irene Cetin, MD; Luigi Greco, MD; Ali S. Khashan, PhD; Fergus McCarthy, MD, PhD; Domenico Martinelli, MD; Francesca Fortunato, MD; Pasquale Martinelli, MD

Celiac disease is a genetically determined autoimmune condition, with an estimated worldwide prevalence of approximately 1%.[1] It usually is diagnosed by duodenal biopsy that is performed at the time of endoscopy.[1] Celiac disease is induced by the ingestion of gluten, and the only treatment available is the elimination of gluten from the diet.[1]

Once considered a gastrointestinal disease of childhood, celiac disease is now recognized as a systemic disease. The most frequent signs and symptoms are weight loss and chronic diarrhea.[1] Complications include disorders of fertility and pregnancy complications.[1,2]

From the Department of Neuroscience, Reproductive Sciences and Dentistry (Drs Saccone, Sarno, Maruotti, and P. Martinelli) and the Department of Translational Medicine, School of Medicine (Dr Greco), School of Medicine, University of Naples Federico II, Naples, Italy; the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA (Dr Berghella); the Department of Biomedical and Clinical Sciences, School of Medicine, University of Milan, Milan, Italy (Dr Cetin); the Department of Epidemiology and Public Health (Dr Khashan) and the Irish Centre for Fetal and Neonatal Translational Research (INFANT) (Drs Khashan and McCarthy), University College Cork, Cork, Ireland; the Division of Women's Health, Women's Health Academic Centre, King's College, London, UK (Dr McCarthy); the Department of Medical and Surgical Sciences, School of Medicine, University of Foggia, Foggia, Italy (Drs D. Martinelli and Fortunato).

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Corresponding author: Pasquale Martinelli, MD. martinel@unina.it

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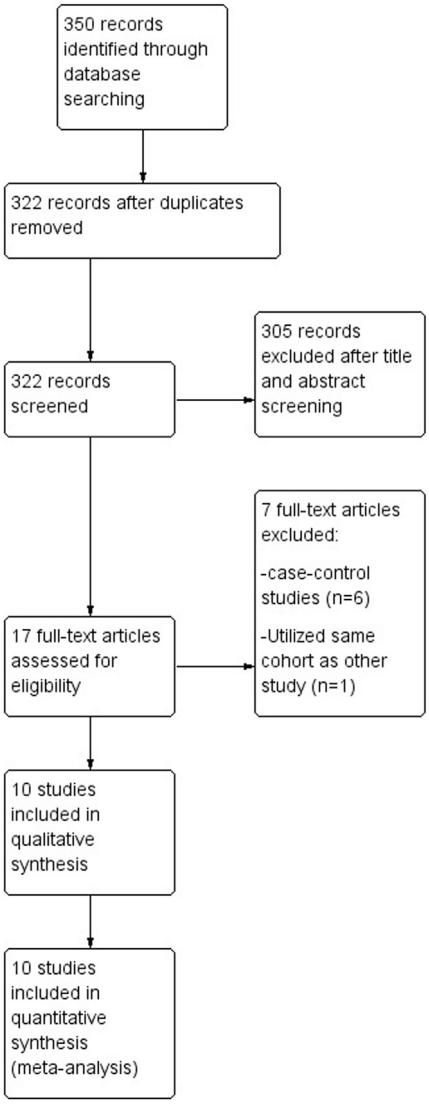
The aim of this metaanalysis was to evaluate the risk of the development of obstetric complications in women with celiac disease. We searched electronic databases from their inception until February 2015. We included all cohort studies that reported the incidence of obstetric complications in women with celiac disease compared with women without celiac disease (ie, control group). Studies without a control group and case-control studies were excluded. The primary outcome was defined a priori and was the incidence of a composite of obstetric complications that included intrauterine growth restriction, small for gestational age, low birthweight, preeclampsia and preterm birth. Secondary outcomes included the incidence of preterm birth, intrauterine growth restriction, stillbirth, preeclampsia, small for gestational age, and low birthweight. The review was registered with PROSPERO (CRD42015017263) before data extraction. All authors were contacted to obtain the original databases and perform individual participant data metaanalysis. Primary and secondary outcomes were assessed in the aggregate data analysis and in the individual participant data metaanalysis. We included 10 cohort studies (4,844,555 women) in this metaanalysis. Four authors provided the entire databases for the individual participant data analysis. Because none of the included studies stratified data for the primary outcome (ie, composite outcome), the assessment of this outcome for the aggregate analysis was not feasible. Aggregate data analysis showed that, compared with women in the control group, women with celiac disease (both treated and untreated) had a significantly higher risk of the development of preterm birth (adjusted odds ratio, 1.35; 95% confidence interval, 1.09—1.66), intrauterine growth restriction (odds ratio, 2.48; 95% confidence interval, 1.32—4.67), stillbirth (odds ratio, 4.84; 95% confidence interval, 1.08—21.75), low birthweight (odds ratio, 1.63; 95% confidence interval, 1.06—2.51), and small for gestational age (odds ratio, 4.52; 95% confidence interval, 1.02—20.08); no statistically significant difference was found in the incidence of preeclampsia (odds ratio, 2.45; 95% confidence interval, 0.90—6.70). The risk of preterm birth was still significantly higher both in the subgroup analysis of only women with diagnosed and treated celiac disease (odds ratio, 1.26; 95% confidence interval, 1.06—1.48) and in the subgroup analysis of only women with undiagnosed and untreated celiac disease (odds ratio, 2.50; 95% confidence interval; 1.06—5.87). Women with diagnosed and treated celiac disease had a significantly lower risk of the development of preterm birth, compared with undiagnosed and untreated celiac disease (odds ratio, 0.80; 95% confidence interval, 0.64—0.99). The individual participant data metaanalysis showed that women with celiac disease had a significantly higher risk of composite obstetric complications compared with control subjects (odds ratio, 1.51; 95% confidence interval, 1.17—1.94). Our individual participant data concurs with the aggregate analysis for all the secondary outcomes. In summary, women with celiac disease had a significantly higher risk of the development of obstetric complications that included preterm birth, intrauterine growth restriction, stillbirth, low birthweight, and small for gestational age. Since the treatment with gluten-free diet leads to a significant decrease of preterm delivery, physicians should warn these women about the importance of a strict diet to improve obstetric outcomes.

(continued)

Future studies calculating cost-effectiveness of screening for celiac disease during pregnancy, which could be easily performed, economically and noninvasively, are needed. In addition, further studies are required to determine whether women with adverse pregnancy outcomes should be screened for celiac disease, particularly in countries where the prevalence is high.

Key words: celiac disease, metaanalysis, pregnancy, preterm birth, small for gestational age

FIGURE 1
Flow diagram of studies identified in the systematic review



Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) template.

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Women with unexplained infertility or recurrent miscarriage were found to have a significantly higher risk of celiac disease than the general population, maybe because of the nutrient deficiencies and the increased level of serum autoantibodies.[1,2] In 2014 a large epidemiologic study showed an increased risk for malformation among the offspring of mothers or fathers with celiac disease.[3] Moreover, so far, the effect of a gluten-free diet on prevention of celiac disease complications in pregnancy is still a subject of debate.[1]

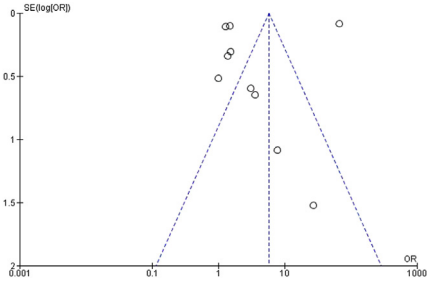
The aim of this metaanalysis was to evaluate the risk of the development of obstetric complications in women with celiac disease.

Methods

Search strategy

This review was performed according to a protocol designed a priori and recommended for systematic review.[4] Electronic databases (MEDLINE, PROSPERO, Scopus, ClinicalTrials.gov, EMBASE, Science direct, the Cochrane Library) were searched from their inception until February 2015 with no limit for language. The following search terms were used: "celiac," "celiac disease," "coeliac," "coeliac disease," "preterm birth," "small for gestational age," "miscarriage," "pregnancy," "premature," "newborn," "low birth weight," "fertility," "preeclampsia," "recurrent," "intrauterine growth restriction," "stillbirth," "pregnancy," "obstetric," "complications," and "spontaneous preterm birth." No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were assessed independently by 2 of the authors (G.S., V.B.). Differences were discussed, and consensus reached.

FIGURE 2
Funnel plot for the assessment of publication bias



Funnel plot for assessing publication bias. The symmetric plot suggested no publication bias.

OR, odds ratio; *SE*, standard error.

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Study selection

We included all cohort studies that reported the incidence of obstetric complications in women with celiac disease compared with women without celiac disease (ie, control group). Studies without a control group and case-control studies were excluded.

Data extraction

Data abstraction was completed by 2 independent investigators (G.S., L.S.). Each investigator independently abstracted data from each study separately. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Disagreements were resolved by consensus with a third reviewer (P.M.). Information on potential confounders that were adjusted for and adjusted risk estimates were collected when available. All authors were contacted to obtain the original databases and perform individual patient-level metaanalysis.

Two reviewers (G.S., V.B.) independently assessed the risk of bias of the included studies via the Methodological Index for Non-Randomized Studies.[5] Seven domains that are related to risk of bias were assessed in each study: (1)

TABLE 1
Characteristics of the included studies

Study	Study location	Study period	Type of study	No. of included women[a]	Confounders adjusted	Outcomes assessed
Sher and Mayberry, 1996[9]	United Kingdom	2005-2006	Prospective cohort	136 (68 vs 68)	None	Miscarriage,[b] stillbirth
Martinelli et al, 2000[10]	Italy	1998-1999	Prospective cohort	218 (12 vs 206)	Maternal age, previous preterm birth, socioeconomic status, smoking	Preterm birth,[b] stillbirth
Greco et al, 2004[11]	Italy	2001-2002	Retrospective cohort	5,076 (79 vs 4,997)	Maternal age, smoking, socio-economic status	Intrauterine growth restriction[b]
Tata et al, 2005[12]	United Kingdom	1987-2002	Retrospective cohort	9,244 (1,521 vs 7,723)	Socio-economic status	Cesarean delivery,[b] stillbirth, preeclampsia, intrauterine growth restriction
Ludvigsson et al, 2005[21]	Sweden	1964-2001	Population-based cohort	2,817,400 (2,071 vs 2,815,329)	Maternal age, parity, nationality	Preterm birth, intrauterine growth restriction, low birthweight[c]
Sheiner et al, 2006[13]	Israel	1988-2002	Retrospective cohort	143,711 (48 vs 143,663)	None	Intrauterine growth restriction,[b] preeclampsia
McCarthy et al, 2009[22]	Ireland	N/R	Retrospective cohort	270 (118 vs 152)	Maternal age, maternal body mass index, gestational age, infant sex and year of birth	Small for gestational age,[b] birthweight
Khashan et al, 2010[23]	Northern Europe	1979-2004	Population-based cohort	1,504,342 (1,451 vs 1,502,891)	Maternal age, parity, paternal age, maternal chronic medical conditions	Preterm birth,[b] small for gestational age
Martinelli et al, 2010[24]	Italy	2008	Prospective cohort	228 (49 vs 179)	None	Intrauterine growth restriction[b]
Abdul Sultan et al, 2014[14]	United Kingdom	1997-2012	Population-based cohort	363,930 (892 vs 363,038)	Body mass index, smoking	Preterm birth, stillbirth, low birthweight, preeclampsia[c]
Total	—	—	—	4,844,555 (6,309 vs 4,838,246)	—	—

N/R, not reported.

[a] Number (N) of included women: total N (N of women with celiac disease vs N of women with no celiac disease); [b] Primary outcome; [c] Primary outcome not reported.

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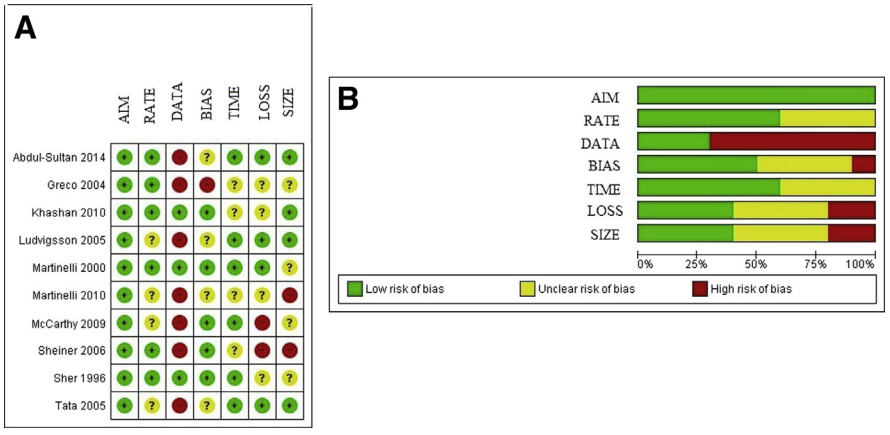
FIGURE 3
Assessment of risk of bias



A, Summary of risk of bias for each study. Definition of terms: *Aim*, clearly stated aim; *Rate*, inclusion of consecutive patients and response rate; *Data*, prospective collection of data; *Bias*, unbiased assessment of study endpoints; *Time*, follow-up time appropriate; *Loss*, loss to follow-up; *Size*, calculation of the study size. Definition of symbols: +, low risk of bias; −, high risk of bias; ?, unclear risk of bias. **B,** Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

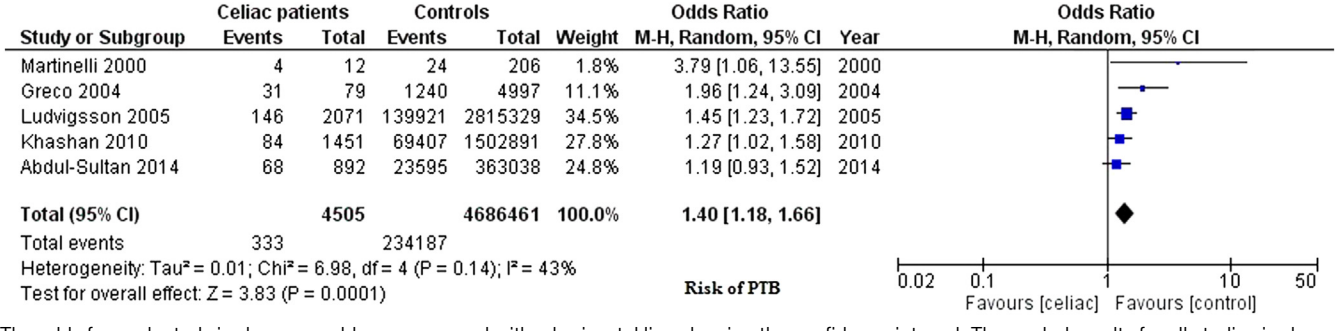
aim (ie, clearly stated aim), (2) rate (ie, inclusion of consecutive patients and response rate), (3) data (ie, prospective collection of data), (4) bias (ie, unbiased assessment of study end points), (5) time (ie, follow-up time appropriate), (6) loss (ie, loss to follow-up), (7) size (ie, calculation of the study size).[5] Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk of bias." Discrepancies were resolved by discussion with a third reviewer (P.M.).

The primary outcome was defined a priori and was the incidence of a composite of obstetric complications that included at least 1 of the following complications: intrauterine growth restriction (IUGR; ie, ultrasound estimated fetal weight <10th percentile for gestational age), small for gestational age (SGA; ie, birthweight <10th percentile for gestational age), low birthweight (LBW; ie, birthweight <2500 g), preeclampsia, and preterm birth (PTB; ie, PTB <37 weeks). Secondary outcomes included the incidence of PTB, IUGR, stillbirth, preeclampsia, SGA and LBW. We planned to assess the incidence of PTB in a subgroup analysis in women with treated and untreated celiac disease. Diagnosed and treated celiac disease thereafter is called, for simplicity, just "treated celiac disease"; and undiagnosed and untreated celiac disease is called, for simplicity, just "untreated celiac disease." Women were classified as having the celiac disease diagnosis and treatment before pregnancy (treated celiac disease) or afterward (untreated celiac disease).

Data analysis

The data analysis was completed independently by 2 authors (G.S., V.B.) with the use of Review Manager software (version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark) and Statistical Package for Social Sciences software (version 19.0; IBM Inc, Armonk, NY). Inconsistencies were discussed by the reviewers, and consensus was reached. Heterogeneity across studies was assessed using the Higgins I^2 test.[4] In case of statistically significant heterogeneity ($I^2 \geq 0\%$), the random effects model of DerSimonian and Laird[4] was used; otherwise, a fixed effect model was performed. The pooled results from the aggregate metaanalysis were reported as odds ratio (OR) with 95% confidence interval (CI). Potential publication

FIGURE 4
Unadjusted estimates forest plot for the risk of preterm birth in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test; *PTB*, preterm birth

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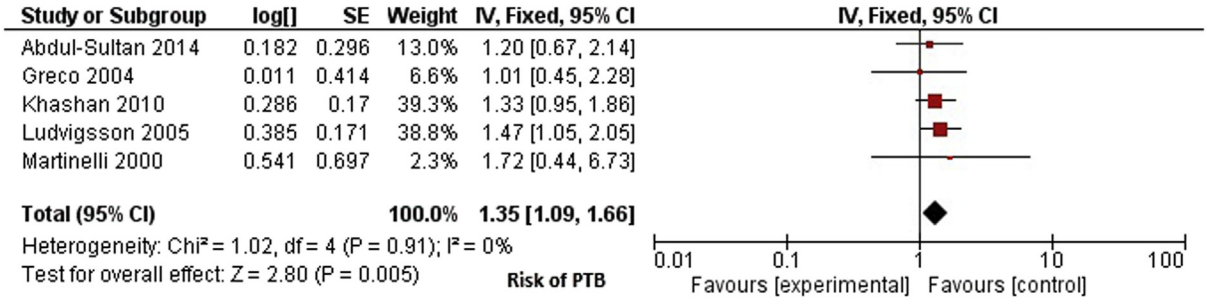
FIGURE 5
Adjusted estimates forest plot for the risk of preterm birth in women with celiac disease



The odds for each study is shown as a red square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *IV*, independent variable; *PTB*, preterm birth; *SE*, standard error

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biases were assessed graphically by the use of the funnel plot and statistically by the use of the Begg's and Egger's tests.[4]

In line with other metaanalyses, no adjustment for risk estimates was made.[4] For studies that reported both unadjusted and adjusted risk for confounders statistically proved, we performed an aggregate data metaanalysis using generic inverse variance method to obtain the adjusted odds ratio (aOR) for the incidence of PTB in the aggregate data analysis.[4,6]

To use the data as best as possible, we also combined the obtained databases to assess an individual patient-level metaanalysis. Primary and secondary outcomes were assessed in both aggregate and patient-level data analysis. We expressed continuous variables as mean with standard deviation and categoric variables as number with percentage. Chi-square test and Fisher's exact test were used for categoric variables, and the Student *t* test or Mann-Whitney test for normally and nonnormally distributed continuous variables, respectively. A probability value $<.05$ was considered statistically significant.

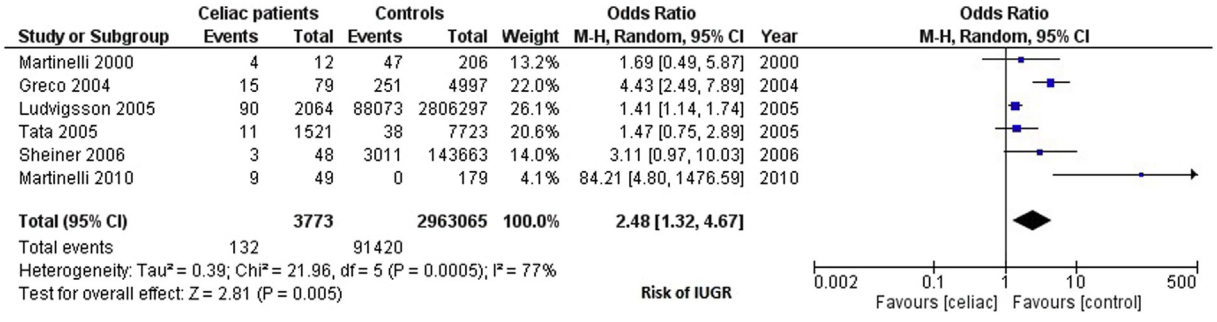
The metaanalysis was reported according to the Preferred Reporting Item for Systematic Reviews and Metaanalyses statement.[7] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42015017263) according to the Preferred Reporting Item for Systematic Reviews and Metaanalyses guidelines for protocols.[8]

Results

Study selection and study characteristics

The flow of study identification is shown in Figure 1. Seventeen full-text articles were assessed for eligibility.[9-25] Seven studies were excluded.[15-20,25] Six studies were excluded because they evaluated the incidence of celiac disease among women with obstetric complications (ie, case-control studies),[15-20] and one study[25] was excluded because it was based on the same cohort as a more recent study.[23]

FIGURE 6
Forest plot for the risk of intrauterine growth restriction (ie, ultrasound estimated fetal weight <10th percentile for gestational age) in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *IUGR*, intrauterine growth restriction; *M-H*, Mantel-Haenszel test

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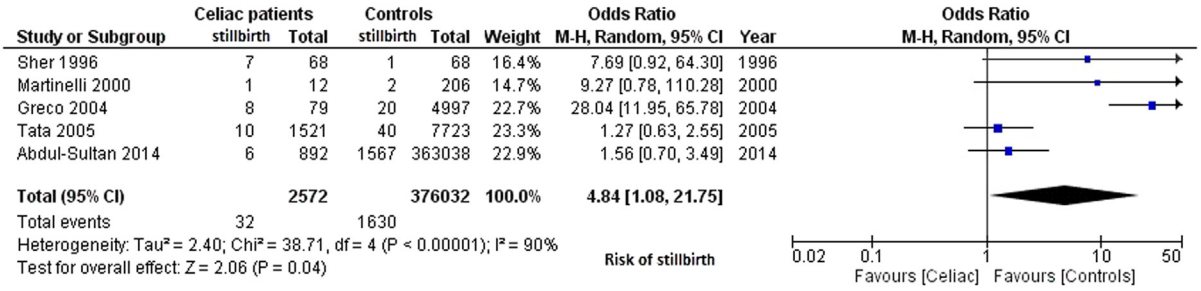
FIGURE 7
Forest plot for the risk of stillbirth in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

Ten cohort studies, which included 4,844,555 women, were analyzed.[9-14,21-24] All studies reported the incidence of obstetric complications in women with celiac disease compared with women without celiac disease (ie, control group). Four studies reported separate analyses and subgroup analysis for women with undiagnosed and untreated celiac disease (ie, untreated celiac disease).[11,14,21,23] In all included studies, a diagnosis of celiac disease was based on either duodenal biopsy or level of serum autoantibodies.

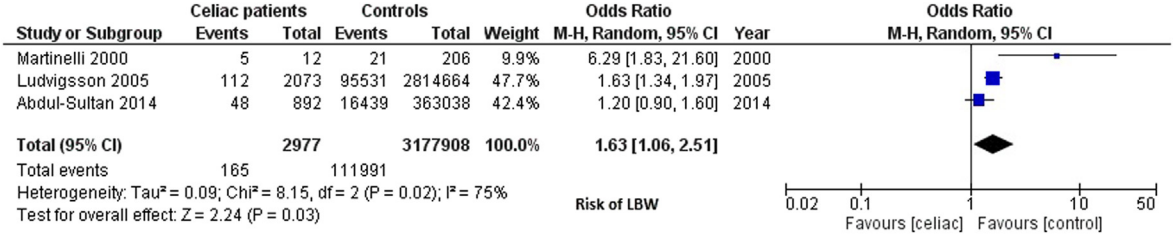
The risk of publication bias was assessed by visual inspection of funnel plot; the symmetric plot suggested no publication bias (Figure 2). Publication bias, which was assessed with the use of Begg's and Egger's tests, showed no significant bias ($P = .19$ and $P = .10$, respectively). Table 1 shows the characteristics of the included studies. Most of them (9 of the 10) originated from Europe. Eight studies included only singleton gestations.[9-11,14,21-24] The quality of the studies included in our metaanalysis was assessed by the Methodological Index for Non-Randomized Studies' tool for assessment of the risk of bias (Figure 3).[4] All studies had low risk of bias in "aim" and most risk in "rate" and in "time." Four of the them were retrospective cohort studies[11-13,22]; 3 studies were prospective[9,10,24]; the other 3 studies were large high-quality population-based cohort studies.[14,21,23] Four authors kindly provided the entire databases from their study to obtain additional and unpublished data and to perform individual patient level metaanalysis.[10,11,22,24]

Synthesis of results

Because that none of the included studies stratified data for the primary outcome (ie, composite outcome), assessment of this outcome for the aggregate data analysis was not feasible.

Compared with the control group, women with celiac disease (both treated and untreated) had a significantly higher risk of the development of PTB (OR, 1.40; 95% CI, 1.18−1.6 [Figure 4]; aOR, 1.35; 95% CI, 1.09−1.66; [Figure 5]), IUGR (OR, 2.48, 95% CI, 1.32−4.67 [Figure 6]), stillbirth (OR, 4.84; 95% CI, 1.08−21.75 [Figure 7]), LBW (OR, 1.63; 95% CI, 1.06−2.51 [Figure 8]), and SGA (OR, 4.52; 95% CI, 1.02−20.08 [Figure 9]); no statistically significant difference was found in the incidence of preeclampsia (OR, 2.45; 95% CI, 0.90−6.70 [Figure 10]).

FIGURE 8
Forest plot for the risk of low birth weight (ie, birthweight, <2500 g) in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval, *LBW*, low birthweight; *M-H*, Mantel-Haenszel test

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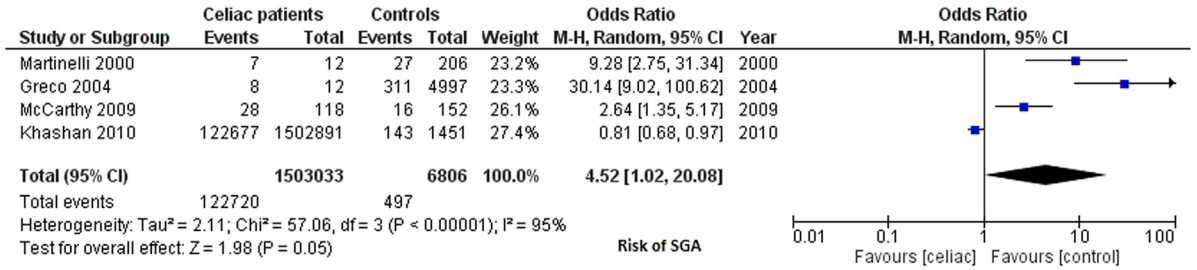
FIGURE 9

Forest plot for the risk of small for gestational age (ie, birthweight, <10th percentile for gestational age) in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test; *SGA*, small for gestational age

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The risk of PTB was still significantly higher both in subgroup analysis of only the women with treated celiac disease (OR, 1.26; 95% CI, 1.06–1.48 [Figure 11]) and in subgroup analysis of only untreated celiac disease women (OR, 2.50; 95% CI, 1.06–5.87 [Figure 12]). However, women with treated celiac disease had a significantly lower risk of the development of PTB compared with those with untreated celiac disease (OR, 0.80; 95% CI, 0.64–0.99).

Table 2 shows the characteristics of the women who were included in the individual participant data metaanalysis. The 2 groups were similar in terms of maternal demographics. Four studies that included 5792 singleton gestations were analyzed.[10,11,22,24] Two hundred fifty-eight of the women who were included were women with celiac disease (both treated and untreated); 5534 were women without celiac disease. Table 3 shows the pooled results of the individual patient level metaanalysis. Not all the outcomes have been registered in every database; results therefore are accompanied with the number of cases in which the outcomes were registered. Compared with the control group, women with celiac disease (both treated and untreated) had a significantly higher risk of the development of PTB (OR, 2.08; 95% CI, 1.36–3.20), IUGR (OR, 5.01; 95% CI, 1.25–20.04), stillbirth (OR, 24.94; 95% CI, 11.13–55.84), LBW (OR, 6.29; 95% CI, 1.83–21.60), and SGA (OR, 8.50; 95% CI, 1.85–38.97), ; no statistically significant difference was found in the incidence of preeclampsia (OR, 20.17; 95% CI, 0.81–502.43). Using the individual participant data metaanalysis, we were able to assess also the primary outcome (defined as at least 1 of the following complications: IUGR, SGA, LBW, or PTB); women with celiac disease had a significantly higher risk of composite obstetric complications compared with control subjects (OR, 1.51; 95% CI, 1.17–1.94).

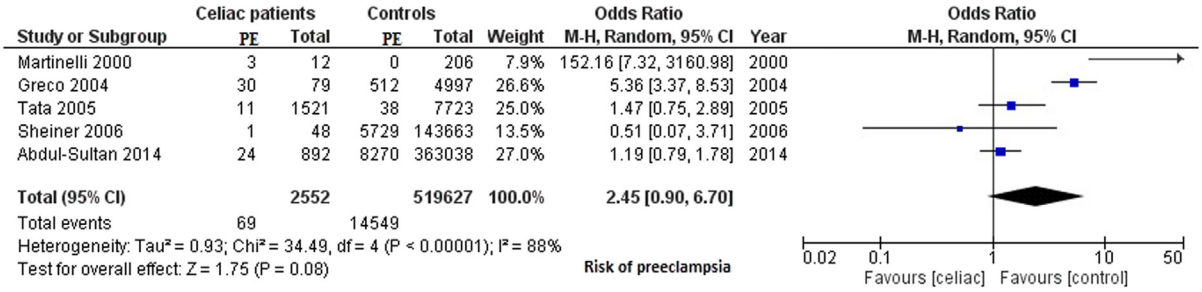
Comment

Main findings

This metaanalysis showed that women with celiac disease (both treated and untreated) had a significantly higher risk of the development of obstetric complications, including PTB, IUGR, stillbirth, LBW, and SGA; no statistically significant difference was found in the

FIGURE 10

Forest plot for the risk of preeclampsia in women with celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test; *PE*, preeclampsia

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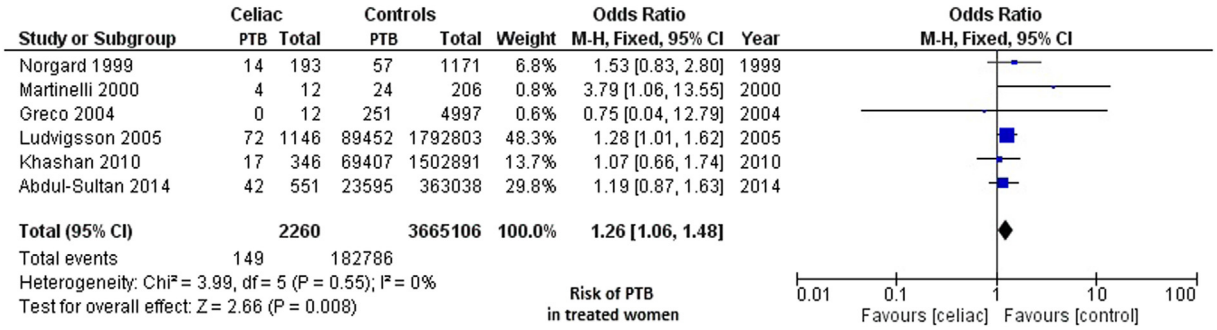
FIGURE 11
Forest plot for the risk of the development of preterm birth in women with treated celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test; *PTB*, preterm birth

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

incidence of preeclampsia. The risk of PTB was higher both in treated and in untreated women. However, women with diagnosed and treated celiac disease had a 20% significant decrease of PTB compared with those with undiagnosed and untreated celiac disease at the time of pregnancy. Our individual patient-level analysis concurs with the aggregate analysis.

Comparison with existing literature

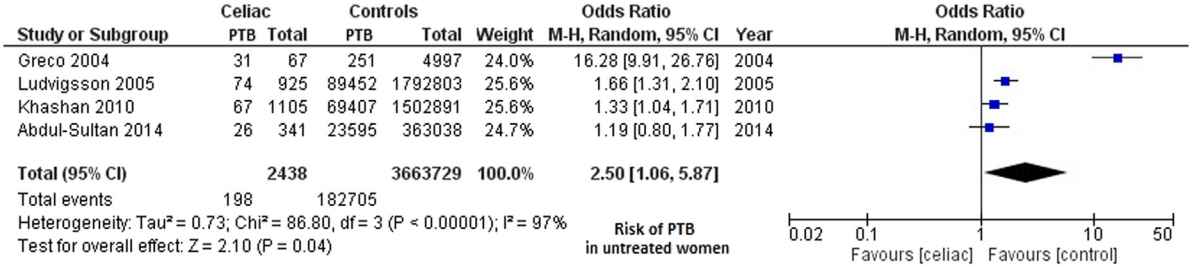
A previous metaanalysis showed that celiac disease was associated with reproductive disorders and pregnancy complications (ie, unexplained infertility and recurrent miscarriage).[2] However, it did not include all currently available studies; outcomes that were considered were different; subgroup analyses and individual patient-level metaanalysis were not performed, and the number of included women was lower. Moreover, pooled adjusted risk estimates were not assessed.[2] No other previous pertinent metaanalyses were found during the search process.

Strengths and limitations

Our study has several strengths. To our knowledge, no previous metaanalysis on this issue is as large or comprehensive. The number of the included women is very high. Most of the included studies had low risk of bias. Statistical heterogeneity between the studies was low. Individual patient-level metaanalysis was assessed for studies in which the original databases were obtained.

Limitations of our study are inherent to the limitations of the included studies. All the included studies were cohort studies. Although all authors of the included studies were contacted, only 4 of them provided the entire database for the individual patient-level analysis. Data regarding PTB referred to both spontaneous and was indicated as a cause of PTB. Notably, although the OR was 2.45 for preeclampsia in the celiac vs non-celiac disease group, this was not statistically significant with the frequency occurring in these 2 groups (2.7% vs 2.8%, respectively; Figure 10). This could suggest that the difference noted in the PTB rate between the 2 groups was due to a spontaneous cause, such as a preterm labor or preterm rupture of membranes. The prespecified primary outcome of

FIGURE 12
Forest plot for the risk of the development of preterm birth in women with untreated celiac disease



The odds for each study is shown as a blue square, and with a horizontal line showing the confidence interval. The pooled results for all studies is shown as a black diamond.

CI, confidence interval; *M-H*, Mantel-Haenszel test; *PTB*, preterm birth

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

TABLE 2
Characteristics of the women included in the individual patient level metaanalysis

Variable	Women with celiac disease (n = 258)	Women without celiac disease (n = 5534)	*P* value
Mean age, y ± SD	27 ± 4.5	26 ± 3.7	.87
Ethnicity			
European	25 (98.8)	5504 (99.5)	.91
Others, n (%)[a]	3 (1.2)	30 (0.5)	
Mean body mass index, kg/m^2 ± SD	23 ± 3.2	23 ± 4.4	.92
Smoker, n (%)	25 (9.7)	500 (9.0)	.94
Maternal diabetes mellitus, n (%)	4 (1.6)	105 (1.8)	.72
Maternal hypertension or renal disease, n (%)	5 (1.9)	112 (2.0)	.96
Nulliparous, n (%)	113 (43.8)	2190 (39.8)	.09
Untreated celiac disease women, n (%)[b]	67 (26.0)	—	—

[a] Includes Caribbean, Asian, Sub-Saharan Africa, Middle East; [b] Women who received the celiac disease diagnosis after the index pregnancy.

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

our review registered on PROSPERO (CRD42015017263) was an obstetric complication composite; however, assessment of this outcome in the aggregate data analysis was not feasible. The individual patient-level metaanalysis was post hoc, so it is not reported in the PROSPERO. Most outcomes had very high statistical heterogeneity, and this was a major shortcoming of the meta-analysis. Older studies may not reflect current practice and outcomes. None of the included studies adjusted for weight gain as a possible confounder.

Conclusions and implications

The biologic plausibility to explain the higher risk of obstetric complications in women with celiac disease is not completely clear. However, 2 main hypotheses can be made. The malabsorption that characterizes celiac disease may lead to nutrient deficiencies, which can be associated with adverse pregnancy outcomes.[26] Specifically, IUGR, SGA, and LBW have been associated with maternal micronutrient deficiencies.[27] Furthermore, women with celiac disease often show increased levels of serum autoantibodies, including anti-transglutamines and anti-thyroid antibodies,[1,28-31] that have been linked to several pregnancy complications such as PTB and stillbirth.[32-34]

Because a gluten-free diet reduces antibodies and leads to an improvement

TABLE 3
Outcomes of the women included in the individual patient level metaanalysis

Outcome	Women with celiac disease, n/N (%)	Women without celiac disease, n/N (%)	Higgins I^2 test, %	Odds ratio (95% confidence interval)
Primary outcome[a]	107/258 (41.5)	1,769/5,534 (32.0)	10	1.51 (1.17–1.94)
Preterm birth	35/91 (38.5)	1,264/5,203 (24.3)	0	2.08 (1.36–3.20)
Intrauterine growth restriction	28/140 (20.0)	298/5,382 (5.6)	0	5.01 (1.25–20.04)
Stillbirth	9/91 (9.9)	22/5,203 (0.5)	0	24.94 (11.13–55.84)
Preeclampsia	33/91 (36.3)	512/5,203 (9.9)	78	20.17 (0.81–502.43)
Small for gestational age	43/142 (30.3)	354/5,355 (6.7)	5	8.50 (1.85–38.97)
Low birthweight	5/12 (41.7)	21/206 (10.2)	0	6.29 (1.83–21.60)

Note: Not all the outcomes have been registered in every database; therefore, results are accompanied with the number of cases in which the outcomes were registered (n). Proportions are presented as percentage of n, rather than as percentages of the total population.

[a] Incidence of composite obstetric complications including intrauterine growth restriction, small for gestational age, low birthweight, preeclampsia, and preterm birth.

Saccone. Celiac disease and obstetric complications. Am J Obstet Gynecol 2016.

of intestinal function and nutrient availability,[1,35-37] this may explain the reason that treated women with celiac disease have better pregnancy outcomes than untreated women.

In summary, women with celiac disease (both treated and untreated) had a significantly higher risk of the development of obstetric complications. Because the treatment with gluten-free diet leads to a significant decrease of PTB, physicians should warn these women about the importance of a strict diet to improve obstetric outcomes. Future studies that will calculate the cost-effectiveness of screening for celiac disease during pregnancy, which could be performed easily, economically, and noninvasively,[38] are needed. In addition, further studies are required to determine whether women with adverse pregnancy outcomes should be screened for celiac disease, particularly in countries where the prevalence is high. ■

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