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Untreated Material Celiac Disease and Low Birth Weight Infants: A Systematic Review of the Literature

Abstract

Background: Celiac Disease (CD) an autoimmune disease triggered by gluten is becoming more widespread. While there has been vast improvement in understanding the complications having CD, they are still not fully understood. There has been increasing research over the last decade looking at CD and undesirable pregnancy outcomes. The question of whether or not undiagnosed CD is associated with low birth weight infants, will be addressed in this paper. The evidence presented by the studies included will be evaluated using GRADE.

Method: An exhaustive search of available medical literature was conducted using Medline, PubMed, ISI Web of Science, EBM Multifile of Review, Cochrane Systematic Reviews and CINHAL with the search terms: celiac disease, gluten intolerance and low birth weight.

Results: Three articles were found in the search and reviewed in this paper. The studies reviewed found that women with undiagnosed/untreated CD were at an increased risk of having low birth weight infants when compared to women who were unexposed to or without CD. The case control study found an OR of 0.91 (95% CI 0.12-6.49) and the two population cohorts, Danish and Swedish reported OR of -15g (95%: -70-41)] and -170g (95% CI: -215g, -127g, p

Conclusion: Undiagnosed maternal CD results in an increased risk of low birth weight infants as compared to no CD, although the exact mechanism is unknown. The overall GRADE assigned to the outcome of LBW was moderate.

Keywords: Celiac Disease, Gluten Intolerance, Low Birth Weight

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Untreated Maternal Celiac Disease and Low Birth Weight Infants: A Systematic Review of the Literature

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A course paper presented to the College of Health Professions

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Biography

Elizabeth Rupp is a native of Bozeman, Montana where she majored in Business Management at Montana State University. After graduation she worked in clinical research and quickly discovered that she enjoyed working with the patients much more than pushing papers and found herself leaning more towards healthcare and less towards its business aspect. To the shock of her professors and friends she decided to switch gears and applied to PA school. In the summer of 2009 she left the beautiful mountains of Montana and moved to Hillsboro, Oregon to start PA school and subsequently gave up the next two years of her life. She hopes to one day return to Montana and pay off her loans, until then she would just like a job!

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[Redacted for privacy]

ABSTRACT

Background: Celiac Disease (CD) an autoimmune disease triggered by gluten is becoming more widespread. While there has been vast improvement in understanding the complications having CD, they are still not fully understood. There has been increasing research over the last decade looking at CD and undesirable pregnancy outcomes. The question of whether or not undiagnosed CD is associated with low birth weight infants, will be addressed in this paper. The evidence presented by the studies included will be evaluated using GRADE.

Method: An exhaustive search of available medical literature was conducted using Medline, PubMed, ISI Web of Science, EBM Multifile of Review, Cochrane Systematic Reviews and CINHAL with the search terms: celiac disease, gluten intolerance and low birth weight.

Results: Three articles were found in the search and reviewed in this paper. The studies reviewed found that women with undiagnosed/untreated CD were at an increased risk of having low birth weight infants when compared to women who were unexposed to or without CD. The case control study found an OR of 0.91 (95% CI 0.12-6.49) and the two population cohorts, Danish and Swedish reported OR of -15g (95%: -70-41)] and -170g (95% CI: -215g, -127g, $p<0.001$)], respectively.

Conclusion: Undiagnosed maternal CD results in an increased risk of low birth weight infants as compared to no CD, although the exact mechanism is unknown. The overall GRADE assigned to the outcome of LBW was moderate.

Keywords: Celiac Disease, Gluten Intolerance, Low Birth Weight

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INTRODUCTION

Background

Celiac disease (CD), a disease that until recently was considered to be uncommon, effecting only children, has gained respect as a health issue worldwide over the last decade (Olsson, Hernell, Hornell, Lonnerg, & Ivarsson, 2008). This disease with its long history, the first occurrence dating back to the years before Christ was not afforded credibility in the medical community until recent decades, especially in the United States. CD, also known as gluten-sensitive enteropathy, is an immune-mediated inflammation of the small intestines in response to gluten or prolamines which are found in barley, wheat and rye. Prolamines are more specifically gliadin in wheat, secalin in rye and hordein in barley (Sandberg-Bennich, Dahlquist, & Kallen, 2002). Oats, while excluded in the gluten free (GF) diet, do not contain gluten but are significantly cross contaminated during growth, harvesting and milling (Norris et al., 2005). CD is found in individuals with the associated human leukocyte antigen (HLA) class II genes HLA-DQ2 and/or HLA-DQ8 haplotypes located on chromosome 6p21. Gluten when ingested by individuals with CD results in an auto-immune attack on the mucosal layer of the intestines damaging the microvilli responsible for absorption of nutrients (Farrell, 2005).

Serological testing for CD with antigladin antibodies (AGA) and anti-endomysial antibodies (EMA) is relatively new and has improved the number of individuals with CD who are correctly diagnosed (Fasano et al., 2003). Prior to the development of serological testing, the only way to test for CD was an small

bowel intestinal biopsy. While there has been improvement in ability to test for the disease, the only treatment for CD is strict adherence to a GF diet. There are occasionally some refractory cases of CD where the damage to the intestinal microvilli is not resolved by adherence to a gluten free diet. New studies are looking at the effects of mesalamine in these cases (Jamma et al., 2011).

Celiac disease, in the absence of GF diet causes chronic inflammation along the mucosal lining of the small intestine and results in a variety of other health problems including malnutrition, weight loss, anemia, hypocalcemia, and deficiencies in folic acid, vitamin B12 and zinc (Olsson et al., 2008; & Strazi & Mantovani, 2000). Unfortunately, the wide spectrum of symptoms associated with CD ranging from completely asymptomatic to severe adnominal pain, cramping, diarrhea and weight loss, make it difficult to diagnosis. This can cause problems for individuals unaware they have the disease and who are not following a GF diet. Studies suggest that CD affects up to 1% of most of the world's population but most individuals with the disease are not aware they have it (Olsson et al., 2008). While there is speculation as to the precise percent of the world's population effected, it has been accepted that overall prevalence of CD, varies geographically. It is estimated that 1:130 to 1:300 individuals in Europe or of European descent have the disease and it is being found in other countries such as Africa, South America and Asia previously thought to be free of what was considered to be European disease (Fasano et al., 2003).

As the number of individuals with CD continues to grow due to improved diagnostic testing, improved knowledge of the disease, and other genetic and

environmental factors, there has been a growing interest in research on the disease. There has been a particular push among researchers to look at undiagnosed parental celiac disease and its potential impact on unfavorable pregnancy outcomes or adverse risks and maternal outcomes. With the growing number of individuals estimated to have CD, ensuring treatment of the disease in women of reproductive age might be warranted given the possible risks passed to the fetus.

These studies look at CD's effect on infertility, spontaneous abortion or miscarriage, preterm birth and low birth weight (Ludvigsson, Montgomery, & Ekbom, 2006). Among these studies conducted, there have been three that look specifically at CD in pregnant women not following a GF diet and the effect on the birth weight of the infant. This is a systematic review of those articles to see if there if untreated CD does result in an increased risk of low birth weight infants.

Purpose of the Study

The purpose of this paper is to perform a systematic review of the literature on undiagnosed maternal celiac disease in pregnant women and the possible risk it poses of having low birth weight infants or very low birth weight infants using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using Medline, PubMed, ISI Web of Science, EBM Multifile of Review, Cochrane Systematic Reviews and CINHAL. These databases were accessed through the Pacific University Library system. The keywords searched included “celiac disease”, “gluten intolerance” and “low birth weight” both individually and in combination with each other. The search was then limited to studies including only human subjects, the English language and full text articles published since the year 1999. The initial limited search resulted in a total of 38 articles. Duplicate articles, phone interviews and conference topics or review abstracts were then excluded. The included studies were further limited to those looking specifically at undiagnosed maternal celiac disease and birth weight. This resulted in a total of 3 studies, all of which were included in this systematic review. Of these studies, each was conducted in a different European country, Spain, Sweden and Denmark. The final studies included and reviewed in this paper were one case-control, prospective study and two population based cohort studies.

RESULTS

Sanchez et al., (2008) published a case-controlled, prospective study which looked at undiagnosed maternal CD and risk of low birth weight infants in Cabuenes Hospital. The study was conducted over a three year period from 2003-2005 in Austuias, a town in northern Spain. In total the authors studied 1103 women between the ages of 15-49. Of these, 577 women were assigned to

the case group and 526 women in the control group. The case group was comprised of mothers with infants weighing less than 2,500g at birth, whereas mothers with infants weighing more than 2,500g were assigned to the control group. All women in both the case and control group were interviewed and provided a blood sample for serological evaluation using the Celikey Tissue Transglutaminase IgA antibody Assay and Anti-Endomisium antibodies. If the serologic tests were positive, a duodenal biopsy was done to confirm the diagnosis of CD.

Sanchez et al. (2008) did not identify any significant age or origin/ethnicity difference between women the case and control groups. The mean age of the mothers in both groups was 31.1 years old (95%CI: 30.9-31.5). The authors found that low birth weight and elementary maternal education levels were found to be associated with an odds ratio (OR) of 1.54 (95% CI 1.21-1.96). The study found four of the 1,103 women had positive serological antibodies and duodenal biopsies for CD. Three of these four women had never been diagnosed with CD. The other participant diagnosed with CD had been diagnosed in childhood but thought she was cured and was not following a GF diet. Two of the four confirmed cases of CD were in the case group; the other two were in the control group. Three of the four infants born the mothers with undiagnosed/untreated CD were term newborns, the 4th infant was preterm. The authors reported the OR for low birth weight infants as 0.91 (95% CI 0.12-6.49), low birth weight for gestational age was 3.19 (95% CI, 0.44-22.79), and prematurity was 0.61 (95% CI 0.06-5.89). This case control study found that

there was a clinical association between mothers with CD and low birth weight for gestational age but that it was not statistically significant.

The second study reviewed was performed by Khashan et al. (2009) who conducted a population based cohort study looking at the impact of maternal CD on birth weight and preterm birth. This study looked specifically at the Danish population using the Danish Medical Birth Register. The authors of this study looked at all live singleton births between January 1979 and December 2004, during which a total of 1,504,342 babies were born to 836, 241 mothers. Study outcomes measured included low birth weight, small for gestational age (birth weight <10th percentile), very small for gestational age (birth weight <5th percentile) and preterm births. Mothers with CD were identified through the Danish National Hospital Register if they had received a diagnosis of CD during any hospitalization or outpatient care. The women included in the study were placed into three different groups depending on the timing of their diagnosis of CD; Untreated (women who received the diagnosis after giving birth), treated (women who were diagnosed >90 days prior to date of gestation or date of delivery minus gestational age) and women without CD.

The authors discovered 1, 563,322 births recorded between 1979-2004; 58, 331 were excluded due to invalid birth weight or gestational age, 29 were excluded due to the timing of maternal CD diagnosis (<90 days date of gestation) and 620 were excluded due to fathers with confirmed or diagnosed CD. Infants born between 1 Jan 1973 and 31 December 1978 were excluded from the study because birth weight during this time period was recorded in intervals of 250g.

Infant birth weights of >5500g and <500g, birth weight >1500g and <29 weeks gestational age, birth weight >2800g and gestational age between 29-33 weeks were all considered invalid and excluded. Infants with a gestational age <23 weeks or >44 weeks, and those with missing gestational age were also excluded from the study. Infants born to celiac fathers were excluded due a previous study that linked paternal CD to lower birth weight and shorter gestational age. Birth weight from 1979-1991 was recorded in 10g intervals and after 1991 in 1g intervals allowing for some discrepancy between the recorded birth weights.

Khashan et al. (2009) conducted linear regression analysis to examine associations between the different groups, more specifically those with treated CD versus those with untreated CD. The authors of the study adjusted categorical variables within the study population for parity, gender, maternal age, and maternal medical history including diabetes, hypertension, myocardial infarction, renal disease, year of infant birth and paternal age. The authors used further multiple logistic regressions for associations found involving maternal CD and low birth weight and looked into whether parity (nulliparous versus multiparous) had any effect on birth weight. One important confounder that the authors tried to account for was maternal smoking which has been found in previous studies to have an association with low birth weight and preterm birth. Maternal smoking was not recorded until 1997 so the authors restricted the cohort until after 1997, both including and excluding mothers who smoked to see if there was statistical significant difference between the two.

During the 25 years that Khashan et al. (2009) conducted their study, 785

women were diagnosed with CD and gave birth to a total of 1451 infants. Of these 1451 infants, 346 were born after maternal diagnosis of CD and were considered to be treated. The remaining 1105 infants were born prior to maternal diagnosis and considered untreated. The mean birth weight of the infants born to treated mothers with CD was 3503g (546 infants) while the mean weight of infants born to untreated mothers with CD was 3354g (579 infants).

The authors found after using adjusted analysis that untreated CD reduced the mean birth weight by 100g (adjusted difference = -98 (95% CI: -108, -67). Similar results were obtained when further restricting the analysis to only term infants (adjusted difference = -100 (95%CI: -132, -68). When looking at untreated CD in nulliparous women they found that birth weight was reduced by 70g [adjusted difference = -70 (95% CI: -108, -31)]. In multiparous women with untreated CD, birth weight was reduced more than in nulliparous women at 121g [adjusted difference = - 121 (95% CI: -160, -82)]. When the authors restricted the cohort to 1997-2004 to account for maternal smoking they found that during those years untreated CD reduced birth weight by 130g (adjusted difference = -130: -190, -70)]. When allowing for adjustment with maternal smoking there was a small variation in the results (adjusted difference = - 140 (95% CI: -200, -80)]. The authors did more exclusion based on the remaining confounding variables; diabetes, hypertension, myocardial infarction and renal disease. The data for these results were not reported by the authors. However, the authors did state that the data found did not change their conclusions. The authors did not find an association between treated CD and the confounders listed above; low birth

weight, [adjusted difference= -15 (95%: -70-41)], small for gestational age [adjusted OR= 1.01 (95% CI: 0.67-1.50)] or very small for gestational age infants [adjusted OR = 0.92 (95% CI; 0.57-1.46].

The authors of this cohort study looking at the Danish population concluded that that untreated maternal CD in pregnancy, is in fact, associated with low birth weight as well as increased risk of having small for gestational age infant or very small for gestational age infant as compared to women with treated CD or without CD.

The next study reviewed was performed by Ludvigsson, Montgomery, & Ekbom (2006). The authors conducted a population based cohort study investigating the risk of adverse fetal outcomes in Sweden for mothers with CD. The authors used the Swedish National Board of Health and Welfare to identify births from 1973-2001 as well as specific maternal medical information including the diagnosis of CD. Individuals included in the study were infants born between 1973 and 2001 to women between the ages of 15-44. Over the 28 years reviewed and included in the study; 2078 infants were born to mothers with CD. Of these 2078 infants, 1149 infants were born to mothers with a diagnosis of CD prior to delivery and considered treated, 929 infants were born to women diagnosed after delivery and considered untreated and 2,822,805 infants born to mothers without CD. The main outcomes addressed in this study were low birth weight (<2500g) and very low birth weight (<1500g). Mothers with the diagnosis CD prior to the birth of their baby were compared with mothers who were undiagnosed until after the birth of their baby. The maternal diagnosis of CD

came as a hospital discharge diagnosis between 1964 and 2001 and was identified by the authors using the Swedish National Board of Health and Welfare. The authors allowed mothers to contribute more than one infant to the study.

Information included and accounted for by the researchers was gender/infant sex, maternal age at delivery which was further sectioned in the following: 15-19, 20-24, 25-29, 30-34, 35-40, and 41-44, parity, nationality, smoking and diabetes mellitus. Maternal smoking status was not available until after 1983. Infants with gestational age <22 weeks or >46 weeks were excluded as were birth weights <300g and >7000g.

The authors used logistic regression to calculate the odd ratios and confidence intervals for each specific fetal outcome measured. Multivariate models were used to adjust for confounding factors such as gender/infant sex, parity, maternal age at delivery, nationality, calendar period and smoking after 1983. If a mother had more than one infant in the study, this too was adjusted for by the authors who performed additional analysis limited to 1 birth per female to determine any dependence of the results. The authors reported that women with undiagnosed CD had lower birth weight infants than women who were unexposed or without CD [-170g (95% CI: -215g, -127g, p<0.001)]. Women with diagnosed CD were also found to have lower birth weight infants as compared to women without CD [-53g (95%CI -92 to -14g, P=.004)]. After adjusting for all measures except smoking, women with undiagnosed CD were found to have, on average, an infant with a birth weight of 165g lower than infants born to women

without CD [95% CI -200 to -129g, P<.001) and when adding in maternal smoking 178g lower (-178g; 95% CI: -233 to -123g P<.001). Infants born to women with diagnosed CD were also found to have a lower birth weight when compared with women without CD [adjusted birth weight difference -62g (95%CI: -94 to -30g, P<.001)]. When comparing infants of women with untreated CD to infants of women with treated CD, infants with undiagnosed CD were found to have lower birth weight after adjusting for all other confounding factors except smoking [-87g (95%CI: -154g to -20g; P<0.011)]. To take into account the effect maternal smoking had on the finding of low birth weight, the authors conducted interaction tests which found that maternal smoking in those with undiagnosed CD did not result in any statistically significant results for the outcomes and therefore, did not modify the outcomes of undiagnosed CD and low birth weight infants. The authors also stratified maternal smoking into two different time periods 1983-1993 and 1994-2001 in which they found no effect in either time period on undiagnosed CD and low birth weight or on other adverse fetal outcomes.

The authors of this study took the information they found a step further and looked at the time of maternal diagnosis of CD, and the effect it had on low birth weight after adjusting for all factors except smoking. They found that infants born to women who had been diagnosed with CD 0-2 years before birth had an increased risk of low birth weight babies [adjusted OR 3.93; (95% CI 2.02-7.65, P=0.001)]. Infants born to women who had been diagnosed with CD >2-4 years before birth were at an increased risk of very low birth weight [adjusted OR

=5.02, (95% CI: 1.23-20.45, P=0.005)]. Infants born to women who had been diagnosed with CD >5 years before birth had no increased risk of low birth weight or very low birth weight infants. The authors of this population based cohort study concluded that undiagnosed CD is a risk factor for low birth weight infants.

DISCUSSION

Celiac disease is becoming more recognized worldwide in areas where the disease is already known and there is a rise in the number of individuals affected. Cases of the disease are also showing up in places previously thought to be free of this autoimmune disease. As a result there is now more knowledge about the potential complications of the disease, including gestational and maternal complications. A list of important studies looking at these complications can be found in the appendix. While CD was previously thought to be present only in certain geographical areas, serological testing is showing that that is no longer the case. As a result, the complications of CD are present in areas where most people are unaware of the disease itself. With the wide range of symptoms (asymptomatic to severe) present with the disease, some individuals who have CD may know they have it but chose not to follow a GF diet due to the inconvenience and limitations associated with it. Others may choose to cheat and only eat gluten some of the time, unaware of the lasting damage this causes. In cases such as these it is important that they are aware of the gestational and obstetrical complications the disease can have on them and their unborn child. In women with undiagnosed CD, these complications are harder to prevent

without screening everyone for the disease, however, it may prompt providers to look at CD as a possible cause for adverse fetal outcomes in patients where a cause is unknown.

The studies, one case control and two population based cohorts, reviewed and appraised in this paper looked at three different geographical locations in Europe; Spain, Denmark and Sweden. Each of these studies investigated undiagnosed CD and birth weight which was further divided into low birth weight and very low birth weight. While there are other fetal outcomes addressed in these studies, this review is focused only on birth weight. Combined, these three studies looked at over 53 years worth of medical records and over 3 million women who gave birth to 4, 328, 250 infants during that time. The outcome addressed in this paper, low birth weight and very low birth and the studies that provided information on these outcomes will be evaluated for quality and strength according to the GRADE Working Group.

Study Limitations

There were limitations in each of the three studies reviewed and need to be addressed as the limitations affect the overall quality of the outcomes and factor into the GRADE assigned to the outcomes.

The first study reviewed was a case control published by Sanchez et al., (2008). There were several limitation to this study, one being that, although the authors made some effort the cases and control groups were not successfully matched. There was the small size of the study and limited geographical location.

The time over which the study took place was also very short, lasting only three years. In addition to the above limitation the participants could chose whether or not they wanted to participate and the medical history was obtained directly from the individual themselves not from documented medical records, which might result in reporting bias. There were three doctors who conducted the interviews, while the authors mention they were trained in homogenous criteria; they do not provide any specific questions designed prior to the study allowing for bias to be measured. Of the four infants born to mothers with undiagnosed/untreated CD, three of them were term and one was preterm. Although the authors report this information, they do not provide information to which of the two groups, case or control, the infants belonged. This information is relevant to the study as preterm birth has been found in other studies to be a risk factor associated with CD (Behrman, Kliegman, & Jenson, 2000; Ludvigsson & Ludvigsson, 2001).

The next study reviewed was the Danish cohort published by Khashan et al., (2009). One limitation was that once the diagnosis of CD was received, the authors considered the patients to be treated and assumed that individuals diagnosed with CD were following a GF diet. This is not always the case and a diagnosis of CD as with any disease does not ensure compliance with treatment, in this case a GF diet. Another limitation was the database used to compile the information used, looked only at inpatient cases. This would subsequently exclude any patient who received a diagnosis of CD in a family or private practice. The database was started in 1977 and any patients receiving a diagnosis of CD prior to 1977 were unknown to the authors. Therefore, any

patient with a diagnosis prior to that date who gave birth during the study period would be incorrectly classified as belonging to the group of mothers without CD. Smoking a known cause of low birth weight infants might also present a limitation and might not have been correctly accounted for since information pertaining to maternal smoking was not recorded until 1997. One further limitation is that although it was a large study with a long duration the study was limited to the Danish population which is a predominantly white Scandinavian country in Europe where CD is thought to be most common.

The final study reviewed was a Swedish cohort published by Ludvigsson, Montgomery and Ekbom (2006). The limitations in the study were similar to those found in the Danish cohort. The first was that as in the Danish cohort once the diagnosis of CD was received, the authors considered the patients to be treated and that they were following a GF diet. Another limitation was the national databases used to compile the information used by the authors which looked at inpatient cases. This would subsequently exclude any patient who received a diagnosis of CD outside an inpatient facility. The authors thought this seemed unlikely as a surgical biopsy is needed for confirmation of CD and must be done on an inpatient. In addition, women who received the diagnosis of CD did so because they had symptoms of the disease and the diagnosis was not done through screening. This may further increase the number of women with undiagnosed CD, as some may be asymptomatic or not seeking treatment for their symptoms. Smoking, a known cause of low birth weight infants might also present a limitation, since there is a strong stigma associated with maternal

smoking, some mothers may not have admitted to smoking. While the authors did not find a remarkable change in results when adjusting for maternal smoking, this may not be completely accurate if information had been withheld.

GRADE EVALUATION

GRADE (Grading of Recommendations Assessment, Development and Evaluation), is a grading tool designed by the GRADE Working Group designed in 2000 to provide a more thorough and standardized method for grading the evidence and strength of recommendations provided in medical literature. Depending on the study design a study is given a starting grade. Randomized control trials are given a starting grade of high, observational studies are given a starting grade of low and all other studies are given a starting grade of very low. Studies given a starting grade of high can only be downgraded and studies starting with a grade of low or very low can only be upgraded. There are specific results and categories according to which a study can be downgraded or upgraded. A study can be downgraded according to study quality, consistency, directness, precision, publication bias and upgraded by large magnitude, dose response and confounders. By using a standardized grading tool accuracy, bias, and other shortcomings in studies are better addressed (Guyatt et al., 2008).

As a case-control study the starting grade for the study is low for both outcomes addressed, low birth weight and very low birth weight. Since the study is a case-control with a starting grade of low, it cannot be decreased further and can only increase its grade. The three areas in which the study can increase its

GRADE are large magnitude, dose-response and confounders. In this study looking at the designated outcomes there was no large magnitude found and there was no dose-response, as it was not applicable to this study. Some confounders were addressed by the authors including that of maternal smoking but they were not accounted specifically in both the case and control group for enough to warrant an increase the initial GRADE.

The Danish population based cohort study received a starting GRADE of low and therefore, was not further downgraded. The study was upgraded for its large magnitude of association between low birth weight and undiagnosed CD. The study looked at information collected over 25 years using several databases to account for all the information obtained and used in the study. Healthcare in Denmark is also free and therefore the decreases but does not eliminate socioeconomic bias that might potentially influence the association and magnitude of the study. The study was upgraded for the confounders which were accounted for by the authors conducting the study. The authors ran adjusted odds ratios, linear and multivariable regression analysis to account for these confounders and the impact they might have on the studied outcomes. These confounders included maternal smoking, co-morbidities, parity, birth year, gestational age and gender. The authors reported that after adjusting for these cofounders there was little effect on their reported findings.

The starting GRADE for the Swedish population based cohort study was low and was not downgraded. The study received an increase in GRADE based on its large magnitude. The study included a very large population and was

conducted over 25 years giving credibility to the association found, and limiting any particular trends that might weigh too heavily on the findings. The study also received an increase in GRADE based on its confounders which were adequately addressed and accounted for by the authors. The authors of this study performed calculation and adjusted OR to account for each of the confounding factors identified; smoking, age, parity, diabetes mellitus and number of infants included from a single mother.

The outcomes specifically addressed in this review are, low birth weight and very low birth weight. All three of the studies discussed above had an outcome of low birth weight. Two of the three studies reviewed here had an outcome of very low birth weight, the case-controlled study and the Swedish cohort study. The limitations of each study have already been addressed.

The starting grade for the outcome of low birth weight was low, given the study designs used and evaluated in this article. The starting grade was not downgraded for study quality, consistency, directness, precision or publication bias as these downgrades are not applicable to outcomes in which the starting grade is low. The outcome of low birth weight was upgraded for both large magnitude and confounders. The case control study did not contribute to the decision to upgrade the outcome given its incredibly small sample size and very short duration of three years as compared to the two cohort studies which, when combined, looked at over 50 years of information and at over three million mothers and their infants. Both cohort studies, reported that risk of low birth weight infants in undiagnosed maternal CD to be statistically significant with

small confidence intervals. The authors of both cohort studies also adequately identified and adjusted for confounders present in their data and made sure that the confounders did not alter the statistical significance of the outcome. Therefore, the GRADE of evidence for outcome given to low birth weight was a grade of moderate. The GRADE working group defines a grade of moderate as "one where further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate" (Guyatt et al., 2008, p.924).

The second outcome addressed in this article also looks at birth weight; looking at very low birth weight in the setting of maternal CD was given a starting grade of low given the study designs. The starting grade was not downgraded given its starting grade of low. The outcome did not receive an upgrade for the large magnitude or dose response. The outcome was upgraded for the confounders which were adequately accounted for by the authors of the Swedish cohort study which looked at 28 years of data. The authors of this cohort did statistical linear regression and multivariate models to account for potential confounders that could affect the final outcome. The authors did not find any statistically significant changes in the outcome based on the identified confounders. The case-control study which while looking at possible confounders did not do a thorough identification and statistical check of all possible confounders and alone, would not be awarded any upgrade but given its small size and duration it did not prevent the outcome from receiving the upgrade. The GRADE of evidence for outcome given to very low birth weight is low. GRADE

Working Group defines a grade of low as “one in which further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate” (Guyatt et al., 2008, p.924).

The overall GRADE for evidence for undiagnosed maternal CD and low birth weight infants was awarded a GRADE of moderate. The decision to grade the overall evidence as moderate instead of low is due to the much larger study population looking specifically at low birth weight. As well as the fact that outcome of very low birth weight infants was a subset and further division of low birth weight.

Conclusions

There is an association between undiagnosed maternal CD and the risk of low birth weight infants. This presents a problem as CD continues to become more prevalent in modern society and many individual are living with the disease undiagnosed which puts them at greater risk for having lower birth weight infants and opens those infants up to potential health risks. The same risk, applies to individuals who while diagnosed, do not follow a GF diet. Many individuals with CD are unaware of the complications aside from the symptomatic discomfort that not complying with a GF diet presents. Undiagnosed or untreated CD, presents a risk not only to the individual with the disease but in the case of pregnancy, ones offspring as well. Women with CD need to be counseled about risk of having a low birth weight infant if they do not follow a GF diet prior to and during pregnancy.

While the two population based cohort studies reviewed in this paper show a statistically significant association between undiagnosed maternal CD and low birth weight infants, further similar studies are needed to strengthen this association. Since all of the studies in this paper were conducted in European countries, their geographical location needs to be taken into account. Further studies looking at similar outcomes in other areas such as South America, Asia or Africa would lend further validity to these findings. This would allow for further understanding of the role geographic location plays in CD as well as the risk that undiagnosed CD presents for low birth weight infants.

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APPENDIXES

APPENDIX A
Table 1: GRADE Table

Comparison	Outcome	Quantity and Type of evidence	Findings	Starting grade	Decrease GRADE					Increase GRADE			Grade of Evidence for Outcome	Overall GRADE of Evidence
					Study Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose-Response	Confounders		
Undiagnosed maternal CD and infant birth weight	Low birth weight	1 case control 2 cohort	Decreased birth weight	Low	0	0	0	0	0	1	0	1	Moderate	**Moderate**
	Very low birth weight	1 case control 1 cohort	Decreased birth weight	Low	0	0	0	0	0	0	0	1	Low	

APPENDIX B
Table 2: Studies Table

Important Epidemiological Studies on the Association of Undiagnosed CD and Birth Weight

Author	Publication	Population	Country	Conclusion
Ciacci, C	American Journal of Gastroenterology 1996	94 mothers with undiagnosed CD; 34 mothers with treated CD	Italy	Untreated CD was found to have LBW, shorter breast feeding and increased abortion
Norgard	American Journal of Gastroenterology 1999	127 women with CD	Demark	Untreated CD shown to have higher risk of LBW and IUGR
Martinelli	GUT 2000	845 women, 12 with CD	Italy	Unfavorable gestation
Ludvigsson JF	GUT 2001	10,500 mothers and fathers; 53 mothers with CD, 27 fathers	Sweden	Parental CD; a higher risk of LBW
Greco L	GUT 2004	5,000 women	Italy	No association between CD and LBW
Ludvigsson JF	GUT 2005	2078 women with CD	Sweden	Undiagnosed CD is a risk factor for adverse fetal outcome including LBW
Salvatore S	American Journal of Gastroenterology 2007	1,714 LBW and premature babies	Italy	LBW is higher in Coeliac than general population
Khashan AS	Human Reproduction 2009	1,504,342 babies born to 836,241 mothers	Sweden	Undiagnosed CD increases risk of LBW, SGA, VSGA and preterm birth
Sanchez, C	Pediatrics 2008	1103 women, 4 with CD	Spain	No association between CD and LBW

Sanchez et al., 2008

APPENDIX C
Figure 1: Abbreviations

List of Abbreviations

CD……..…….Celiac Disease

CI…….Confidence Interval

GF.....Gluten Free

IUGR……Intrauterine Growth Restriction

LBW……..……Low Birth Weight

PTB…….....Preterm Birth

SGA…….Small for Gestational Age

VLBW……..Very Low Birth Weight

VSGA……..Very Small for Gestational Age