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Vitamin C Supplementation in Pregnancy – Does it Decrease Rates of Pre-term Birth: A Systematic Review

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Abstract

Objective: To assess the evidence available on the use of vitamin C supplementation greater than recommended dietary intake to reduce pre-term birth rates.

Study Design: Systematic review of randomized controlled trials using vitamin C alone or with one other supplement other than iron. Trials must report pre-term birth rates but can have other primary outcomes. Pre-term birth is defined as birth at less than 37 weeks gestational age for this review. Review focused on studies with populations representative of Organization for Economic Co-operation and Development countries.

Results: Inadequate level of evidence on the use of vitamin C alone to prevent preterm birth rates in low risk populations based on one study. Three studies provided convincing evidence of no benefit in low risk groups to use vitamin C and E combined. Three studies provided adequate evidence of no benefit in high risk groups to use vitamin C and E combined.

Conclusion: The available evidence supports no benefit gained from using vitamin C to prevent preterm birth. Evidence does not support limiting use of vitamin C supplementation for other indications.

Keywords

‘Vitamin C’; ‘Ascorbic Acid’; ‘Pre-term Birth’; ‘Prevention’

Introduction

Almost one third of all infant deaths within the first year of life in the United States (US) are associated with preterm birth.[1] If a premature infant survives the first year of life, they continue to have higher death rates throughout childhood compared to children born at full term.[2] In 2009, 12.2% of all births in the US were pre-term.[3] The World Health Organization estimates an incidence rate 9.6% for preterm births worldwide and found

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increasing trends in preterm birth rate similar to the US in the United Kingdom and the Scandinavian countries.[4] There are many risk factors for preterm birth and some of the better defined ones pertinent to this review include multiple gestations, history of preterm birth, smoking, history of preeclampsia, medical diseases (e.g. diabetes and hypertension), and second trimester abortions.[5–11]

In the US, around 50% of preterm births are due to preterm labor, 30% secondary to premature rupture of membranes, and 20% secondary to another condition (e.g. preeclampsia).[12] For preterm births related to premature rupture of membranes, Woods et al suggested a link between vitamin C use and the prevention of premature rupture of membranes based on biochemical evidence.[13] Myatt and Cui also described histological and biochemical evidence that vitamin C's antioxidant properties may benefit pregnancies with intrauterine growth retardation and preeclampsia.[14] Similar data has been provided by other studies in the past as well.[15,16] Vitamin C is also involved in the metabolism of iron in the body and therefore may exert an additional beneficial affect during pregnancy by preventing anemia.[17] Based on this growing body of evidence regarding the potential benefits of antioxidants, many trials were begun to investigate the benefits and harms of using vitamin C at high doses. This review was performed to gather and analyze all the available data on the link between vitamin C supplementation and preterm birth in populations representative of Organization for Economic Co-operation and Development (OECD) member countries. OECD member countries were chosen to identify the utility of vitamin C supplementation beyond the normal dietary requirements during pregnancy.

Materials and Methods

This review was performed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We searched PUBMED, Cochrane library, and EMBASE using variants of ascorbic acid/vitamin C and pregnancy from inception to Feb. 28, 2012. Clinicaltrials.gov was also searched and hand searches of the references from relevant articles were performed. Results were limited to the English language.

We included all randomized controlled trials found comparing vitamin C versus placebo and reporting data on preterm births (birth prior to gestational age of 37 weeks). Trials were included if they began the intervention prior to the third trimester. No specific limit on the dose of vitamin C was used during the search. The relationships between dose used, participant use of supplements outside of the study, and dietary patterns were assessed during the grading of each study's validity. Studies were included only if performed in (OECD) member countries. This limitation helped reduce confounding due to benefits of vitamin supplementation in women with inadequate daily intake and helped focus on the possible benefits of supplementation with doses of vitamin C beyond the recommended daily intake. Trials were included if they used up to one other supplement with vitamin C unless the second supplement was iron.

The search results were reviewed independently by two authors (P.S. and I.A.) to determine inclusion and exclusion in the review. Disagreements were discussed and if no consensus was reached, a third author was used to determine the study's inclusion. Study data was

extracted by one author (P.S.) and reviewed for accuracy by a second (I.A.). When reported the risk ratio was directly taken from the study and if unavailable the risk ratio was calculated by the authors using methods described by Armitage and Berry.[18]

Once studies to be included in the review were identified, two authors (P.S. and I.A.) evaluated all studies and gave grades of 'good', 'fair', or 'poor' for both internal and external validity of the study. The evaluations were performed separately and then reviewed for differences which were then resolved through discussion. The methods used to analyze validity followed the USPSTF criteria for randomized controlled trials.[19] The risk ratio and validity grades for each study were used to develop a synthesis of the evidence available regarding vitamin C to prevent preterm birth. Studies receiving a grade of 'poor' on either internal or external validity were not included in the data synthesis or conclusions. The synthesized evidence was given a grade using the USPSTF procedure manual as guidance which establishes levels of evidence as being 'convincing', 'adequate', or 'inadequate'.[19]

Results

Search Results

The database searches provided 230 unique studies of which 32 studies underwent full text review after excluding the remainder based on title and abstract. After full text review, 8 studies were included in the review for grading and discussion.[20–27] The 8 remaining studies all used either vitamin C alone or a combination of vitamin C and E as their intervention. The studies were stratified at this point based on the risk profile of the study participants. Population risk profile was defined as: High risk profile included previous history of obstetrical complications, abnormal uterine artery Doppler waveforms or chronic medical condition (e.g. diabetes mellitus or hypertension requiring medication). Low risk profile did not have previous history of obstetrical complications or chronic medical disease. The study by Xu et al included a mixture of both profile types; however, the low risk group made up more than 70% of the total population and even the high risk portion of the population excluded many risk factors for preterm birth and therefore it was included in the low risk group for analysis.[21]

Studies using vitamin C and E included 18,262 women with 9,151 in control groups and 9,111 in intervention groups. One study using vitamin C only as intervention included 109 women with 57 in control groups and 52 in intervention groups. The studies are summarized in Table 1 below.[20–27]

Study Quality

One study by Beazley et al[26] could not be appropriately assessed due to a lack of information available in the available article. An email was sent to the contact information provided within the article to request further information; however, no response was received prior to the completion of this review.

The remaining seven studies were assessed for validity. Three received good internal validity grades. The most common reason a study received a 'fair' internal validity grade was differences in risk factor rates between intervention and control groups or limited data

reported on the rates of risk factors. Two studies were stopped early which also affected their internal validity rating.[21] Five of the seven studies were rated 'good' with respect to external validity. The two 'fair' grades were given partly due to narrow inclusion criteria limiting generalizability.

Study Results and Synthesis

The study by Casanueva et al[20] was the only study that used vitamin C alone. It studied a low risk population which excluded women with medical disease, multiple gestations, and obstetrical indications for a Cesarean section. The results showed a preterm birth risk ratio of 0.548 when using vitamin C; however, the small sample size meant the result was not statistically significant with a 95% confidence interval of (0.24,1.25). The study included only 109 women and reported a minimal number of incidence rates for preterm birth risk factors resulting in 'fair' internal validity. The study had 'fair' external validity partly due to possible differences in dietary vitamin intake levels and other risk factors between its source population and the general population in most OECD countries. The primary outcome of the study was premature rupture of membranes which is a likely reason the authors' did not report the incidence rate of previous preterm birth (and other risk factors) in the study population. Since this is the only study with vitamin C only as the intervention in a low risk group, the level of evidence is 'inadequate' to conclude whether vitamin C use alone in a low risk population will prevent preterm birth.[20]

Three studies included in this review used vitamin C and E in low risk women. Two studies by Roberts et al[22] and Rumbold et al[23] received grades of 'good' for internal and external validity, had high study populations n=9,969 and 1,877 respectively, and reported outcomes showing no significant differences between the intervention and control group (RR=0.97 and 1.02 respectively). The third study by Xu et al[21] contained a population with a slightly higher risk profile. Despite being stopped early due to safety concerns and conclusions from other studies published during the trial, Xu et al's article included 2,536 participants and was given an internal validity grade of 'fair'. The study had 'good' external validity. The outcome of the Xu et al study showed no statistically significant difference in preterm birth between the intervention group and control group with a risk ratio of 1.07. Roberts et al's study population was approximately twice the size as the other two studies combined. Given this data, the conclusion of this review is the level of evidence for vitamin C and E use during pregnancy is 'convincing' that there is no effect on preterm birth rates in a low risk population.[21–23]

The remaining three studies in this review assessed the use of vitamin C and E in high risk study populations. The total number of study participants is less than in the low risk studies: 3,780 high risk study participants versus 14,382 low risk study participants. Also, these studies had a higher degree of variability in their study population characteristics and internal and external validity. Only one study by Poston et al[25] was assessed to have 'good' internal and external validity and also had the highest number of study participants with more than twice as many as the remaining studies combined. This study with 2,748 women possessing at least one obstetrical risk factor, including 21% having more than one risk

factor, reported a non-statistically significant difference between the intervention group and placebo group that was slightly above null (RR=1.07).[25]

The remaining two studies were deemed to contribute less to the level of evidence for the following reasons: The McCance et al[24] study with 749 women reported a risk ratio of 0.83 that was statistically significant 95% CI of (0.69,1.00) and p=0.046. However, the study was graded 'fair' for internal validity partly due to its high risk of confounding (higher incidence of prior preeclampsia, hypertension, antihypertensive treatment, and microalbuminuria in the placebo group) that would push its reported risk ratio of 0.83 closer to the null. The study had 'fair' external validity mainly due to its low level of generalizability because it used only women with type 1 diabetes. Finally, Chappell et al's[27] study with 203 women had 'fair' internal validity for a variety of reasons (adherence rates not reported, high dropout rate compared to other studies (~20%), and a higher proportion of women of African descent in the placebo group-a preterm birth risk factor) and 'good' external validity. Chappell et al reported a risk ratio of 1.209; however, the confidence interval was very wide due to the low sample size (95% CI=0.377-3.869).[24,27]

Statistically combining the results of the three studies assessing vitamin C and E in high risk women was beyond the scope of this review and would be limited due to their heterogeneity. Therefore, looking at the three studies and what they say about the evidence as an aggregate we considered the following key points: the number of study participants giving outcomes below the null (749) and above (3031) were not insignificant nor extremely large, all risk ratios approached null especially when accounting for possible confounders that would push the risk ratio closer to null in studies[24,27] with results further from it, and the study with the best internal validity[25] produced the results closest to null. Based on this information we determined that the level of evidence is adequate that using vitamin C and E in high risk pregnant women will not decrease preterm birth rates.[24,25,27]

All studies included in this review reported other important obstetrical outcomes and these results are tabulated in Table 2 below. The results reported are preeclampsia, birth weight, preterm birth at less than 34 weeks gestational age, and preterm premature rupture of membranes (PPROM). Most of these outcomes resulted in non-significant findings except as discussed below. Chappel et al[27] reported a significant decrease in rates of preeclampsia in their intervention groups. However, more recent studies with larger sample sizes failed to repeat these findings. Xu et al[21] reported a significant increase in PPROM and Casanueva et al[20] found a significant decrease in PPROM. Casanueva et al recommended further evalutation of this conclusion while promoting appropriate dietary intake. Xu et al concluded their results combined with information from other trials indicated the high doses of vitamin C and E being used in their trial could result in an increased rate of PPROM and we agree with their concern. The increased rate of PPROM was a contributing factor in their decision to end the study early.

Discussion

Summary of Evidence

One study by Casanueva et al[20] used a low risk population and vitamin C alone as the intervention. The study produced a risk ratio with a wide confidence interval including the null; therefore the level of evidence for vitamin C in low risk women was considered 'inadequate'. The group of three studies using vitamin C and E in a low risk population were all well done and taken together produce 'convincing' evidence that there is no effect of the rate of preterm birth with vitamin C 1000mg/day and vitamin E 400IU/day.[21–23] There were three studies using high risk populations with vitamin C and E as the intervention. From these studies we concluded the level of evidence was 'adequate' to say vitamin C and E use during pregnancy for high risk groups would not reduce the rate of preterm birth.[24,25,27]

Harms

None of the studies included in this review reported outcomes related to the typical side effects of vitamin C toxicity: diarrhea or other gastrointestinal disturbances which typically occurs at >3g/day (more than the dose used in these studies). Xu et al[21] reported an increased risk of fetal loss or perinatal death and preterm premature rupture of membranes in their intervention group. Roberts et al[22], Rumbold et al[23], and Poston et al[25] found an increased risk of gestational hypertension and the need for antihypertensive therapy within their intervention groups. Poston et[25] al also found higher rates of small and growth restricted singleton babies born to women with diabetes taking vitamin C and E in some of their sub-group analyses. While these results were not significant, they suggest the need for caution when considering widespread use of vitamin C to prevent preterm birth, especially without evidence of benefit.

Limitations of this review

One limitation of this review is that most studies had a primary outcome different than our outcome of interest which is preterm birth. Therefore, we could not assess the comparability between the intervention and placebo groups on some preterm birth risk factors because they were not reported in the articles. However, since most studies included adequate randomization techniques we can assume the groups were comparable. Therefore the limitation is the need for an assumption and not necessarily that the groups were not comparable.

Another limitation is a lack of data the published articles on the background vitamin C intake. Some studies used food surveys and other methods to give information on the level of vitamin C consumption but these methods can be inaccurate and many studies provided no data. Without this information we cannot make conclusions on whether a threshold intake level that would demonstrate some benefit in patients with poor nutritional statuses. Some studies focused on populations where poor nutrition was more relevant; however, without specific data no comparison could be made between study results from populations with different nutritional levels. Similarly although most studies had exclusion criteria related to intake of vitamin supplements containing vitamin C, the level used in the exclusion criteria

varied among the studies. Therefore, as above it would be difficult to know what amount of vitamin C intake would be confounding.

Another limitation of this review is related to the difference in preterm delivery due to spontaneous labor versus medically indicated iatrogenic causes of preterm birth. As mentioned in the introduction, around 20% of all preterm births are secondary to other obstetrical complications. Most of the articles used in this review did not report data on the preterm birth rate separately for spontaneous labor versus other causes. Therefore, this review cannot draw any conclusions on vitamin C's effect on the different causes of preterm birth.

One of the primary concerns of any systematic review is publication bias affecting the conclusions. In general, it is impossible to prove that a bias is not present. Some attempts made to look for publication bias were searches of clinicaltrials.gov to look for registered studies that were completed but not published and expert interviews to found out if they could identify trials not included in the studies identified by the database search. We also searched multiple databases for conference abstracts and similar pieces of information about studies done that may not have been published as journal articles captured by the search. After performing all of the above, no trials that fit this review were found which would support a low probability of publication bias.

Another limitation of this review was the requirement that any individual study have information published in English to allow for the reviewers to assess the study and abstract the relevant data necessary for the review. This limitation is mitigated somewhat since most trials with study populations similar to OECD countries are often published in English as well as native languages.

A limitation of every review is the possibility of missing trials published and present in the databases searched but missed by the reviewers due to a poor search strategy. A research librarian was consulted in developing the overall search strategy for this review. However, the search was focused using MEDLINE categories in PUBMED and filters in EMBASE. Using these may exclude trials inaccurately. We did a search of un-indexed PUBMED articles to control for part of this limitation.

One study identified from the database searches could not be assessed due to lack of information present in the published article. Attempts were made to obtain more information from the authors of each of these studies but none was received before the conclusion of this review.

During this review's literature search studies were identified meeting most of the inclusion criteria but performed in non-OECD countries. Studies by Steyn et al[28], Spinnato et al[29], and Villar et al[30] are examples which can be useful in drawing our conclusions about vitamin C use to prevent preterm birth. Steyn et al was a study involving vitamin C only and a high risk population in South Africa. The results of the study showed a significant increase in preterm birth in the intervention group with a risk ratio of 1.43 and 95% CI of (1.03,1.99). Spinnato et al studied a high risk group in Brazil taking vitamin C and E. Their results showed a non-significant increase in preterm birth rate in the intervention group with a risk ratio of 1.17

and 95% CI of (0.90,1.52). Villar et al used a high risk group from four countries (India, Peru, South Africa, and Vietnam) and their intervention was vitamin C and E. The results of the study showed a non-significant decrease in preterm birth in the intervention group with a risk ratio of 0.9 and 95% CI of (0.7,1.0). These results demonstrate a lack of benefit and possibly even harm to the intervention even in populations with higher proportions of nutritional deficiencies.

Conclusion

Using vitamin C alone to prevent preterm birth was only addressed in one study identified by this review. The study had 'fair' validity. Therefore, the level of evidence is 'inadequate' to make any recommendations related to public health policy or clinical decision making. The evidence does not preclude the use of vitamin C supplementation on an individual patient basis and should be considered especially in patients with low nutritional status.[31]

There were six studies on vitamin C and E which produced a high level of evidence showing no beneficial effect of the intervention on preterm birth rates. The evidence was graded as 'convincing' in low risk groups and 'adequate' in high risk groups. In addition, there was some evidence in the studies of increased harms in the intervention groups indicating harms may outweigh any unproven benefits related to preterm birth. With this evidence we recommend not implementing a public health policy based on using vitamin C supplementation beyond adequate daily intake to reduce preterm birth. However, we do not believe the evidence prevents the use of vitamin C supplementation for individual patients if there is another indication for supplementation or an identified deficiency.

Typically the lack of studies on vitamin C alone combined with the biochemical evidence suggesting a benefit would encourage further research in this area. However, the biochemical evidence is based on the antioxidant properties of vitamin C. Therefore, studies using vitamin C and E, both antioxidants should also have showed a benefit if we expected vitamin C alone to be beneficial based on biochemical data related to its antioxidant effects. However, six studies on vitamin C and E in this review provided a high level of evidence of no benefit. If an effect had been seen with vitamin C and E, there would be a stronger impetus to perform more vitamin C only studies to determine if the effect was due to vitamin C or E. Likewise if new evidence becomes available suggesting a benefit to vitamin C beyond its antioxidant properties, then more studies utilizing vitamin C alone would be beneficial. At this point we do not see a need for further investigations related to vitamin C use to prevent preterm birth in the population of interest based on the evidence found in this review.

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Abbreviations

OECD	Organization for Economic Co-operation and Development

USPSTF	United States Preventive Services Task Force
US	United States
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
IU	International Units
PPROM	Preterm Premature Rupture of Membranes

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Table1:

Summary of Studies

Vitamin C Only									
Author(s)	**Year**	**Population Risk Profile***	**Intervention**	**No. of Controls**	**No. receiving Intervention**	**Internal Validity Grade**	**External Validity Grade**	**Risk Ratio**	**95% Confidence Interval**
Casanueva, E. et al[31]	2005	Low	Vitamin C 100mg/d	57	52	Fair	Fair	0.5481†	(0.2400,1.2516) †
Vitamin C and E									
Author(s)	**Year**	**Population Risk Profile***	**Intervention**	**No. of Controls**	**No. receiving Intervention**	**Internal Validity Grade**	**External Validity Grade**	**Risk Ratio**	**95% Confidence Interval**
Xu, H. et al[21]	2010	Low‡	Vitamin C 1000mg/d & Vitamin E 400IU/d	1293	1243	Fair	Good	1.07	(0.89,1.29)
Roberts, J. et al[22]	2010	Low		4976	4993	Good	Good	0.97	(0.87,1.09)
Rumbold, A. et al[23]	2006	Low		942	935	Good	Good	1.02	(0.73,1.43)
McCance, D. et al[24]	2010	High		374	375	Fair	Fair	0.83	(0.69,1.00)
Poston, L. et al[25]	2006	High		1376	1372	Good	Good	1.07	(0.93,1.22)
Beazley, D. et al[32]	2005	High		48	52	§	§	1.319§	(0.75,2.31) §
Chappell, L. C. et al[27]	1999	High		142	141	Fair	Good	1.209†	(0.377,3.869) †

*Population risk profile defined as: High=Previous history of obstetrical complications, abnormal uterine artery Doppler waveforms or chronic medical condition (e.g. diabetes mellitus or hypertension requiring medication). Low=No previous history of obstetrical complications or chronic medical disease.

†Not reported in original article: Calculated from available data.

‡Study included a high and low risk group; however, many of the risk factors mentioned above were excluded from both groups and the high risk group was less than 30% of the study population

§Unable to assess study given information available in published article. Authors were contacted but no response received when this review was finalized. These studies were not included in the final analysis and conclusion. Results shown for comparison only.

Table 2:

Summary of Other Outcomes From Studies

Vitamin C Only					
Author(s)	**Year**	**Preeclampsia – Relative RiskRatio**	**Birth Weight Increase – Difference of Means**	**Birth <34wks Gestational Age – Relative Risk Ratio**	**Preterm Premature Rupture of Membranes – Relative Risk Ratio**
Casanueva, E. et al[31]	2005	NR	0 (−219.21,219.21)	NR	0.31 (0.11,0.89) *
Vitamin C and E					
Author(s)	**Year**	**Preeclampsia – Relative Risk Ratio**	**Birth Weight Increase – Difference of Means**	**Birth <34wks Gestational Age – Relative Risk Ratio**	**Preterm Premature Rupture of Membranes – Relative Risk Ratio**
Xu, H. et al[21]	2010	1.04 (0.75,1.44)	†	1.05 (0.76,1.47)	1.97 (1.31,2.98)
Roberts, J. et al[22]	2010	1.07 (0.93,1.24)	3.0 (−19.70,25.70) *	‡	0.96 (0.75,1.22)
Rumbold, A. et al[23]	2006	1.20 (0.82,1.75)	6.0 (−48,59)	1.06 (0.57.1.97)	1.31 (0.77.2.25)
McCance, D. et al[24]	2010	0.81 (0.59,1.12)	†	1.08 (0.50,2.34)	0.74 (0.44.1.24)
Poston, L. et al[25]	2006	0.97 (0.80,1.17)	-59 (−122,4) *	1.23 (0.95,1.59)	NR
Beazley, D. et al[32]	2005	NR	-139 (−520.49,242.49) *,§	NR	NR
Chappell, L. C. et al[27]	1999	0.46 (0.24,0.91)	-60 (Unable to calculate)	NR	NR

* Not reported in original article: Calculated from available data.

† Birth weight not reported. No statistically significant differences in number of small for gestational age infants.

‡ Relative risk ratio for infants born prior to 32 weeks gestational age was 0.86 (0.69–1.06)

§ Unable to assess study given information available in published article. Authors were contacted but no response received when this review was finalized. These studies were not included in the final analysis and conclusion.

NR Not reported.