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Letters to editor

Preeclampsia prevention: a case-control study nested in a cohort

La prevención de la preeclampsia: un estudio de casos y controles anidado en una cohorte

Preeclampsia prevention

Prevención de la preeclampsia

Dear Editor:

I read two articles about preeclampsia in Colomb Med (Cali) published by Alzate *et al.*[1], (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4732504/) and Herrera *et al.*[2], and I would like to address some related comments. Colombia and Brazil are developing countries where pregnancy-related hypertensive disorders and associated conditions constitute major concerns in public health area[1-3]. Preeclampsia (PE) is characterized by the development of arterial hypertension and proteinuria after 20 weeks of pregnancy in previously normotensive pregnant women[1-3]. Alzate *et al.*, compared the protective effects of calcium alone and of calcium plus conjugated linoleic acid, in Colombian nulliparous women under higher risk of PE[1]. Their study included 387 women with diagnosis of PE and 1,054 normotensive controls, with mean age of 26.4 (13-45) years, and entered the study before week 12 of gestation. The group of adolescents (13-18 years old) was represented by 49 (12.7%) of the total. Calcium plus conjugated linoleic acid used by pregnant adolescents had preventive effect on PE, but the prevention did not occur with utilization of calcium alone[1]. The authors emphasized the similarity of biochemical changes in PE and in the metabolic syndrome - hypertension, hyperlipidemia, low HDL, and insulin resistance. In animals, the supplementation with conjugated linoleic acid may reduce inflammation, hyperlipidemia, and insulin resistance, which are well-known risk factors for PE[1] Moreover, conjugated linoleic acid can improve the metabolic syndrome in humans, but its combination with calcium is necessary for an efficacious protection against PE[1]. Herrera *et al.*, evaluated results of the Colombian prenatal care program based on the bio-psychosocial model (BPSM) after five years of the implementation. The general maternal mortality and the rate of PE were reduced in 23% and 22%, respectively[2]. Therefore, one should implement similar programs in other low-income populations[2]. They also commented gestational hypertensive disorders and complications like the HELLP syndrome and eclampsia, with maternal and neonatal morbidity and mortality[2]. Eclampsia is episode of tonic-clonic seizures in people with PE, without other causes[2,3]. Santos *et al.* reported a Brazilian young with late postpartum eclampsia, characterized by the onset of convulsions more than 48 hours, but less than four weeks after delivery. Worthy of note, this severe condition may occur even without any antecedent of PE[3]. Therefore, the early diagnosis and prompt treatment constitute a challenging task. Current prevention of PE is not satisfactory; however, a reduction in maternal mortality due to preeclampsia/eclampsia can be achieved by implementation of prenatal programs based on BPSM, in addition to use of calcium plus conjugated linoleic acid[1,2].

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None to disclaim

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Calcium and linoleic acid supplements in the prevention of pre-eclampsia

Los suplementos de calcio y el ácido linoleico en la prevención de la preeclampsia

Dear Editor:

Alzate *et al.*[1], (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4732504/) conducted a nested case-control study to (quote) "*estimate the protective effect from calcium [supplement] alone [CC], compared to calcium plus conjugated linoleic acid [CC+CLA] in nulliparous women at risk of preeclampsia*". Based on a crude analysis of the data in Table 3,[1] they concluded that neither CC nor CC+CLA reduced the risk of preeclampsia in the whole sample, but that CC+CLA significantly decreased risk among women 13-18 years old. A quick look analysis of the data in this table shows this conclusion is mostly based on the fact that none of the cases in 13-18 year old women was treated with CC+CLA. Contrary to the authors' interpretation, this does not point to a protective effect of CC+CLA, it simply indicates that the assumption of positivity has being violated and, consequently, that an effect for this age group cannot be estimated[2]. In fact, the probability of getting no treated cases in this age-group was 28%, since only 15.5% of all women received CC+CLA. Also, accurate estimates of effect in women 34-45 years old were not possible, because there were only seven women who used CC+CLA in this age group. In spite of the limited sample size, the authors restricted their attention to the apparent protective effect of CC+CLA in 13-19 year old women, while ignoring apparent harmful effects in older women. I estimated age-specific rate ratios (RR) by fitting a saturated conditional complementary log-log[3] to the data in Table 3 and found that CC+CLA was protective among women 13-19 (RR= 0.61, 95% CI: 0.41- 0.90), but harmful in women 19-34 (RR= 1.74, 95% CI: 1.21- 2.50) and 35-45 years old (RR= 4.98, 95% CI= 1.74-14.30). Of course, this approach is an improvement over a naive crude analysis, but does not solve the problem of violation and near violation of positivity described above. An overall age-adjusted RR was 1.02 (95% CI= 0.89-1.17; p= 0.756). Thus, this study provides no evidence of a beneficial effect of CC+CLA in preventing preeclampsia in any age group.

On the other hand, the authors neglected to explain why the total number of women is 2,703 in Table 3 and 1,441 in Figure 1 and Table 2[1]. More important, it is surprising that they restricted their attention to the age-specific effects of CC+CLA, which were obviously unidentifiable, while ignoring the obvious age-related decrease in the effect of CC shown in Table 3: odds ratios of 1.3, 0.9, and 0.4 in 13-18, 19-34, and 35-45 years old, respectively. In fact, corresponding age-specific RR from a clog-log model with a treatment-by-age interaction (p= 0.069) were 1.44 (95% CI= 0.85-2.44), 0.92 (95% CI= 0.73-1.16), and 0.59 (95% CI= 0.34-1.01). This pattern could have resulted not from an effect of CC, but from CC being more frequently prescribed to younger women, who have a higher risk of preeclampsia. This selective use of treatment leads to confounding by indication, a well-recognized limitation of observational studies of the effectiveness of therapeutic interventions.[4] Unfortunately, the authors made no attempt to address this type of bias, since they disregarded any clinical factor, such as blood pressure, that could increase the likelihood of both treatment with calcium supplements and risk of preeclampsia.

Moreover, the authors' claim that the beneficial effects of CC+CLA were greater than those of CC is not supported by the data. First, one treatment could not be better than the other because neither of them decreased the risk of preeclampsia. Second, no formal comparison of the two treatments was made. I tested this hypothesis by fitting a saturated clog-log model to the data (Table 3, n= 2,703) and found that none of the treatments decreased the risk of preeclampsia, and that CC (RR= 0.89) seemed more protective than CC+CLA (RR= 1.01), but not significantly so (p= 0.60). Of course, the authors' findings as well as those from my analyses are likely biased, due to the lack of adjustment for confounding factors. Basically, these findings are of no use for clinical or policy decision making.

In spite of very large trials showing no clinical benefits[5, 6], calcium supplements are still widely offered to women at high risk of preeclampsia in developing countries[7]. Maybe it is time to re-evaluate their usefulness to prevent preeclampsia by looking again at the existing data. But this time with the clear purpose of avoiding confirmation bias[8] and keeping in mind, as Feynman argued, that "*the first principle [of science] is that you must not fool yourself—and [yet] you are the easiest person to fool*"[9].

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I have no conflict of interest to declare.

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Conceptual, epidemiological and methodological design aspects for the study of pre-eclampsia

Aspectos de diseño conceptual, epidemiológicas y metodológicas para el estudio de la preeclampsia

Dear Editor:

We read with high interest the article by Alzate *et al.*[1], (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4732504/) and hereby we share comments about its design, study population and statistical approach along with revisiting some key concepts of the disease.

The prevalence of preeclampsia in Colombia is 4.5%[2] and a case-control study is appropriate to investigate risk and protective factors associated in such setting and their corresponding Odds Ratios. However, in the population studied by Alzate *et al.*, the proportion of preeclampsia is 10% (387/3,866). Under this scenario, a retrospective cohort study design is also appropriate and allows for direct estimation of incidences and relative risks could also be considered with direct estimates of relative risk. The exposure under study here (calcium prescription) is easy to measure from medical or administrative records or electronic files, therefore its comprehensive assessment in the whole population is feasible, cheap and easy to detect. Case-control studies are usually recommended when these requirements are not met for the exposure variable.

The study data was collected from two time periods. Consequently, we do not know what could have possibly changed during these years, as well as the difference in such changes between these two time periods, in the study population or in other contextual factors (health care quality, health system, regulations, physician's attitudes, medication prescription, blood pressure approaches, etc.) and how they effect on the outcome (preeclampsia) and its determinants (the way prescriptions are registered and recordered could even change over time). There is no assurance regarding the data was collected by the same team or under the same standards. This can introduce severe biases due to unmeasured confounders in both time periods. A stratified analysis for each time period can help in this regards at least partially.

In regards to its pathophysiology and management, one of the suggested interventions is calcium supplementation. At least one systematic review establishes the protective effect of calcium occurs at doses greater than 1 g/d of elemental calcium[4]. However, Alzate *et al.,* refer to studies[5,6] that administered 600 mg/d of elemental calcium and 450 mg/d of linoleic acid in a population of women with high risk for preeclampsia on whom calcium dosage was performed to confirm the depletion of calcium before starting the suplementation. Alzate *et al.,* do not report such values or even if such dosage was performed. If this calcium depletion exists, then there is a physiological and biological plausibility grounds to attribute the positive protective effect of calcium administered. The study population belongs to the Colombian Social Security System and is likely to not have severe calcium deficiency. This is a key consideration since the effectiveness of calcium supplementation is reported in women with a pre-pregnancy deficit, so the recovery of calcium reservoirs prevents the development of preeclampsia[7].

In the statistical section we consider appropriate to take into account the variable "age" because it was different between cases and controls. However, the stratification by age is not the right approach. The reasons for this is the reduction of the sample size which leads to small numbers in specific cells and lead us to an OR of 0.0. Table 3 shows that none of the patients supplemented with CC+ALC developed preeclampsia and perhaps this is due to the stratification. A better approach is an age-adjusted multiple logistic regression to compute adjusted Odds Ratios as well as other confounders.

Finally, the exposure variable was randomized in previous studies and the actual adherence to treatment was verified by close monitoring in each prenatal visit, questionnaires, and counting pills left in the medication container. These methods are the best to assess adherence to supplementation during pregnancy[8]. This was not done by Alzate *et al.,* and questions whether the CC+ALC combination really was what prevented preeclampsia in these pregnant women. If it is not possible to measure the actual implementation (calcium intake) then we cannot assess in a valid and reliable way its effectiveness.

In general, research about preeclampsia is important in order to better understand and manage this disease. However, we also believe all conceptual, epidemiological and methodological aspects must rigorously be taken into account in order to obtain reliable valid and generalizable results.

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The authors declare no conflict of interest

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Authors Response: Preeclampsia prevention: a case-control study nested in a cohort

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To the Editor:

When Bautista affirm that "none of the cases in 13-18 year old women was treated with CC+CLA" there is a misinterpretation of the fourfold table in case control studies. What you can read in the four fold table for age 13 to 18 (Table A)
Meaning that only 29 primigravidae received CC+CLA and that among them there was not any case of preeclampsia, becoming all the exposed controls. Remember that we are working with incident cases in a nested case control design. Their odds of becoming a "case" are 0/49 compared to the odds of 29/150 of becoming a "control". And the sample size is bigger enough to assess an OR with a 95% confidence interval between 0.00 and 0.44. The purpose of the authors in publishing the paper was to ask to the scientific community what is happening in this age group that we don't know, and why is Calcium still recommended despite of the alarming perspective of no effect and increasing incidence rates of preeclampsia.

With respect to the apparent discrepancy between Tables 2 and 3 (original article), it is easy to see that the sum of cases and controls before 2013, during the only calcium period (Table B).

Table A. Frequency of exposed and unexposed women.

Exposition	Preeclampsia	Controls
Exposed (CC+CLA)	0	29
Unexposed (CC)	49	150

Whereas the table when all cases and controls were evaluated after the introduction of the administration of calcium citrate plus conjugated linoleic acid during the second period (2013-2014) in Table 3 (original article) (Tabla C)

This is because during 2013, 59 new cases and 110 controls were recruited into the study. There is no way to sum the 1,441 + 1,262, and nowhere it is suggested in the paper.

With respect to Monteverde, Coronel-Acosta and Segura letter [xref ref-type="bibr" rid="r03"]3[/xref], the 4.5% prevalence mentioned by them is the prevalence in Villavicencio, Colombia in 2004. The proportion of new cases among primigravidae of medium and high class income, privately insured, in Cali, Colombia between 2010 and 2014 was 10%, and the risk in primigravidae is always higher than in other pregnant women. The nested case control is recommended in situation when you have 387 incident cases in the cohort and a pool of 3,866 possible controls and, instead of searching 3,866 clinical histories, which takes about half an hour for each clinical history in our electronic records, it is cost saving and equally effective to pick up randomly 1,054 controls.

Table B. First period before 2013.

Treatment CC	Exposition	Preeclampsia	Controls	Total
13-18	Exposed (CC)	13	40	
	Unexposed (CC)	28	115	196
19-34	Exposed (CC)	82	244	
	Unexposed (CC)	174	489	989
35-45	Exposed (CC)	11	26	
	Unexposed (CC)	20	20	77
		328	934	1,262

Table C. Second period 2013-2014.

Tratment CC+CLA	Exposition	Preeclampsia	Controls	Total
13-18	Exposed (CC+CLA)	0	29	
	Unexposed (CC+CLA)	49	150	228
19-34	Exposed (CC+CLA)	57	131	
	Unexposed (CC+CLA)	244	696	1,128
35-45	Exposed (CC+CLA)	4	3	
	Unexposed (CC+CLA)	33	45	85
		387	1,054	1,441

Obviously case control studies are not clinical trials, like our correspondents pointed out, and its role in the evaluation is to assess the safety and effectiveness in clinical care, using like in our case the information available in clinical histories in insurance funds. It is clear that the result is not casual ("fortuito"), when the odds ratio is cero (OR= 0.00) with 0.05% confidence intervals between 0.0 and 0.44 in adolescent primigravidae as mentioned above.

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