INVESTIGACIÓN ORIGINAL

ASSOCIATION BETWEEN PREGNANCY-INDUCED HYPERTENSION AND POST-PARTUM INFECTION IN THE INSTITUTO MATERNO INFANTIL, BOGOTÁ, COLOMBIA. CASE CONTROL STUDY

ASOCIACIÓN ENTRE HIPERTENSIÓN INDUCIDA POR EL EMBARAZO E INFECCIÓN POSTPARTO EN EL INSTITUTO MATERNO INFANTIL DE BOGOTA, COLOMBIA. ESTUDIO DE CASOS Y CONTROLES

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RESUMEN

Introducción: la infección puerperal es una de las principales causas de morbimortalidad materna en los países en desarrollo. La identificación de factores predisponentes a infección permitirá intervenirlos para prevenir su aparición o si no son prevenibles, utilizar otras medidas que disminuyan su impacto. La toxemia al parecer favorece el desarrollo de infección por alteraciones de la inmunidad celular y humoral. El objetivo del presente trabajo es evaluar si las pacientes con preeclampsia tienen mayor riesgo de presentar infección puerperal.

Materiales y Métodos. se realizó un estudio de casos y controles pareados por el día del parto. Criterios de inclusión: Mujeres que tuvieron parto en el Instituto Materno Infantil, entre 15 y 45 años. Criterios de exclusión: pacientes con infección clínica al ingreso, inmunosupresión, expulsivo mayor a dos horas, antibioticoterapia una semana antes del parto, eclampsia posparto tamaño muestral:

nivel de confianza del 95%, poder 80%, relación 1:1, frecuencia de exposición de los controles 8%, OR estimado: 2, se determinó se requerían 369 pacientes por grupo. Se compararon los dos grupos usando la prueba t student pareada *Wilcoxon signed ranks tests*, según normalidad en variables continuas y *test* de McNemar para proporciones. Se hizo análisis bivariado al estratificar por la vía del parto y se evaluó el OR crudo y ajustado por las variables de confusión utilizando regresión logística condicional.

Resultados: el riesgo de infección estuvo aumentado en preeclampsia leve (OR 8,28 IC95% 2,04 – 33,5) y preeclampsia severa (OR 9,42 IC95% 2,10 – 41,3). En adolescentes (OR 3,87 IC95% 1,75 – 8,54) y cesáreas también se aumentó el riesgo de infección (OR 8,17 IC95% 2,71 – 24,62).

Conclusiones: se deberán evaluar posibles alternativas en la duración y los esquemas antibióticos considerados de primera elección en la actualidad para la profilaxis en operación cesárea no complicada por toxemia.

Palabras clave: infeccion puerperal, preeclampsia, estudios de casos y controles, factores de riesgo.

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SUMMARY

Introduction. Post-partum infection is one of the main causes of maternal morbidity-mortality in developing countries. Identifying factors predisposing to infection will allow intervention for preventing them or (if they cannot be prevented) using other means for reducing their impact. Toxaemia seems to increase the risk of infection developing due to alterations in cell and humoral immunity. The present work's object is to evaluate whether patients having preeclampsia have a greater risk of presenting post-partum infection.

Materials and Methods. A matched case control study was carried out. Pairing by day of birth was done. Inclusion criteria: women giving birth in the Instituto Materno Infantil aged between 15 and 45. Exclusion criteria: clinical patients having infection on being admitted, immunosuppression, second stage of delivery greater than two hours, antibiotic-therapy one week before birth, post-partum eclampsia. Sample size: 95% level of confidence, 80% power, 1:1 ratio, 8% frequency of controls' exposure, estimated OR 2. It was determined that 369 patients would be required per group. The two groups were compared by using t student test paired or Wilcoxon signed ranks test (according to normality in continuous variables) and McNemar's test for percentages. Bivariable analysis was done on stratifying by birth route. Crude and adjusted OR were estimated for controlling confounders using conditional logistical regression.

Results. The risk of infection was increased in mild preeclampsia (OR 8.28, 95%CI 2.04–33.5) and severe preeclampsia (OR 9.42, 95%CI 2.10–41.3). The risk of infection was also increased in adolescents (OR 3.87, 95%CI 1.75 – 8.54) and who underwent caesarean section (OR 8.17, 95%CI 2.71 – 24.62).

Conclusions. Using prophylactic antibiotics must be evaluated in vaginal birth and alternatives should be evaluated in terms of duration and currently considered first-choice antibiotic schemes for prophylaxis in caesarean section in patients suffering from preeclampsia.

Key words: Pre-Eclampsia, Puerperal infection, Case control studies, Risk factors.

INTRODUCTION

Post-partum infection is one of the main causes of maternal mortality in Bogotá and Colombia.[1-4] It is an important cause of morbidity, since it affects between 2% to 10% of mothers in the immediate post-natal period.[5] It has a negative impact on an Institutions' image, meaning that it has become an indicator of the quality of services being offered.[6] It also represents high costs for the health system and society in general as it prolongs hospital stay, requires costly medicaments in most cases and frequently leads to surgical procedures.

There are recognised factors increasing the risk of post-partum infection which can be detected during prenatal control, such as anaemia, poor nutrition, obesity, diabetes and lower genital tract infections or factors associated with labour such as time for premature rupture of membranes, duration of labour, intrauterine foetal monitoring and factors associated with birth such as caesarean operation, poor surgical technique and hypovolemic shock.[7-9] Recognising risk factors has been shown to be a useful technique as it allows preventative interventions destined to reduce the frequency of post-partum infection.

A high frequency of post-partum infection has been observed in the Instituto Materno Infantil in patients suffering from pregnancy-induced hypertension (PIH).[10] Few references have been found sustaining how the presence of PIH increases the frequency of post-partum infection in both vaginal and caesarean birth when reviewing such association in the literature.[11]

Possible causes of this association have been argued: immunosuppression, micronutrient deficiency, hyperalbuminaemia and the presence of ischemic tissue due to the vasospasm present in patients suffering from PIH. On the other hand,

patients suffering from preeclampsia are more frequently submitted to caesarean which in itself increases the risk of infection.

Determining whether patients suffering from preeclampsia have a greater risk of infection is important as it could lead to proposing possible interventions such as using antibiotic prophylaxis in patients with vaginal birth or in those submitted to a caesarean operation or using other antibiotics instead of current prophylactic schemes. The purpose of the present work is thus to evaluate the possible association between pregnancy-induced hypertension and post-partum infection, taking other possible confounders into account which could affect such possible association.

MATERIALS AND METHODS

A matched case control study was designed. Cases were paired by day of birth. Pregnant women attending the Instituto Materno Infantil (IMI) in Bogotá between 18th February 1995 and 21st December 1998 were eligible. The IMI is a perinatal maternal reference hospital dealing with people having few financial resources.

Patients presenting post-partum infection during the period mentioned above were considered as being cases. Patients giving either vaginal or caesarean birth in the IMI during this lapse of time without presenting post-partum infection were considered to be controls. The inclusion/exclusion criteria are presented in **table 1**.

Sample

Sample size was calculated on 95% confidence level, having 80% power and a 1:1 case-control ratio paired by day of birth to avoid secular tendencies regarding post-partum infection. An 8% exposure frequency was considered in the non-exposed group and 0.12 Spearman coefficient of correlation, with an estimated Odds Ratio of 2 according to prior crude estimate based on IMI data giving us a calculation of 369 patients per group.

Sampling was done at the convenience of the cases presented. Once the day of birth had been determined, controls were sought coinciding with the period of exposure. Simple random sampling was done on these, based on a random number table. Selection criteria were then reviewed to see whether patients complied as controls; if they did not comply, they were replaced by the following history or that immediately before.

Information was noted concerning socio-demographic variables: age, years (level) of schooling and civil status. Factors associated with pregnancy such as: gestational age on being admitted, associated diseases, proteinuria and severity of toxaemia. Factors associated with birth such as: birth route and number of hours between premature membrane rupture and birth.

The following definitions were used for establishing exposure and outcomes:

Pregnancy-induced hypertension: figurers regarding blood pressure measured by sphygmomanometer, greater than or equal to 140/90 mmHg, obtained after week 20 of gestation and up to 48 hours post-birth (according to ACOG recommendations). If this was associated with proteinuria it was classified as preeclampsia, in turn

Table 1. Selection criteria in studying cases and controls for evaluating the association between preeclampsia and post-partum infection

Inclusion criteria
- Women aged between 15 and 45.
- Vaginal birth or Caesarean in IMI.

Exclusion criteria
- Patients having diagnosed or suspected urinary infection, pneumonia, infections of the ear or upper respiratory tract on being admitted.
- Women having demonstrated immunosup-pression (HIV, diabetes, etc.).
- Prolonged expulsion (longer than 2 hours).
- Antibiotic-therapy prior to birth (1 week).
- Postpartum eclampsia.
- Women having fever, membrane rupture last-ing more than 12 hours, diagnosed or sus-pected chorioamnionitis before birth.

being classified according to severity as: mild or severe preeclampsia which included eclampsia.[12]

Post-partum infection: poly-microbial invasion of tissues of the uterus or peritoneal surface following a birth. It was considered that post-partum infection was present if the following criteria were present: fever, tachycardia, purulent or fetid lochia, leukocyte count greater than 15,000, neutrophil count greater than 80, uterine subinvolution and pain on uterine palpation.[4] It was classified according to the site of the invasion as: endometritis, myometritis and peritonitis.

Premature membrane rupture: continuity solution in chorioamniotic membranes with consequent loss of amniotic liquid before the clinical onset of labour. This was categorised in terms of time being more or less than 12 hours as base risk.

Gestational age: time in weeks of gestation when a patient was admitted calculated from the first day of the last menstruation or by ecography of the first three-month period. This was categorised as pregnancy being greater or lesser than 37 weeks.

Associated diseases: presence of diseases or predisposing factors existing before a pregnancy or during it.

Caesarean operation: giving birth by abdominal route.

Age was categorised as being in the adolescent category if a patient was aged 19 or less.

Analysis

The two groups' base characteristics were described by means of central tendency and dispersion for continuous variables and percentages for categorical variables.

Univariable analysis was done by paired student t test or Wilcoxon signed ranks test for continuous variables according to normality and McNemar's test for percentages when comparing categorical variables between cases and controls. Bivariable analysis was done for evaluating association between possible risk factors and post-partum infection when stratified by birth route.

The crude OR was estimated by conditional logistical regression for evaluating association between pregnancy-induced hypertension and post-partum infection, as well as possible association with other risk factors. This method was used for controlling confounders.

RESULTS

Information relating to 375 cases and 375 controls was collected between 18th February 1995 and 21st December 1998.

The two groups' base socio-demographic characteristics can be observed in **table 2**. It can be seen that in spite of statistically significant differences in age, previous number of births and the number of hours of membrane rupture, these variables lack clinical relevance. No statistically significant differences were found in level (years) of schooling. On the other hand, birth route, not having a stable partner, antecedents of pregnancy-induced hypertension and time spent in labour were different from the clinical and statistical point of view.

Increased clinical and statistically significant risk of post-partum infection, OR 1.74 (1.26 − 2.40), was generally found in patients having pregnancy-induced hypertension, without taking the severity of the disease into account. If discrimination is made between mild and severe preeclampsia then it can be seen that the risk was greater in the latter group.

On evaluating other possible factors associated with post-partum infection, it was observed that belonging to the adolescent age group and caesarean birth group increased the risk of infection. A protection-inducing effect was observed in primipara patients and those having longer membrane rupture time (**table 3**).

A protection-inducing effect was observed in patients who had been in labour regarding patients who did not go into labour, patients with labour lasting 1 to 6 hours OR 0.53 (0.30 − 0.94), 7 to 12 hours 0R 0.19 (0.12 - 0.32) and more than 12 hours 0R 0.13 (0.07 − 0.23) when stratifying the data by the number of hours spent in labour.

It can be seen that increased risk persisted with a similar tendency in the aforementioned variables on stratifying according to birth route, except in patients submitted to caesarean section in which premature rupture of membranes and mild preeclampsia had a protection-inducing effect. A greater risk of infection was observed in those giving vaginal birth and caesarean section amongst patients suffering from severe preeclampsia (**table 4**).

The regression model best explaining the appearance of infection took the variables shown in **table 3** into account. It was observed that adolescents and patients suffering from severe preeclampsia and those submitted to caesarean section had a high risk of infection. This risk was also high in patients suffering from mild preeclampsia, but only became manifest on controlling interaction due to caesarean section and labour lasting more than six hours, caesarean section and slight preeclampsia. The model also confirmed the protection-inducing effect of the aforementioned factors (i.e. time spent in labour), however the greater risk disappeared in multivariable analysis since the most parsimonious model did not include this variable.

DISCUSSION

Developing post-partum infection has been associated with multiple factors present before pregnancy, factors associated with pregnancy and birth factors. This study evaluated the possible association between pregnancy-induced hypertension and post-partum infection based on the clinical histories of patients presenting it, based on the presumption that a diagnosis of preeclampsia was made before birth leading to the supposition that hypertension came before infection.

This study found a greater risk of infection in patients suffering from preeclampsia; persistent association was seen in univariable, bivariable and multivariable analysis. Such association could have been over-estimated since patients suffering from preeclampsia had a greater risk of being submitted to caesarean section (an intervention increasing risk of infection *per se*[13]), an association confirmed in the present study. Analysis stratified by birth route showed that patients suffering from preeclampsia had 2 to 3 times more chance of presenting post-partum infection following vaginal birth. A protection-producing effect arising from slight preeclampsia was observed in the group of patients submitted to caesarean section, an effect which disappeared in multivariable analysis.

Some studies have shown an association between preeclampsia and infection. Preeclampsia increases

Table 2. Base characteristics of patients in the study of cases and controls for evaluating the association between preeclampsia and post-partum infection			
Variable	**Cases n=375**	**Controls n=375**	**p value**
Age	24.9 ± 0.3	22.7 ± 0.3	0.000*
Gestational age	38.6 ± 0.14	38.5 ± 0.13	0.51*
Hours spent in labour	10.15 ± 0.27	6.85 ± 0.29	0.000*
Hours of membrane rupture	2.4 ± 0.15	1.7 ± 0.13	0.0005*
Number of births	1 (0-8)	1 (0-9)	0.003**
Civil state			
No stable union	29.5%	21.1%	0.008***
Stable union	70.5%	78.9%	
Type of birth			
Caesarean	48.8%	36.5	0.0003***
Presence of PIH	34.1 %	22.9	0.001***

*   t Student test for non-independent samples
**   Wilcoxon signed ranks test
*** McNemar test

Table 3. Risk of infection regarding possible confusion factors in studying cases and controls for evaluating association between preeclampsia and post-partum infection

Variable	Cases n=375	Controls n=375	OR (95% CI)	Adjusted OR Conditional Logistic regression
Adolescents	37.6%	20.8%	2.55 (1.63 – 3.98)	3.87 (1.75 – 8.54)
Gestational age (less than 37 weeks	11.0%	7.7%	1.56 (0.83 - 2.92)	1.61 (0.49 – 5.31)
Less than 6 years schooling	51.2%	48.8%	0.98 (06.66 – 1.45)	0.88 (0.44 – 1.78)
More than 12 hour premature rupture of membranes	6.1%	11.5%	0.48 (0.24 – 0.95)	1.26 (0.38 – 4.1)
Primigravid	14.1%	34.5%	0.28 (0.17 – 0.47)	0.22 (0.09 – 0.53)
Caesarean section	48.8%	36.5	2.03 (1.31– 3.14)	8.17 (2.71 – 24.62)
Mild preeclampsia	17.6%	16.3%	1.64 (0.99 – 2.69)	8.28 (2.04 – 33.5)
Severe preeclampsia	16.5%	6.7%	3.60 (1.78 – 7.25)	9.42 (2.10 – 41.3)

Table 4. Risk of infection of possible confusion factors stratified by type of birth in studying cases and controls for evaluating the association between preeclampsia and post-partum infection

Characteristics	Vaginal birth	Caesarean
Adolescence	2.43 (1.58 – 3.71)	2.27 (1.35 – 3.81)
Primipara	0.32 (0.20 – 0.52)	0.28 (0.16 – 0.49)
Pre-term birth	1.42 (0.69 – 2.89)	1.37 (0.67 – 2.77)
Unstable union	1.56 (1.00 – 2.45)	1.54 (0.92 – 2.58)
Premature membrane rupture	0.73 (0.40 – 1.34)	0.23 (0.07 – 0.69)
Labour lasting more than six hours	0.21 (0.08 – 0.57)	0.29 (0.10 – 0.64)
Mild preeclampsia	2.18 (1.27 – 3.74)	0.40 (0.27 – 0.83)
Severe preeclampsia	3.43 (1.43 – 8.19)	2.21 (1.89 – 4.05)

the frequency of urinary infection (OR 3.21, 95%CI 2.36-4.38),[14] frequency of endometritis[15] and infection of the wound (OR 2.3, 95%CI 1.1-4.9);[12] however, only the last mentioned study was prospective. Another study did not find increased risk; however, this research did not have enough power for finding a difference.[16] There is thus no decisive evidence for supporting or rejecting such possible association.

Teran *et al* considered that preeclampsia is caused by a series of nutritional, environmental and genetic factors leading to creating imbalance between nitric oxide (NO), superoxide (O_2^-) and peroxinitrate free radicals in the vascular endothelium.[18] Increased

cytokine response (IL2, IL6 and FNTα) and an increase in leukocytes and neutrophyls have also been found in these patients when comparing them with normal pregnancies, suggesting that perturbation of the immune system could precede clinical manifestations of toxaemia.[17,18]

It has been found that patients suffering from severe preeclampsia present alterations in cellular and humoral immunity which could make them susceptible to infection. A possible cause of overestimating the risk of association in a study is the fact that patients with toxaemia admitted to IMI are routinely given an uterine revision which could be a risk factor for developing infection later on, above all in patients suffering from the disease's severe form where multiple manifestations deriving from the systemic liberation of inflammatory mediators could be taken as signs of infection. On the other hand, infection frequently being presented in severe forms could be considered as being biologically plausible.

The association found between being an adolescent and the greater risk of post-partum infection could be explained by a greater frequency of lower genital tract infection[19-21] or greater frequency of the same socio-cultural factors determining other poor perinatal results in this age-group such as pre-term birth;[22] however, prospective studies must be carried out for evaluating such possible association.

As bacteriological sample-taking for bacterial vaginitis or germs producing sexually-transmitted infections is not a routine procedure in IMI then no information could be provided in this respect. This also meant that the effect of anaemia, nutritional state, obesity and the number of prenatal controls on later development of post-partum infection could not be evaluated since this information was differentially estimated to a greater degree in cases and controls.

The protection-producing effect of factors such as membrane rupture time, the number of hours spent in labour and caesarean section was probably related to the use of prophylactic antibiotics in patients considered to be at high risk at the time in the Institution. However, this information could not be precisely obtained from the clinical histories.

The study also suggested that a high or low risk of infection approach is not suitable for deciding on using prophylactic antibiotics, as patients considered to be at low risk have a greater risk of infection. This concept was brought into practice in IMI as part of an ongoing quality-improvement programme which reduced maternal morbidity arising from infection.[5]

It still remains to test these findings by designing cohorts taking the presence of lower genital tract infection, uterine examination, the liberal use of prophylactic antibiotics in caesarean section and vaginal birth into account. However, prophylactic antibiotic schemes covering a greater number of germs in these patients or being applied for a longer period should be considered as opposed to currently implemented routine schemes.

CONCLUSIONS

Both slight preeclampsia and severe preeclampsia carry a greater risk of post-partum infection. Using prophylactic antibiotics must be evaluated in vaginal birth patients given possible base pathology complications or those arising from post-partum infection and alternatives evaluated in terms of duration and currently considered first-choice antibiotic schemes for prophylaxis in caesarean operations which do not become complicated by toxaemia.

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