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Original Article

Reduction of maternal mortality due to preeclampsia in Colombia-an interrupted time-series analysis

Reducción de la mortalidad materna por preeclampsia en Colombia - un análisis de series de tiempo interrumpido

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Abstract

Introduction. Preeclampsia is the most important cause of maternal mortality in developing countries. A comprehensive prenatal care program including bio-psychosocial components was developed and introduced at a national level in Colombia. We report on the trends in maternal mortality rates and their related causes before and after implementation of this program.

Methods: General and specific maternal mortality rates were monitored for nine years (1998-2006). An interrupted time-series analysis was performed with monthly data on cases of maternal mortality that compared trends and changes in national mortality rates and the impact of these changes attributable to the introduction of a bio-psychosocial model. Multivariate analyses were performed to evaluate correlations between the interventions.

Results: Five years after (2002-2006) its introduction the general maternal mortality rate was significantly reduced to 23% (OR= 0.77, CI 95% 0.71-0.82). The implementation of BPSM also reduced the incidence of preeclampsia in 22% (OR= 0.78, CI 95% 0.67-0.88), as also the labor complications by hemorrhage in 25% (OR= 0.75, CI 95% 0.59-0.90) associated with the implementation of red code. The other causes of maternal mortality did not reveal significant changes. Biomedical, nutritional, psychosocial assessments, and other individual interventions in prenatal care were not correlated to maternal mortality ($p= 0.112$); however, together as a model we observed a significant association ($p= 0.042$).

Conclusions: General maternal mortality was reduced after the implementation of a comprehensive national prenatal care program. Is important the evaluation of this program in others populations.

Resumen

Introducción. La preeclampsia es la causa más importante de mortalidad materna en los países en desarrollo. Se desarrolló e introdujo en Colombia y a nivel nacional un programa de cuidado prenatal que incluyó componentes bio-psicosociales. Se muestran las tendencias de las tasas de mortalidad materna y las causas relacionadas antes y después de la implementación del programa.

Métodos: Las tasas de mortalidad general y específica fueron monitoreadas durante 9 años (1998-2006). Un análisis de series de tiempo ininterrumpido se realizó con datos mensuales de casos de mortalidad materna y se compararon las tendencias de cambio en las tasas de mortalidad nacional y el impacto de los cambios atribuibles a la introducción del modelo. Se hizo un análisis multivariado para evaluar la asociación entre las intervenciones.

Resultados: Cinco años después de la introducción del programa (2002-2006) la tasa de mortalidad materna se redujo significativamente en 23% (OR= 0.77, CI 95% 0.71-0.82). La implementación del MBPS redujo la incidencia de la preeclampsia en 22% (OR= 0.78, CI 95% 0.67-0.88), igual la mortalidad materna por complicación del parto por hemorragias en 25% (OR= 0.75, CI 95% 0.59-0.90). Otras causas de mortalidad materna no mostraron cambios significativos. No se correlacionó la mortalidad materna con intervenciones de cuidado prenatal individuales como las biomédicas, nutricionales y psicosociales ($p= 0.112$), sin embargo, ellas en conjunto como un modelo (biopsicosocial) si observaron una asociación significativa ($p= 0.042$).

Conclusiones: La mortalidad materna general se redujo después de la implementación de un programa nacional de cuidado prenatal. Es importante evaluar este programa en otras poblaciones.

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Introduction

In developing countries, maternal mortality is a national public health problem¹, and reducing it is a millennium development goal. The social and family life implications, the hospital financial costs and the therapeutic management repercussions are very important points to consider in developing countries.

To achieve this goal, a comprehensive prenatal care program based on the bio-psychosocial model (BPSM) was developed, introduced, and implemented as a national standard of healthcare in Colombia. The BPSM was previously reported to impact obstetric and psychosocial risk factors reducing maternal morbidity and mortality^{2,3}.

The first population trial was performed in the western region of Colombia (1995-1997) (n= 14,354)⁴. The implementation of the BPSM in this region was associated with lower maternal mortality rates (range: 60-63 x 10⁵ live newborns) as compared with the remaining geographic regions of the country during the same time (range: 74-100). Similar results were reproduced and validated in national and international trials⁵⁻⁸.

The baseline data for maternal mortality in the country was gathered during 1998-1999. In 2000, the government promulgated the standard obstetric protocols for the reduction of maternal mortality at the national level (Resolution 412, April 2000, Ministry of Health and Social Protection). In 2001-2002, health teams throughout the country were trained on the BPSM. During 2002-2006 the BPSM model was introduced as public health policy at the national level.

To date, the effectiveness of this national program on maternal mortality is not known. This paper reports the trends and changes in maternal mortality rates before and after introduction and implementation of the BPSM at the national level.

Materials and Methods

A quasi experimental study was performed. The Colombian Ministry of Health and Social Protection launched the norms, regulations, adopted the model, and trained the health teams. Adequate implementation of BPSM was verified through official surveillance which also reported coverage on the application of the protocols.

Maternal mortality had a dual notification system for epidemiological surveillance of maternal deaths (SIVIGILA system and vital statistics). Since 1992, the country has had an official quality assurance program to ensure good medical care with surveillance of this program provided by the Ministry of Social Protection. The most frequent causes of maternal mortality were evaluated: preeclampsia, eclampsia, HELLP syndrome, postpartum hemorrhage, abruption of placenta, placenta previa, sepsis, complications during labor, and embolism.

Actions to improve training among health professionals in rural locations, a decrease in the number of pregnancies lacking medical attention, improved institutional attention during deliveries, improved access to antenatal care, and implementation of a red code for postpartum hemorrhage were all implemented since 2000 in accordance with standard obstetric protocols (Resolution

412, April 2000, Ministry of Health and Social Protection).

The programmatic strategy to reduce preeclampsia risk included BPSM for ambulatory care, and best medical practices during hospital care in accordance with standard obstetric protocols. The introduction of BPSM was directly supervised by the Ministry of Health and Social Protection. The application of BPSM included obstetric, nutritional, and psychosocial interventions as elements in an innovative and integrative model²⁻⁸.

The first introductory step was to train health teams to more fully understand the government guidelines and the methodology of the model (2000-2001). During program introduction, a book concerning the methodology (First Edition, 7300 books ISBN 958-670-095-X) was provided along with scientific support, paper copies of the format for gathering information, and BIOPSI software to alert professionals regarding obstetric and bio-psychosocial risks. The software was also used to record all information regarding interventions along with the maternal and perinatal outcomes.

In at least one follow-up meeting, a second edition of the book (3100, ISBN 958-33-3447-2) was provided, the methodology was reinforced, questions were addressed, and the implementation of the software was evaluated. The books were introduced by the Ministry of Social Protection which included a specific declaration of ethical approbation. Informed consent was not required as BPSM was a national public health policy. A third edition of the book was later provided for the implementation of BPSM (1000 books ISBN 978-958-670-716-9) and provided all prophylactic and medical treatments for specific intervention for pregnant women identified with high risk to develop preeclampsia (2002-2006) (Table 1).

Gestational hypertension was defined as pregnancy-induced hypertension ($\geq 140/90$ mm Hg) after twenty weeks of gestation without proteinuria (<300 mg/24 h)¹. Preeclampsia was defined as pregnancy-induced hypertension with significant proteinuria (≥ 300 mg/ 24 h)¹. Eclampsia was defined as preeclampsia with seizures¹. HELLP syndrome was defined as pregnancy-induced hypertension with hemolysis, elevated liver enzymes, and a low platelet count¹. Maternal mortality (MM) was defined as maternal death during pregnancy, birth and forty days in puerperium, and not associated with incidental or accidental causes.

Data collection

The National Department of Statistics (DANE) (www.dane.gov.co/vitalstatistics) collected data on maternal mortality. An epidemiological surveillance committee (COVE) analyzed all maternal deaths. This committee was legislatively established and was composed of the physician in charge of the patient, independent academic gynecologists, epidemiologists, and government officials. This committee analyzed each clinical record, autopsy record, and verbal autopsy to determine the cause of maternal death and associated factors.

Statistical methods

An interrupted time-series analysis was designed and conducted to analyze the Colombian national maternal mortality data between 1998 and 2006. Using monthly data for those years in cases of

Table 1. Description of a biopsychosocial model for the intervention of prenatal risk. Colombia 2002-2006**Definition of high maternal risk**

1. One or more obstetric risk factors¹ and/or high bio-psychosocial risk (≥ 3 points)³ and/or
2. Abnormal result from the routine and specific laboratory screening and/or
3. Abnormal follow-up of obstetric graphic parameters (< percentile 5 or > percentile 95)

Routine screening

First trimester: Identification of Obstetric risk factors¹ and assessment of routine laboratory test (Hemoglobin and Hematocrit, VDRL, fasting glycemic status, HIV, Blood group and Rh factor, and urine sample)

Second and Third trimester: Bio-psychosocial risk assessment³ (Biomedical risk factors and psychosocial risk factors) and specific laboratory tests according to the maternal risk [Urine culture, O'Sullivan screening test (50 g/1 hour) and/or Glucose tolerance test (100 g/3 h)]. An early echography (12-14 weeks of gestational age) to reconfirm gestational age followed by a second echography (24-28 weeks of gestational age)

Second half of pregnancy: Assessment and graphic follow-up of the evolution of the maternal weight, uterine height and blood pressure using standard graphics.

Routine supplementation

Ferrous sulphate (200 mg/d) from 14 weeks of gestational age up to labor.

Folic acid (1 mg/day from 6 weeks of gestational age to 14 weeks of gestational age)

Calcium carbonate (600 mg/d) from 18 weeks of gestational age up to labor.

Specific intervention for patients with high maternal risk to develop preeclampsia

I. Ferrous sulphate (200 mg/d) after 20 weeks of gestational age if the hemoglobin level is ≥ 11 g/L in the first trimester (to avoid early oxidative stress)

II. Folic acid (1 mg/day) from 6 weeks of gestational age up to labor (for development of the placenta and improving the endothelial function)^{10,15}

III. Calcium citrate (600 mg/d) and conjugated linoleic acid (450 mg/d) from 18 weeks of gestational age up to labor (to improve endothelial function⁶ and to decrease intracellular free calcium⁷)

IV. ASA (acetyl salicylic acid 75 mg/d) from 18 to 34 weeks of gestational age applied only to patients with the following three clinical conditions: 1. Previous Chronic blood pressure hypertension. 2. Antiphospholipids antibody syndrome. 3. Antecedent of previous early preeclampsia (<34 weeks of gestational age).

V. Early detection and treatment of Urinary infection, Gestational Diabetes and High bio-psychosocial risk²

maternal mortality, we were able to compare trends and changes in national maternal mortality rates. Specifically, we used the techniques developed by Box and Jenkins⁹, often referred to as the ARIMA models. In this case, an ARIMA impact analysis was used. Intervention components (dummy variables) were constructed to test whether there was any impact of the intervention that could not be accounted for by normal fluctuations and long-term trends. If the C mistake is high there are any evidence that the intervention affected the time-series ($(1)/\sigma^2$; σ^2 = residual variance before of the intervention and after intervention).

The maternal mortality rate is defined as the ratio of the number of maternal deaths per 100,000 live births. The general maternal mortality rates included all causes and specific maternal mortality rates were calculated for the most common causes of death (i.e. preeclampsia, HELLP syndrome, complications of labor, hemorrhage, embolism, sepsis and thrombophilia).

To determine the appropriate application of the BPSM, we evaluated the proportion of pregnant patients at high risk, those receiving calcium supplements, pregnant women receiving treatment for

urinary tract infection and/or gestational diabetes, and those receiving social support when high levels of anxiety were identified. For the multivariate analysis, maternal mortality was the dependent variable. The independent variables were antenatal care during the first trimester, obstetric, nutritional and psychosocial risk interventions. Multiple linear regressions were performed to test the correlations between early prenatal care and the interventions for malnutrition, psychosocial risk and gestational diabetes. Correlation coefficients at their 95% confidence intervals were calculated by using the statistical package SPSS® for Windows (version 20). A $p < 0.05$ was regarded as statistically significant

Results

All pregnant women in antenatal care were included in the study. Table 2 shows socio- demographic and obstetric characteristics for every category. Seventy-four percent of the pregnant women received all protocols designed to prevent the most common causes of maternal morbidity and mortality. The adequate introduction of BPSM was confirmed with the rate of calcium supplementation (range 56.8%-97.1%) for the study population, early identification

and treatment of bio-psychosocial risk¹⁰ (range 8.9%-22.1%), early identification and treatment of urinary tract infections⁴ (range 5.7%-41.6%), and adequate detection and treatment of gestational diabetes (range 0.9%-3.2%) (Table 3).

Pregnant women with pre-paid medical insurance who had access to early prenatal care had the lowest incidence of preeclampsia (range 0.4%-1.4%); pregnant women without medical insurance (low socioeconomic status) had a greater incidence of preeclampsia (range 1.4%-3.2%). The application of BPSM was influenced mainly by superimposed preeclampsia versus preeclampsia de novo.

Macrosomia (birth weight >90th percentile for gestational age) has had a significant reduction in the incidence (5.1% to 4.2% , OR= 0.816, CI95%= 0.809 - 0.822)

Six years after the implementation of BPSM (2002-2006) the general maternal mortality was reduced 23% (OR= 0.77, CI 95% 0.71-0.82). The slight reduction in birth rates during the period was not associated with the reduction in general maternal mortality ($p= 0.83$).

With the introduction of obstetric protocols (2000-2001), changes in the ratio of maternal mortality was insignificant, in addition with the introduction of BPSM (2002-2006) the reduction in general maternal mortality decreased to 23% (Fig. 1) (interrupted time series analysis, Chi-square= 83.61, $p= 0.024$) (Table 5), same results were observed with the specific maternal mortality by preeclampsia (3.6% to 45.0% (median: 28.9 x 10⁵ versus 15.9 x 10⁵ live newborns) (interrupted time series analysis, C= 41.40, $p= 0.968$) (Table 5).

The reduction of complications of labor was of 34.4% (median: 8.6 x 10⁵ versus 6.4 x 10⁵ live newborns), by hemorrhage (postpartum, placenta previa and abruption of placenta) of 25% (median: 11.3 x 10⁵ to 8.5 x 10⁵ live newborns), by embolism of 3.7% (median 2.8x 10⁵ versus 2.7x 10⁵ live newborns), by sepsis of 2.0% (median 10.2x 10⁵ versus 10.0x 10⁵ live newborns), and by thrombophilia of 1.7% (median 2.87x 10⁵ versus 2.82x 10⁵ live newborns).

Incidence of maternal mortality by preeclampsia had a significant reduction (median: 28.9 versus 15.9 x10⁵ live newborns) and by macrosomia (birth weight >90th percentile for gestational age had a significant reduction (5.1% versus 4.2%, respectively) (Table

4). The maternal mortality rate due to labor complications as cephalopelvic disproportion, cesarean section and hemorrhage was correlated with the incidence of preeclampsia (adjusted R²= 0.62, CI95%: 0.27-0.94, $p= 0.006$).

Multiple linear regressions showed that maternal mortality by preeclampsia was not associated to early prenatal care (first trimester) , early identification and treatment of urinary tract infections, nor to early treatment of gestational diabetes (second trimester) ($p= 0.11$). Furthermore, the above interventions together with calcium supplementation were not correlated to maternal mortality by preeclampsia ($p= 0.24$). However, a significant correlation was observed with the above interventions together with nutritional supplementation²⁻⁷ and improved social support (BPSM) (Table 2) ($p= 0.042$).

Discussion

The main cause of maternal mortality in developing countries is preeclampsia, which increases perinatal mortality by fivefold. The problem is of greater concern when we consider that maternal mortality in Colombia is four times higher than in developed countries¹. After five years of implementation of BPSM the general maternal mortality remained reduced by 23% ($p= 0.024$) (Fig. 1), interestingly by preeclampsia (Fig. 2).

This study was conducted during a nine-year period (four years before and five years after BPSM) using a dual notification system for epidemiological surveillance of maternal deaths and with a similar system to guarantee the quality of medical care. Prior to 1998, the country only had one epidemiological maternal-death surveillance system. This caused an important bias resulting in under-reporting of maternal deaths that is not found in today's dual-notification system. Bias was controlled with this dual surveillance system.

A potential confounder was the impact of the small reduction in the number of newborns due to family planning on maternal mortality during this time period; this reduction was not correlated to maternal mortality. Another potential confounder was poor quality in medical care which was well-observed and controlled. The highest proportion of biomedical interventions occurred early in prenatal care (Table 4).

The observed results were attributed to the implementation of obstetric protocols with nutritional and psychosocial interventions (BPSM). Calcium supplementation alone does not reduce free intracellular calcium and does not improve endothelial function, which can be improved with the combined effect of other nutritional factors^{6,7,10}. Urinary and periodontal infections and gestational diabetes are related to preeclampsia risk associated with oxidative stress and endothelial dysfunction¹¹. Early detection and early treatment can decrease endothelial injury⁴. Enhancing endothelial function reduces multisystem failure, which is the most common cause of maternal death associated with preeclampsia.

Currently, preeclampsia prevention is not possible. This is especially true in developing countries where half of the population is poor and where there are nutritional and psychosocial disadvantages. The Colombian social security system guarantees access and

Table 2. Socio-demographic and obstetric characteristic of Colombian pregnant women 1998-2006.

Variables	Before (1998-2001)	After (2002-2006)
	%	%
Mean Age (SD) (years old)	24.2±6.5	25.1± 6.9
Afro-Colombian	16.9	17.8
Indigenous	4.4	4.9
Mixed ethnic backgrounds	78.7	78.2
Illiterate	5.2	5.1
Early adolescents (<16 years old)	5.8	7.1
Primigravidity	34.2	35.8
Chronic blood pressure hypertension	2.8	3.2
Multiple pregnancy	0.7	0.9
Cesarean section	34.8	35.9

*BPSM: bio-psychosocial model

Table 3. Biomedical interventions to reduce preeclampsia risk by Colombian regions 2002- 2006.

	FAC	GDI	UTI	CASUP	GH	PREECL	HBPRS
Region	(%)	(%)	(%)	(%)	(%)	(%)	(%)
North	71.5	1.5	41.5	97.1	3.5	1.4	16.3
Bogota	87.2	2.5	14.8	62.3	1.8	1.6	18.1
Middle	93.7	2.2	20.9	56.8	1.9	0.4	8.9
Tolima	53.9	0.9	5.7	58.6	1.0	2.7	21.2
Cundinamarca	47.0	3.0	21.0	62.8	3.0	1.4	11.1
Valle	63.7	3.2	20.6	62.1	2.1	1.5	12.1
Country	77.7	2.0	17.1	70	1.9	1.4	14.9

FAC: First antenatal control during the first trimester. GDI: Gestational Diabetes Incidence (ACOG criteria). UTI: Urinary tract infection incidence (Urine culture). CASUP: Linoleic acid and/or calcium supplementation. GH: Gestational hypertension (pregnancy-induced hypertension without significant proteinuria ≥ 300 mg/24 h) (ACOG criteria). PREECL: Preeclampsia (pregnancy-induced hypertension with significant proteinuria) (ACOG criteria). ACOG: American College of Obstetrics & Gynecology. HBPRS: High Bio-psychosocial Risk (≥ 3 points)^{2,3}.

quality in prenatal and hospital care. It is widely accepted that the best hospital care reduces maternal mortality due to preeclampsia, complications of labor, hemorrhage, sepsis, and thrombophilia¹. As was observed in this study, general maternal mortality was reduced by 9.0% (Fig. 1) and specific maternal mortality by preeclampsia was reduced by 3.6% (Fig. 2) after the introduction and implementation of the obstetric protocols.

An increased number of health teams in the country were trained and monitored. The BPSM has biological plausibility for reducing preeclampsia risk^{2-8,12}, as was demonstrated in different studies and with different national and international populations. Endothelial dysfunction is an early condition present in pregnant women who later develop preeclampsia. It can develop from nutritional deficiencies, metabolic disorders, psychosocial stress, or asymptomatic infections. Inflammation and oxidative stress could be underlying mechanisms that greatly contribute to the development of insulin resistance associated with preeclampsia¹³. The BPSM included early identification and modification of factors with potential influence on endothelial function^{4,15} (Table 2).

Healthy pregnant women present a certain degree of inflammation and preeclamptic women have an excessive inflammatory response¹⁶. Interestingly, high stress and low social support during

pregnancy decreases cellular immunological response¹⁷, increases C-reactive protein IL1 β and IL6¹⁸⁻²¹, and reproduces PE in animals²² (exclusively human disease). The role of these cytokines during normal pregnancy is not entirely understood. Some have been related to the mechanisms involved in the initiation and maintenance of gestation. For instance, tumor necrosis factor (TNF α) and natural killer cells appear to regulate the invasion and growth of trophoblast in maternal and spiral arteries¹⁴. The stimulation of the sympathetic nervous system can alter NK cell function, facilitating poor invasion of extra-villous trophoblast²³. The role of psychosocial factors in preeclampsia is a growing development^{22,24-26}. The impact of psychosocial factors on the pathogenesis of cardiovascular disease is well documented^{25,27}.

Blood pressure assessment, proteinuria screening, and early termination of pregnancy have been successful means to reduce maternal mortality by preeclampsia as was observed with the introduction of the obstetrics protocols (3.6%) (Fig. 1). We believe that the high prevalence of diseases or conditions associated with oxidative stress and endothelial dysfunction can increase the probability of having a multisystem failure if preeclampsia is present. In developing countries the most common cause of maternal mortality by preeclampsia is from a multisystem failure.

A decrease in maternal mortality could be related to the action of many factors and many were intervened with the implementation of obstetric protocols (2000-2001) (Figs. 1 and 2); however, with the introduction of BPSM (2002-2006) the reduction in general maternal mortality increased by three times (Fig. 1); interestingly after the implementation of BPSM the reduction of maternal mortality by preeclampsia increased by seven times. The implementation of the National Public Health Plan (Decree 3037 Ministry of Health and Social Protection) (2007-20210) included the BPSM and the maternal mortality by preeclampsia remained low (Fig. 2).

Today, prevention of preeclampsia is not possible; however, a reduction in maternal mortality by preeclampsia was observed with the introduction and implementation of obstetric protocols and BPSM. The reduction in maternal mortality by postpartum hemorrhage was associated with the implementation of red code. The national experience of a reduction in maternal mortality due to preeclampsia in a developing country is the main contribution of

Figure 1. General maternal mortality. Colombia 1998-2006

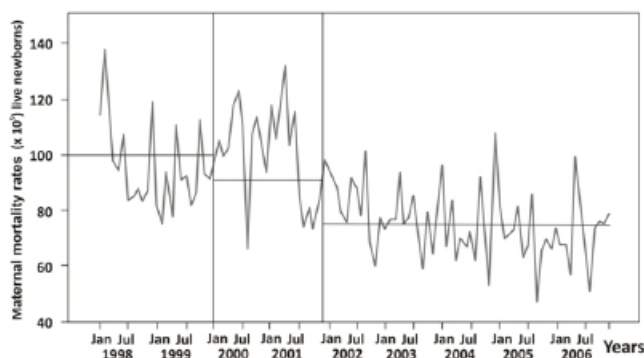


Figure 2. Maternal mortality rates by causes. Colombia 1998-2010

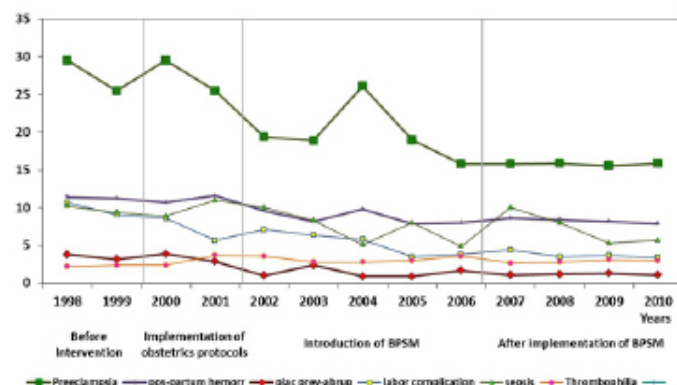


Table 4. Birth weight with the introduction of a biopsychosocial model (2002-2006)

	Newborns	Low Birth Weight	Macrosomia (> 90th percentile)
Year	(N)	(%)	(%)
1998	720.9	7.22	5.4
1999	746.2	7.03	5.1
2000	752.8	7.33	5.1
2001	708.3	7.43	4.8
Before (Mean)*		7.25	5.1
2002	700.5	7.63	4.7
2003	710.7	7.75	4.6
2004	723.1	7.90	4.6
2005	720.0	8.10	4.4
2006	714.5	8.43	4.2
After (Mean)*		7.90	4.6

*Before and after implemented of bio-psycho-social model

this study. There are clear implications for regional public health care. A limitation of the study is the fact that observational prospective studies can be biased; however, randomized double-blind controlled trials are not possible due to ethical considerations. Community work to evaluate the impact of this model in other populations is still being done.

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Conflict of interest

The authors report no competing or conflict of interest with the project and participating institutions.

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Table 5. Interrupted time series analysis. Colombia 1998-2006.

Maternal mortality	Model	Mistake	Residual Variance	Chi-square*	p value
General	AR (1)	297.489.859	355.796	83.61	0.024
Preeclampsia	AR (1,1)	254.261.887	61.422	41.40	0.968
Eclampsia	AR (1,1)	130.794.681	21.549	60.70	0.451
Severe preeclampsia	AR (1,1)	795.657.253	22.621	35.17	0.996

*Chi square with sixty degree of freedom

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