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Research paper

Post-partum depression: a cross-sectional study of women enrolled in a conditional cash transfer program in 30 Brazilian cities

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ABSTRACT

Objective: Investigate factors associated with symptoms of postpartum depression in mothers from families in social vulnerability.
Methods: Information was used from the baseline of a randomized trial to assess a child development program that enrolled 3,242 children < 12 months of age from beneficiary families of the *Bolsa Família* Program residing in 30 municipalities (counties) in six states of Brazil. The Edinburgh Postnatal Depression Scale (EPDS) was applied to the mothers, and depression was defined as score ≥10. Information on the mother (schooling, age, parity, marital status, skin color, smoking, number of prenatal appointments, and planning of the pregnancy), family (paternal schooling, household crowding, support from the child's father and the family during the pregnancy, and number of children under 7 years living in the household), and infant (sex, gestational age, birthweight, Apgar score, and child's age at the time of the interview) was collected. Prevalence rates for depressive symptoms were calculated with crude and adjusted odds ratios (OR) and 95% confidence intervals (95%CI), using hierarchical logistic regression, in a multilevel model.
Results: The analysis included 3,174 mothers with information on EPDS. The interviews were conducted on average 7.9 months (standard deviation= 2.9) after childbirth. Overall prevalence of depressive symptoms was 26.5% (25.0-28.1%). In the adjusted analysis, higher parity was associated with higher odds of postpartum depression (p <0.001). Women with ≥3 previous deliveries showed an odds 84% higher of presenting depressive symptoms (OR= 1.84; 1.43-2.35) than primiparae. Higher maternal and paternal schooling, presence of husband or partner, and having received support from the child's father and the family during the pregnancy were protective factors against postpartum depression.
Conclusion: The study showed high prevalence of postpartum depressive symptoms. Promotion of parental education, alongside with the promotion of support to the woman during pregnancy by the child's father and by the

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family, as well as family planning leading to birth spacing are measures that may help to prevent postpartum depressive symptoms.

Introduction

Although pregnancy is generally a positive event in the woman's life, for some mothers the postpartum period is a time of sadness and melancholy [1], with depressive symptoms ranging from the so-called "baby blues" in one extreme to psychosis at the other extreme [2].

Prevalence of postpartum depressive symptoms varies according to the time transpired since delivery, with the measurement instrument's properties (sensitivity and specificity), and with the site where the study is performed. Brazilian studies that used the Edinburgh Postnatal Depression Scale (EPDS) [3] found prevalence rates varying from 9.4% to 26.3% with a cutoff of ≥13 [4–7], and 31.3% to 48.0% for EPDS ≥10 [8,9].

Postpartum depression is relevant, not only because it negatively affects the woman's social relations, but also because it harms other members of the family. Studies with population samples indicate that some 30% of mothers with postpartum depression remain depressed throughout and after the first year after giving birth [1], jeopardizing their marital relations and negatively affecting the family environment [10,11]. Depressed mothers talk less with their children, express fewer positive emotions, and are more likely to use physical punishment to correct or control their children's behavior, when compared to non-depressed mothers [12,13].

Various factors such as poverty, low schooling, teenage pregnancy, previous psychiatric illness, poor marital relations, stressful life events, negative attitudes towards the pregnancy, lack of social support, and depression during the pregnancy have been associated with postpartum depression in various studies [1,2,14]. The current study aimed to investigate the prevalence and association between maternal, family, and newborn's factors and the presence of depressive symptoms in the first year after childbirth, in a sample of women from poor families in 30 Brazilian municipalities (counties), during the baseline study of the Impact Assessment of the Happy Child Program [15].

Methods

The Happy Child Program (PCF in Portuguese) is offered by the Ministry of Citizens' Affairs to children under three years age [16]. Through weekly visits to the families and other actions, the PCF aims to promote child development through strengthening of family ties, prevention of situations of neglect and violence against the child, and reduction of malnutrition. The target population for the PCF is children of beneficiary families of the *Bolsa Família* Program [17], whose per capita monthly income is less than BRL 85.00 (U$ 16.00); if the family includes children or adolescents up to 17 years of age, this cutoff increases to BRL 170.00 (U$ 32.00) per month. Maintenance of the *Bolsa Família* transfer is conditioned on some requirements that the family must meet: enrolling and keeping the children and adolescents from six to 17 years of age in school and taking children under seven years of age to health units for immunization and monitoring growth and development, according to the schedule recommended by the health teams. For pregnant women, the conditionality also includes appearing for prenatal appointments.

Baseline of the Impact Assessment of the Happy Child Program [15]

The Impact Assessment Study of the PCF is a randomized, controlled trial that enrolled 3,242 children residing in 30 municipalities (counties) from six states of Brazil. The assessment is limited to children enrolled in the first year of life, who will be followed prospectively for three years. None of the children were participating in the PCF when the baseline was performed, so all the mothers were included in the current study. Further details on the assessment methodology have been published in a previous article [15].

Maternal depressive symptoms

Assessment of maternal depressive symptoms used the EPDS [3]. The scale contains 10 questions that assess the most common symptoms of depression. Each question has four possible answers, ranging in score from 0 to 3, and interviewees must choose the answer that describes how they felt in the last seven days. The sum of the values produces the scale's total score. The scale was applied verbally by the interviewer in a single session, according to the questions' order in the instrument. The scale was validated in Brazil for use in postpartum women [18] and in the general population, both for men and women [19]. The main analyses used EPDS ≥10, with sensitivity of 82.6% (75.3-89.9%) and specificity 65.4% (59.8-71.1%) [18]. The cutoff ≥13, with 59.6% sensitivity (49.5-69.1%) and 88.3% specificity (83.9-91.9%) [18], was used in supplementary analyses.

Independent variables

We studied the family and individual characteristics of the PCF beneficiary children and their parents. These variables were arranged in a hierarchical conceptual model built by the authors (Fig. 1). The most distal level consisted of the family's socioeconomic status, age of the child's father (in complete years, later categorized as <30, 30-39, and ≥40 years), schooling of the child's mother and father (in complete years, later categorized as 0-4, 5-8 and ≥9 years), whether the mother lived with husband or partner (yes or no), and skin color self-reported by the woman (white, brown, or black). The family's socioeconomic status was defined by principal components analysis, and was based on questions extracted from the *Demographic and Health Survey (DHS) Wealth Index* [20], that includes source of potable water, type and number of toilets, materials used in the household's flooring, walls, and ceiling, energy source used for cooking (gas, firewood, electricity), and household assets such as electricity, television, radio, vacuum cleaner, clothes washing machine, freezer/refrigerator, microwave, air conditioner, microcomputers, automobile, and housekeeper. Households were arranged from the poorest to the wealthiest, and for analysis they were divided into household wealth quintiles [21].

The second level included the mother's age (in complete years, later categorized as <20, 20-24, 25-29, 30-34, and ≥35); parity, defined as the number of previous gestations that resulted in live birth or stillbirth, and not including gestations that ended in abortion, and later categorized as 1, 2, and ≥3 deliveries; and household crowding (more than three persons per bedroom, yes or no).

The third level consisted of the mother's behavioral characteristics: current smoking (yes or no); planning of the pregnancy (yes or no), and number of prenatal appointments in the pregnancy with the index child (yes or no); and support from the child's father (yes or no) and the family during the pregnancy (yes or no).

The fourth and most proximal level consisted of the child's characteristics: sex (male or female), gestational age (infants born at < 37 weeks were classified as preterm), birthweight (in grams), 5-minute Apgar <7 (yes or no), and child's age at the time of the interview in months (later grouped as <3, 3-4, 5-6, 7-8, 9-10, 11-12). For the analysis, gestational age and birthweight were combined, generating a variable with four categories: "term birth with adequate weight for gestational age (AGA)", "preterm with AGA", "term, small for gestational age (SGA)", and "preterm SGA". SGA was classified as children

with weight for gestational age and sex below the 10th percentile of the standard curve defined by the INTERGROWTH-21st Project [22].

The number of children under seven years of age living in the household was obtained with two questions. First, the mother was asked the number of children that lived in the house. Then she was asked how many children there were in the house besides the PCF beneficiary child that were under seven years of age. The number of children under seven years was tabulated by adding one to the number furnished by the mother, in order to include the index child.

The interviewers in the Impact Assessment of the PCF had at least secondary education and prior experience in survey activities. Training of the interviewers from the six states lasted 40 hours and was conducted in the national capital, Brasília. The data were collected by applying a standardized questionnaire with questions taken from the *Multiple Indicator Cluster Survey (MICS),* used by UNICEF in various countries, and from questionnaires used in the birth cohorts in Pelotas, Rio Grande do Sul, Brazil, from 2004 to 2015. The interviews were stored in tablets in the REDCap software. The detailed research protocol and instrument are available at http://www.epidemio-ufpel.org.br/site/content/pesquisas/index.php?study=518.

Statistical analysis

The analysis consisted of the sample's description, followed by calculation of the prevalence of maternal depressive symptoms with 95% confidence intervals (95%CI) in the entire sample and according to the independent variables. Logistic regression was then used to obtain crude and adjusted Odds Ratios with the respective 95%CI. The adjusted analysis was hierarchical, according to the conceptual model in Fig. 1. We initially analyzed the first-level variables and retained in the multivariate model those that were associated with the outcome with $p \leq 0.20$, as has been recommended for the retention of confounding variables in a model [23]. We then included the second-level variables and so on until the most proximal level. In each level, variables associated with the outcome at $p > 0.20$ were removed in backward stepwise fashion. All analyses were multilevel, considering the natural clustering of data by state and municipality of the mother's residence: the first level consisted of the states of Brazil, the second of the study's municipalities, and the third of the postulated risk factors according to the conceptual model.

Ethical aspects

The Impact Assessment Study of the Happy Child Program was approved by the Institutional Review Board of the Federal University in Pelotas, affiliated with the Brazilian National Council for Research Ethics (CONEP) of the Ministry of Health, under review number 2.148.689, and is deposited in ReBEC (Brazilian Clinical Trials Registry) with the identifier RBR-4 × 7dny.

Results

Of the 3,242 mothers assessed in the baseline assessment of the of the PCF impact evaluation study, 3,174 had information on EPDS and were included in the current analysis. The proportion in the first (poorest) quintile was higher among mothers with no information on EPDS than among those with EPDS information (32.3% and 18.9%, respectively; p= 0.043). Postpartum time ranged from 0.1 to 12.9 months, with a mean of 7.9 months (standard deviation = 2.9). Only 26 of the 3,174 children were older than 12 months, due to the time elapsed between the family identification and the actual interview that was originally planned to occur in the first year of the child's life. Overall prevalence of depressive symptoms was 26.5% (25.0-28.1%) with a cutoff of ≥10 and 15.3% (12.0-18.5%) with a cutoff of ≥13 points.

Table 1 shows that due to the methodology, about 20% of the families belonged to each of the quintiles for socioeconomic status. As for the age of the child's father, slightly over half (51.7%) were under 30 years of age. More than half of the mothers (60.2%) and fathers of the children (52.4%) had nine or more years of schooling. The majority of the women self-reported their skin color as brown (75.2%), and 63.1% lived with husband or partner (Table 1).

Fewer than 15% of the mothers were adolescents (<20 years), and 30.2% were primiparous. More than one-fifth of the mothers lived in households with crowding (22.6%) (Table 1).

As for behavioral characteristics, 7.8% were smokers and 19.0% reported fewer than six prenatal appointments during the index pregnancy. Fewer than one-third had planned the pregnancy (30.1%), and the majority reported having received support from the child's father (85.8%) and the family (92.8%) during the pregnancy.

The proportion of children born at term with intrauterine growth restriction was 7.3%, and the preterm SGA rate was 0.5%. Only 1.2%

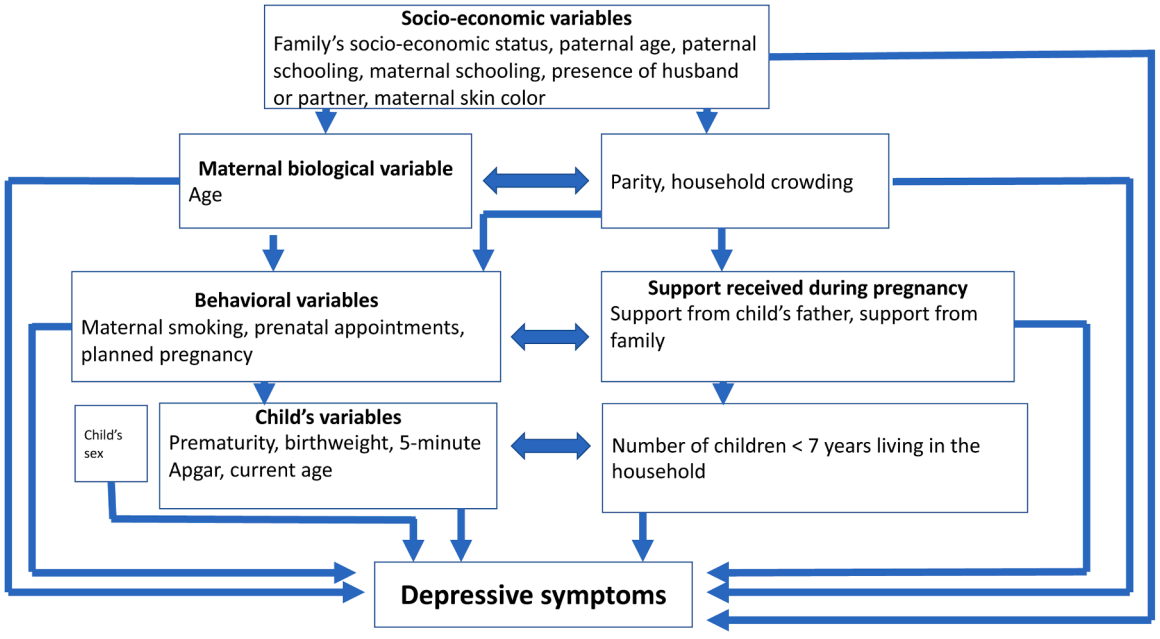

Fig. 1. Conceptual model for hierarchical analysis of the variables associated with maternal depressive symptoms (EPDS ≥13).

Table 1
Description of sample and prevalence of postpartum depressive symptoms (EPDS ≥10). Baseline of the Impact Evaluation of the Happy Child Program. Brazil, 2018

Characteristics	N	%	EPDS ≥ 10 Prevalence[¥](%)	95% CI	p*
1st level of the conceptual model					
Family's socioeconomic status (quintiles)					0.157
1st (poorest)	599	18.9	30.1	23.7 - 36.6	
2nd	620	19.6	30.6	24.4 - 36.7	
3rd	655	20.7	25.8	20.2 - 31.4	
4th	661	20.9	27.8	22.0 - 33.6	
5th	636	20.1	25.1	19.6 - 30.6	
Age of child's father					0.233
< 30	1580	51.7	26.5	22.1 - 30.9	
30-39	1038	33.9	27.2	22.5 - 31.9	
≥ 40	441	14.4	30.6	24.7 - 36.6	
Paternal schooling					<0.001
0-4	450	16.8	36.4	29.0 - 43.8	
5-8	818	30.6	29.3	23.2 - 35.4	
≥ 9	1404	52.4	22.9	17.9 - 27.9	
Maternal schooling					<0.001
0-4	273	9.2	39.7	31.7 - 47.8	
5-8	914	30.7	33.0	27.0 - 39.0	
≥ 9	1792	60.2	23.1	18.5 - 27.7	
Lives with husband or partner					0.001
No	1170	36.9	31.0	26.0 - 36.0	
Yes	2003	63.1	25.5	21.3 - 29.7	
Skin color					0.443
White	461	14.6	25.3	19.7 - 30.9	
Brown	2379	75.2	29.3	22.6 - 35.9	
Black	321	10.2	27.8	23.2 - 32.3	
2nd level of the conceptual model					
Maternal age					<0.001
< 20	462	14.6	20.1	15.1 - 25.0	
20-24	893	28.1	25.8	21.0 - 30.7	
25-29	738	23.2	32.1	26.5 - 37.7	
30-34	630	19.9	28.3	22.9 - 33.8	
≥ 35	450	14.2	30.4	24.4 - 36.5	
Parity					<0.001
1	976	30.2	18.4	14.6 - 22.2	
2	1017	32.1	29.2	24.3 - 34.1	
≥ 3	1177	37.1	33.5	28.4 - 38.5	
Household crowding, >3 persons/bedroom					0.012
No	2453	77.4	26.5	22.2 - 30.8	
Yes	718	22.6	31.3	25.8 - 36.8	
3rd level of conceptual model					
Current smoking					<0.001
No	2925	92.2	26.2	22.2 - 30.2	
Yes	247	7.8	42.5	34.8 - 50.2	
Number of prenatal appointments					<0.001
0-5	580	19.0	33.2	27.5 - 39.0	
≥ 6	2468	81.0	26.2	22.1 - 30.3	
Planned pregnancy					0.067
No	2214	69.9	28.5	24.1 - 32.9	
Yes	954	30.1	25.3	20.6 - 30.0	
Support from child's father during pregnancy					<0.001
No	450	14.2	39.5	33.0 - 46.1	
Yes	2712	85.8	25.6	21.5 – 29.8	
Support from family during pregnancy					<0.001
No	228	7.2	46.0	37.9 – 54.0	
Yes	2927	92.8	26.0	21.9 - 30.2	
4th level of conceptual model					
Sex of index child					0.767
Female	1593	50.2	27.8	23.2 - 32.4	
Male	1579	49.8	27.3	22.8 - 31.9	
Gestational age and birthweight					0.406
Term, AGA[#]	2455	84.5	26.9	22.5 - 31.3	
Preterm, AGA[#]	233	8.0	30.9	23.4 - 38.4	
Term, SGA[##]	203	7.3	29.1	21.5 - 36.7	
Preterm, SGA[##]	14	0.5	15.5	0.0 - 35.2	
5-min. Apgar < 7					0.444
No	2201	98.8	27.5	22.7 - 32.2	
Yes	26	1.2	34.2	15.4 - 53.0	
Current age of index child					0.027
< 3	292	9.2	21.7	15.6 - 27.9	
3-4	382	12.0	28.5	22.4 - 34.6	
5-6	677	21.3	24.8	19.9 - 29.7	
7-8	795	25.1	27.8	22.8 - 32.8	
9-10	737	23.2	28.8	23.7 - 34.0	
11-12	291	9.2	33.6	26.5 - 40.6	
					<0.001

(continued on next page)

Table 1 (*continued*)

Characteristics	N	%	EPDS ≥ 10 Prevalence[¥](%)	95% CI	p*
Number children < 7 years (including index child)					
1	1553	49.5	23.5	19.3 - 27.6	
≥ 2	1587	50.5	31.2	26.4 - 36.0	

[¥] Prevalence rates calculated according to hierarchical levels in the multilevel model (level 3: state; level 2: municipality; level 1: individuals); * Wald test; [#] AGA: adequate for gestational age; [##] SGA: small for gestational age

had a 5-minute Apgar score <7. At the time of the interview, some 9% of the children were less than three months of age, and in one-third the children were nine months or older. Some one-half of the households (49.5%) had only the child in the PCF under seven years of age (Table 1).

Table 1 also shows the prevalence rates for maternal depressive symptoms according to the independent variables. Depression was inversely associated with paternal schooling and was higher among mothers whose husbands/partners had 0-4 years of formal education (36.4%), compared to those with nine or more years of schooling (22.9%). A similar association was observed with the mother's own schooling, where the prevalence was 39.7% in women with 0-4 years of schooling and 23.1& among those with nine years or more. Prevalence was also higher among single mothers (31.0%) and those 35 years or older (30.4%). As for parity, women with three or more deliveries (33.5%) showed higher prevalence of depression than primiparous women (8.4%).

Prevalence of depressive symptoms was higher in mothers that smoked (42.5%) than in non-smokers (26.2%) and among those who reported fewer than six prenatal appointments during the index pregnancy in comparison to those who reported six or more (33.2% *versus* 26.2%). Prevalence was also higher among mothers who had not received support from the child's father (39.5%) or the family (46.0%), compared to those who had received support from the child's father and the family (25.6% and 26.0%, respectively). Mothers whose infants had been born more than six months before and those living with two or more children under seven years presented higher prevalence of depressive symptoms. The other variables were not statistically associated with the presence of depressive symptoms (Table 1).

Table 2 shows the Odds Ratios for maternal depressive symptoms for independent variables with p less than 5% in the adjusted analysis. The odds of depressive symptoms increased directly with parity and were 77% and 83% respectively as high for mothers with two (OR= 1.77; 95% CI 1.38-2.27) or three or more deliveries (OR= 1.83; 95%CI 1.43-2.35) compared to primiparous women (p for trend <0.001). Meanwhile, higher maternal and paternal schooling and living with the husband or partner and receiving support from the child's father and family during the pregnancy were protective factors against depressive symptoms. Time transpired since the delivery was also associated with the odds of the mother presenting depressive symptoms, being 57% higher (OR= 1.57; 95%CI 0.98-2.52) among those whose infants were 11-12 months of age compared to those whose infants were 1-2 months of age, taken as the reference group (p for trend = 0.021).

Supplementary analyses with EPDS ≥13 showed similar results, except that in the crude analyses household crowding and number of prenatal appointments were not associated with prevalence of depressive symptoms (Supplementary Table 1). In the adjusted analysis, the odds of depressive symptoms increased directly with parity and time transpired since the delivery, whereas higher maternal and paternal schooling and living with the husband or partner and receiving support from the child's father and family during the pregnancy were protective factors against depressive symptoms (Supplementary Table 2).

Table 2
Adjusted odds ratio for maternal depressive symptoms (EPDS ≥10). Baseline of the Impact Evaluation of the Happy Child Program. Brazil. 2018

	OR	95%CI	p
Paternal schooling			< 0.001*
0-4	1.00		
5-8	0.76	0.59 – 0.99	
≥ 9	0.61	0.47 – 0.79	
Maternal schooling			< 0.001*
0-4	1.00		
5-8	0.73	0.52 – 1.01	
≥ 9	0.47	0.34 – 0.65	
Lives with husband or partner			< 0.004
No	1.00		
Yes	0.75	0.61 – 0.91	
Parity (including index child)			< 0.001*
1	1.00		
2	1.77	1.38 – 2.27	
≥ 3	1.83	1.43 – 2.35	
Support from child's father during pregnancy			< 0.001
No	1.00		
Yes	0.51	0.38 – 0.70	
Support from family during pregnancy			< 0.001
No	1.00		
Yes	0.48	0.35 – 0.67	
Child's age in months			0.021 *
< 3	1.00		
3-4	1.29	0.82 – 2.01	
5-6	1.16	0.76 – 1.77	
7-8	1.36	0.90 – 2.04	
9-10	1.48	0.98 – 2.23	
11-12	1.57	0.98 – 2.52	

* Test for linear trend

Discussion

This study showed that at the baseline of the Impact Assessment Study of the Happy Child Program (PCF), prevalence of depressive symptoms was 26.5% (25.0-28.1%). In the adjusted analysis, seven factors were associated with increased prevalence of depression: low maternal and paternal schooling, living without husband or partner, having more than one child, not having received support from the family or the child's father during the pregnancy, and longer time since child's birth.

Our study has some strengths and limitations. The limitations include the fact that depressive symptoms were self-reported, with no subsequent assessment by a mental health professional. The sample's homogeneity in terms of economic conditions (all the families are beneficiaries of the *Bolsa Família* Program) limits the capacity for generalization of the results, and it is not possible to state that the observed associations would also occur among mothers from higher-income families.

The strengths feature the large sample size; the use of the EPDS, a widely used instrument in population-based studies and which showed adequate performance for use in the Brazilian population; the collection of data on a large number of potential risk factors; the inclusion of mothers from four of Brazil's five major regions; and standardized data collection in the study's 30 municipalities.

As for prevalence of depressive symptoms, two previous Brazilian studies that employed EPDS ≥10 found prevalence of 31.3% (25.0-37.6%) and 48.0% (31.4-64.5%) [8,9]. Both studies were carried out in the city of Sao Paulo. The first included 208 women assisted by nursing up to 60 days postpartum [8], and the second was a small study (N = 35) with women recruited in three basic health units at four months postpartum [9]. Thus, the prevalence observed in the current study was similar to that found among the nursing mothers from São Paulo and lower than reported in the smaller study, possibly due to sample size and the postpartum period of the mothers.

Four Brazilian studies were identified that employed the EPDS with a cutoff of ≥13. The Birth in Brazil Study featured a telephone survey of

11,925 of the 23,940 women identified in the hospital where they had given birth, 6-18 months postpartum, and found a prevalence of 26.3% (25.5-27.1%) [6]. The sensitivity (52.2%) and specificity (84.4%) of the EPDS applied by telephone are similar to those of the EPDS applied face-to-face [24]. Another Brazilian study was done in Porto Alegre, Rio Grande do Sul, in a probabilistic sample of 271 women, interviewed at their place of residence 6-8 weeks after giving birth, and found a prevalence of 20.7% (15.7-25.7%) [4]. In the Pelotas 2004 Birth Cohort, prevalence at 12 months after childbirth was 14.8% (13.6-16.0%) [5]. In the Pelotas 2015 Birth Cohort, prevalence at 3 months after childbirth was 9.4% (8.4-10.4%).

Among the variables most strongly associated with depression in our analyses, the results of the protective effects of schooling, presence of the husband/partner, and support during the pregnancy are consistent with findings from other studies [1,2,9,14].

In relation to parity, the results differ according to the degree of the country's wealth, the postpartum period in which the studies were performed, and the instruments used to measure depressive symptoms. Studies in Hungary and Finland reported higher risk in primiparous women [25,26], while a study in Canada found increased risk among multiparous women [27]. In low and middle-income countries, a study in Nigeria found higher risk in primiparous women [28,29], while studies in Brazil, Pakistan, and Nepal reported higher risk among multiparous women [6,30,31]. It is possible that the context interferes with the association between parity and the occurrence of depressive symptoms, since a review found that in low and middle-income countries, depression is more common in women with four or more children, mainly if the children are under seven years of age [32]. As suggested by other authors, larger family size, especially with short birth spacing, is part of a specific group of precipitating factors for depressive symptoms, related to psychological stress from being the family caregiver [33].

The majority of studies that found an association with primiparity were performed within six weeks postpartum [26,28]. Except in Canadá [27] (where the study was performed six weeks after delivery), the other studies that found an association with multiparity were performed later: 5-10 weeks postpartum in Nepal [31]; three, six, and twelve months postpartum in Pakistan [30]; and 6-18 months postpartum in Brasil [6]. As for the measurement instrument, the study in Finland [26] employed data from nationwide medical records for a nine-year period, while the others that found an association with parity used screening instruments, mostly EPDS.

Our findings indicate that promotion of parental education, alongside with the promotion of support to the woman during pregnancy by the child's father and by the family, as well as family planning leading to birth spacing are measures that may help to prevent postpartum depressive symptoms.

Authors' contributions

CV and IS contributed with the conception and design of the study; AM, HJ, LS, LC, MS and PL participated in the acquisition of data; and TM and CB contributed with data analysis. RB, CB, EA, EM, RS, EO, MTF provided critical revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.042.

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