Effects of postpartum depression on the behaviour of children born to mothers with epilepsy

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ABSTRACT

Purpose: Postpartum depression (PPD) is a non-psychotic depressive disorder that begins within 4 weeks of childbirth. This study aimed to evaluate the prevalence of PPD by screening mothers with the Edinburgh Postnatal Depression Scale (EPDS), to assess the behavioural outcome of children born to mothers with and without epilepsy and to investigate the relationship between PPD and children's behavioural problems.
Method: We enrolled 80 pregnancies of women with epilepsy, who filled in EPDS after birth, and afterward we asked them to complete the Child Behavior Checklist (CBCL).
Results: 23.8% of patients presented PPD. Children, when the CBCL were completed, had a mean age of 6.05 ± 3.07 years. The CBCL results indicate the occurrence of at least one behavioural issue in 25.0% (20/80) of children.

CBCL scores revealed a higher prevalence of behavioural disturbances with regards to the CBCL Total (P = 0.016), internalizing (P = 0.014) and somatic problems (P = 0.048) in patients with PPD vs. patients without PPD.

We found an association between mothers' EPDS total score and children's CBCL global score (P = 0.034), internalizing score (P = 0.021), anxiety problems (P = 0.05), affective problems (P = 0.027) and withdrawn/depressed (P = 0.05).

We recorded a statistically higher malformation rate in patients with PPD (P = 0.005) compared to the general population.
Conclusions: Children born from mothers with epilepsy have an increased risk for emotional disorders. These findings highlight the importance of screening for emotional distress and providing adequate interventions to children born to women with epilepsy.

1. Introduction

Postpartum depression (PPD) is a major depressive episode with an onset in pregnancy or within 4 weeks of delivery. The Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not recognize PPD as a separate diagnosis; rather, patients must meet the criteria for a major depressive episode and the criteria for the peripartum-onset specifier [1].

Epidemiologic studies have identified the prevalence of PPD as ranging between 9.0% and 13.0%, even if 50.0% of all cases are probably not diagnosed. The prevalence estimates of PPD are difficult to compare across studies because of variations in definitions, screening tools, timing of the assessments, and cultural issues [2,3]. In Italy only a

few studies have been carried out and the prevalence of PPD reported ranged from 1.8% to 38.9%. Predictive factors for PPD in women without epilepsy include a history of depression, physical or sexual abuse, poor social support, and unplanned pregnancy [4].

People with epilepsy are especially vulnerable to mood disorders.

Among the epilepsy population the PPD rate is higher compared to the general population, ranging from 26.7% to 39.0%. The clinical features of PPD are: depressed mood; irritable mood most of the day; loss of interest or pleasure most of the day; change in weight or appetite; insomnia or hypersomnia; psychomotor retardation or agitation; loss of energy or fatigue; worthlessness or guilt; impaired concentration or indecisiveness; or recurrent thoughts of death or suicidal ideation or attempt [2,3].

Several factors seem to contribute to the PPD's onset: aetiology, seizures type, antiepileptic drugs (AEDs) during pregnancy, epileptic seizures and socio-demographical factors, such as previous miscarriages and unplanned pregnancies [5–9].

PPD has been associated with parenting stress, impacting attachment and child development. A number of studies suggested that maternal PPD has prominent effects on offspring: behavioural disorders, poor vocabulary and psychomotor delay were reported [10,11]. Previous investigations have shown that PPD was related to offspring internalizing and externalizing behaviours and depressive symptoms [12–15]. There are limited longitudinal studies investigating the trajectories of language development among children born from mothers with PPD. Language delay in children is associated with delays in school readiness and behavioural disorders in later years [16].

It has been long known that AEDs use during pregnancy could have teratogenic effects on offspring. The rate of major congenital malformation (MCM) in children who have been exposed to AEDs in utero is 6.1%, compared to 2.2% for the general population and 2.8% in children of untreated women with epilepsy [17]. The valproic acid (VPA) seems to have a more harmful effect, since it increases the risk of MCM more than with other common AEDs [18].

Moreover, several studies have shown that AEDs use during pregnancy has negative effects on children's social and behavioural adjustment [19,20]. Specifically, children exposed to VPA have on average lower IQ scores (for a meta-analysis see Banach et al.) [21], lower cognitive performance [22,23] and less impressive language skills [24].

The aim of our study was to compare children of mothers with epilepsy and with or without PPD regarding behavioural problems using a specific questionnaire for psychopathology in children and adolescents, the Child Behavior Checklist (CBCL). We followed the hypothesis that, beside PPD as a risk factor, AEDs use of mothers during pregnancy might have an additional effect on behavioural profile of the child.

2. Materials and methods

Between 2004 and 2016 we performed a study at the Epilepsy Center-Child Neuropsychiatry Unit, San Paolo Hospital in Milan. Patients with epilepsy who between 5 and 8 weeks after giving birth had completed the Edinburgh Postnatal Depression Scale (EPDS) were recruited (retrospectively), subsequently we contacted all women and asked them to fill out the CBCL (prospectively, Fig. 1).

Inclusion criteria were as follows: diagnosis of epilepsy made on the basis of anatomo-electro-clinical criteria (previous clinical history, MRI findings, and EEG or video/EEG recording) according to the International League Against Epilepsy (ILAE) [25], at least 18 years of age, education level equal to or higher than primary school (8 years), and ability to speak, understand and read Italian.

We excluded women who were receiving medication other than AEDs and/or who presented a previous diagnosis of Axis I and II disorders or intellectual disability according to DSM-5 estimated by the neurologist clinically. The control group consisted of eighty children born to women without epilepsy who were randomly selected during routine follow up from our paediatric outpatient clinic, in order to match them with respect to age and sex. The same exclusion criteria were applied to the women without epilepsy. All patients and controls gave their written informed consent prior to completing the questionnaires.

The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki and The Ethics Committee of San Paolo Hospital reviewed and approved the study protocol.

2.1. Questionnaires

2.1.1. Edinburgh Postnatal Depression Scale (EPDS)

EPDS is a 10-item (scored on a scale of 0–3) self-reported scale used to evaluate PPD's symptoms. Mothers were asked to complete the questionnaire referring to how they felt over the previous seven days. Each question is scored 0–3, resulting in a range from 0 to 30 [26].

The EPDS Italian validation suggests a 9/10 cut-off score for its use in community surveys and screening and a 12/13 cut-off score for clinical assessment. At the 9/10 cut-off score, the sensitivity is 83.3%, the specificity 89.5%, and the positive predictive value (PPV) 58.6%. In our study, we used a 9/10 cut-off score [27].

The EPDS is not a substitute for this clinical assessment, and a score just below the cut-off should not be taken to indicate the absence of depression, especially if the health professional has other reasons for considering this diagnosis.

2.1.2. Child behaviour check list (CBCL)

The CBCL allows clinicians to have access to a complete description of children's behavioural and emotional features [28,29].

Two different CBCL versions (parent form) were used, according to the age of the child: the preschool version (CBCL 1 ½–5) and the school-aged version (CBCL 6–18). CBCL 1 ½-5 years and 6–18 years are 99-item and 112-item standardized questionnaires, respectively with 3
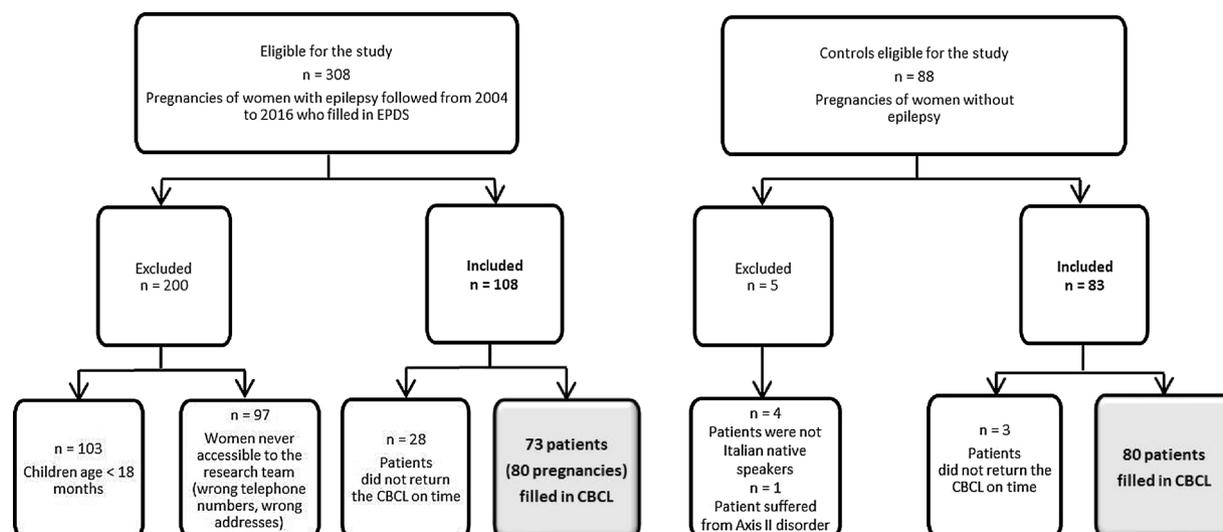

Fig. 1. Flow-chart of study participants.
Flow chart demonstrating the study selection process

response options (0: not true, 1: somewhat or sometimes true, 2: very true or often true).

CBCL ratings were converted into T scores based on population norms (mean of 50, standard deviation [SD] of 10).

Following Achenbach's suggestions, we defined borderline groups (scores of 65–70 in narrowband scales and 60–63 in broad-band scales) and clinical groups (scores greater than 70 in narrow-band scales and greater than 63 in broad-band scales). Higher T-scores are correlated with greater problems severity.

The CBCL is a valid assessment tool in children widely used in research and clinical practice with excellent psychometric properties [28–30].

2.2. Statistical methods

We used an electronic database and analysed the data through the Statistical Package for the Social Sciences (SPSS 24 IBM, Chicago, IL, U.S.A.) for Windows software.

Continuous variables were presented as mean and standard deviation (SD).

After performing kurtosis, skewness, and Kolmogorov-Smirnov 1-sample tests for checking the normality of the distribution, the between-group comparisons of the demographic and clinical characteristics of women with or without PPD were performed using the Mann-Whitney U test (two groups) or the T-Student for independent samples, depending on the distribution. Demographic, clinical variables and CBCL scores of women with or without PPD were compared with U of Mann-Whitney. We performed a group size calculation (r); the group sizes were based on the recruitment capacity of our centre.

We used a linear regression analysis to estimate the relationship between EPDS (independent variable) and CBCL scores (dependent variables).

Moreover, a multiple linear regression analysis was performed to determine the interaction between the demographic and clinical variables (age, education, type of epilepsy, duration and age at onset of epilepsy, seizure frequency, number of AEDs) and the EPDS scores, used as a dependent variable. A stepwise selection procedure was used to enter set at 0.05 and to remove set at 0.10.

Patients and the control group were compared in terms of age, sex and CBCL scores, after performing kurtosis, skewness, and Kolmogorov-Smirnov 1-sample tests for checking the normality of the distribution, using the Mann-Whitney U test (two groups).

P-values of < 0.05 after correction were regarded as being significant.

3. Results

Fig. 1 shows the flow of participants through the study. Participation rate was 74.0% of women with epilepsy and 90.9% of women without epilepsy invited. Eighty pregnancies of 73 patients (mean age: 33.30 years, SD: 4.66, range: 20–42 years) who had completed the EPDS and CBCL were included in this investigation; seven women had two children (siblings); 55 had Focal Epilepsy (68.7%), whereas 25 (31.3%) presented Idiopathic Generalized Epilepsies.

Demographic and clinical characteristics of patients are summarized in Table 1.

Seizure-free patients during pregnancy were 57.5%.

We found a mean EPDS score of 6.58 ± 4.06 (range: 0–20) at 5–8 weeks after birth, PPD was present in 23.8% (19 women) of the patients with epilepsy, while 76.2% (61 women) had not experienced depressive symptomatology.

Monotherapy was used in 65 pregnancies (81.2%) and involved first-generation AEDs for four women (6.2%), second-generation AEDs for forty-seven women (72.3%) and third-generation AEDs for fourteen women (21.5%). Eight different AEDs were used in monotherapy, the most frequently prescribed AEDs were CBZ (44.6%) and VPA (27.7%).

Table 1
Demographic and clinical characteristics.

Variable	n = 80
Age at birth (years)	
Mean	33.30
SD	4.66
Min-Max	20–42
Education (years)	
Mean	13.88
SD	3.25
Primary school	12 (15.0%)
Secondary school	37 (46.2%)
Degree/PhD	31 (38.8%)
Marital status	
Married	79 (98.7%)
Single	1 (1.3%)
EPDS score	
Mean	6.58
SD	4.06
Primiparous	
Yes	60 (75.0%)
No	20 (25.0%)
Type of Epilepsy	
Focal Epilepsy	55 (68.7%)
Structural	32 (58.2%)
Unknown	23 (41.8%)
Idiopathic Generalized Epilepsies	25 (31.3%)
Epilepsy onset (years)	
Mean	15.39
SD	8.40
Epilepsy duration (years)	
Mean	17.80
SD	8.82
Seizure type	
Focal onset	45 (56.2%)
Aware	22 (48.9%)
Impaired awareness	23 (51.1%)
Generalized onset	31 (38.7%)
Non motor	10 (32.3%)
Motor	21 (67.7%)
Unknown	4 (5.0%)
AEDs during pregnancy	
Monotherapy	65 (81.2%)
CBZ	29 (44.6%)
VPA	18 (27.7%)
LTG	6 (9.2%)
OXC	6 (9.2%)
LEV	2 (3.1%)
PHT	2 (3.1%)
PB	1 (1.5%)
ESM	1 (1.5%)
Polytherapy	14 (17.5%)
2 AEDs	12 (85.7%)
CBZ + LEV	2 (14.3%)
3 AEDs	2 (14.3%)
No AEDs	1 (1.3%)
Frequency of seizures during pregnancy (monthly)	
Mean	1.39
SD	2.74
Weekly	14 (17.5%)
Monthly	20 (25.0%)
None	46 (57.5%)
Pregnancy without seizures	
Yes	46 (57.5%)
No	34 (42.5%)
MRI	
Normal	37 (46.3%)
Pathological	23 (28.7%)
Not done	20 (25.0%)
Comorbidity	
Yes	13 (16.3%)
No	67 (83.7%)
Obstetric complications	
Yes	28 (35.0%)
No	52 (65.0%)
Type of delivery	

Table 1 (*continued*)

Variable	n = 80
Vaginal	61 (76.3%)
Caesarean	18 (22.5%)
Vacuum extraction	1 (1.2%)
Weeks of gestation (weeks)	
Mean	38.89
SD	2.20
Min-Max	35-42 + 5
Weight (kg)	
Mean	3.18
SD	0.45
Min-Max	1.75-4.20
Length (cm)	
Mean	49.58
SD	2.17
Min-Max	42.5-53
Occipital front head circumference (cm)	
Mean	34.00
SD	1.39
Min-Max	28-36.5
Apgar at 1 min	
Mean	9.45
SD	0.99
Min-Max	4-10
< 10° percentile	4 (5.0%)
4	1 (1.2%)
6	1 (1.2%)
7	2 (2.5%)
8	2 (2.5%)
9	24 (30.0%)
10	50 (62.5%)
Apgar at 5 min	
Mean	9.89
SD	0.36
Min-Max	8-10
< 10° percentile	0 (0%)
8	1 (1.3%)
9	7 (8.7%)
10	72 (90.0%)
Major congenital malformations	
Yes	5 (6.2%)
Single malformations	
Hip dysplasia	2 (40.0%)
Club foot	1 (20.0%)
Renal pyelectasis	1 (20.0%)
Multiple Malformations	
Hip dysplasia + Renal pyelectasis	1 (20.0%)
Neuropsychiatric disorders	
Yes	2 (2.5%)
Autism Spectrum Disorder + Mild intellectual disability	1 (50.0%)
Mild intellectual disability	1 (50.0%)
No	78 (97.5%)
Perinatal death	
No	80 (100%)
Folic acid before conception (three months)	
Yes	64 (80.0%)
No	16 (20.0%)
First words (months)	
Mean	11.05
SD	3.36
Min-Max	6-24
First steps (months)	
Mean	12.16
SD	2.34
Min-Max	8-20
Nursing	
Breastfeeding	58 (72.5%)
Others	22 (27.5%)

Legend: SD: standard deviation; CBZ: carbamazepine; VPA: valproic acid; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PHT: phenytoin; PB: phenobarbital; ESM: ethosuximide.

Polytherapy, on the other hand, was used for fourteen pregnancies (17.5%), a combination of two AEDs was prescribed for twelve pregnancies (85.7%) and three AEDs for two (14.3%). The most common combination was CBZ and LEV (14.3%). One child (1.2%) had a pre-term delivery (< 37° weeks), seven children (8.7%) had a low birth weight (< 2,500 g), fifteen new-borns babies (18.7%) were small for gestational age (SGA): birth weight < 10th percentile, one infant (1.2%) was admitted to the neonatal intensive care unit for acute respiratory distress syndrome and none presented low Apgar scores (< 7 at 5 min).

Five of our patients' children (6.2%) had MCM including major malformations such as musculoskeletal malformations (hip dysplasia), limb malformations (club foot), urinary system (renal pyelectasis) and one child with multiple major malformations (hip dysplasia associated to renal pyelectasis). Offspring with MCM were exposed to: CBZ (three children), LTG (one child) and PHT + PB (one child). Among these pregnancies, malformations were detected in 1 prenatally, in 1 at birth and in 3 within 2 months after birth. All women filled in EPDS questionnaire after diagnosis of MCM.

Within the cohort, the children, when their mothers completed the CBCL, had a mean age of 6.05 years, (SD: 3.07, range 2–12 years), 50 (62.5%) were male and 30 (37.5%) female.

Two children (2.5%) suffered from neuropsychiatric disorders (one child with autism spectrum disorders associated with a mild intellectual disability and one child with a mild intellectual disability).

Control group had a mean age of 6.5 years, (SD: 2.49, range 2–11 years), 53 (66.2%) were male and 27 (33.7%) female.

3.1. Scores on the CBCL

The CBCL results indicated an occurrence of at least one emotional and/or behavioural problem in 25.0% (20/80) of the children of mothers with epilepsy.

Concerning the preschool-aged sample (1½-5 years), 27.7% (10/36) displayed a clinical range at least in one subscale, 5.5% (2/36) in a borderline one. 66.7% of the sample (24/36) scored within a normal range.

Specifically, six children showed a clinical score in one subscale, two in two subscales, one in three subscales, and one in four subscales. Sleep problems (8.3%) and emotionally reactive (8.3%) presented a greater number of scores below the average, followed by the Total Score (5.6%), internalizing problems (5.6%), withdrawn/depressed (5.6%) and pervasive developmental problems (5.6%).

Moreover, one child showed a borderline score in two subscales and one in three subscales.

In the school-aged (6–12 years) group, ten children (22.7%) showed a clinical range, fourteen (31.8%) a borderline one, while twenty children (45.4%) had no emotional nor behavioural problems.

13.6% of the sample presented clinical range in the internalizing problems, 11.4% in the total score and 9.1% in the externalizing disorders.

Nine children's scores (20.4%) were within borderline range in the anxiety problems subscale, eight children (18.2%) in the internalizing problems, six (13.6%) in ADHD, withdrawn/depressed and somatic complaints subscales.

Concerning the control group sample, 15.5% displayed a clinical range in at least one subscale and 24.1% in a borderline one. 60.3% of the sample scored within a normal range.

The frequencies of normal/borderline/clinical scores for all broad- and narrow-band scales in the study groups and controls are shown in Table 2.

3.2. Comparison between groups with PPD vs. without PPD

With regards to behavioural problems, we found a statistically significant difference between CBCL's children of patients with PPD compared to patients without PPD in terms of the CBCL Total Score (P = 0.016, r = 0.235), internalizing problems (P = 0.014, r = 0.259) and somatic problems (P = 0.048, r = 0.282, Table 3, Fig. 2).

Table 2
CBCL scores for children of mothers with epilepsy (preschool-aged and school-aged) and control group (preschool-aged and school-aged).

	CHILDREN OF MOTHERS WITH EPILEPSY n = 80		CHILDREN OF MOTHERS WITHOUT EPILEPSY n = 80	
Age (years)				
Mean	6.05		6.5	
SD	3.07		2.49	
Min-Max	2-12		2-11	
Gender				
Male	50 (62.5%)		53 (66.2%)	
Female	30 (37.5%)		27 (33.8%)	
CBCL	**Preschool-aged n = 36 (45.0%)**	**School-aged n = 44 (55.0%)**	**Preschool-aged n = 27 (33.7%)**	**School-aged n = 53 (66.3%)**
Total Problems				
Normal range	31 (86.1%)	34 (77.2%)	25 (92.6%)	48 (90.6%)
Borderline range	3 (8.3%)	5 (11.4%)	2 (7.4%)	
Clinical range	2 (5.6%)	5 (11.4%)		5 (9.4%)
Internalizing problems				
Normal range	32 (88.8%)	30 (68.2%)	24 (88.9%)	42 (79.3%)
Borderline range	2 (5.6%)	8 (18.2%)	1 (3.7%)	6 (11.3%)
Clinical range	2 (5.6%)	6 (13.6%)	2 (7.4%)	5 (9.4%)
Externalizing problems				
Normal range	33 (91.7%)	35 (79.5%)	27 (100%)	48 (90.6%)
Borderline range	2 (5.6%)	5 (11.4%)		
Clinical range	1 (2.8%)	4 (9.1%)		5 (9.4%)
Syndrome scales				
Anxious/depressed				
Normal range	34 (94.4%)	40 (90.9%)	25 (92.6%)	47 (88.7%)
Borderline range	2 (5.6%)	1 (2.3%)	2 (7.4%)	5 (9.4%)
Clinical range		3 (6.8%)		1 (1.9%)
Withdrawn/depressed				
Normal range	34 (94.4%)	36 (81.8%)	26 (96.3%)	48 (90.6%)
Borderline range		6 (13.6%)	1 (3.7%)	4 (7.5%)
Clinical range	2 (5.6%)	2 (4.6%)		1 (1.9%)
Somatic complaints				
Normal range	34 (94.4%)	38 (86.4%)	26 (96.3%)	44 (83.0%)
Borderline range	1 (2.8%)	6 (13.6%)	1 (3.7%)	6 (11.3%)
Clinical range	1 (2.8%)			3 (5.7%)
Emotionally reactive				
Normal range	33 (91.7%)		26 (96.3%)	
Borderline range	3 (8.3%)		1 (3.7%)	
Sleep problems				
Normal range	33 (91.7%)		26 (96.3%)	
Borderline range				
Clinical range	3 (8.3%)		1 (3.7%)	
Social problems				
Normal range		42 (95.5%)		49 (92.5%)
Borderline range		2 (4.5%)		2 (3.8%)
Clinical range				2 (3.8%)
Thought problems				
Normal range		40 (90.9%)		52 (98.1%)
Borderline range		3 (6.8%)		
Clinical range		1 (2.3%)		1 (1.9%)
Attention problems				
Normal range	32 (88.9%)	40 (90.9%)	25 (92.6%)	48 (90.6%)
Borderline range	3 (8.3%)	2 (4.5%)	2 (7.4%)	2 (3.8%)
Clinical range	1 (2.8%)	2 (4.5%)		3 (5.7%)%
Rule-breaking behavior				
Normal range		42 (95.6%)		51 (96.2%)
Borderline range		2 (4.5%)		1 (1.9%)
Clinical range				1 (1.9%)
Aggressive behavior				

Table 2 (*continued*)

	CHILDREN OF MOTHERS WITH EPILEPSY n = 80		CHILDREN OF MOTHERS WITHOUT EPILEPSY n = 80	
Normal range	35 (97.2%)	42 (95.5%)	27 (100%)	48 (90.6%)
Borderline range	1 (2.8%)	2 (4.5%)		5 (9.4%)
DSM-Oriented Scales				
Affective problems				
Normal range	34 (94.4%)	41 (93.2%)	27 (100%)	51 (96.2%)
Borderline range		2 (4.5%)		1 (1.9%)
Clinical range	2 (5.6%)	1 (2.3%)		1 (1.9%)
Anxiety problems				
Normal range	34 (94.4%)	35 (79.5%)	25 (92.6%)	42 (79.3%)
Borderline range	2 (5.6%)	9 (20.5%)		7 (13.2%)
Clinical range			2 (7.4%)	4 (7.5%)
Somatic problems				
Normal range		40 (90.9%)		53 (100%)
Borderline range		4 (9.1%)		
Pervasive developmental problems				
Normal range	33 (91.7%)		23 (85.2%)	
Borderline range	1 (2.8%)		2 (7.4%)	
Clinical range	2 (5.6%)		2 (7.4%)	
Attention deficit/ hyperactivity (ADHD) problems				
Normal range	34 (94.4%)	37 (84.1%)	27 (100%)	50 (94.3%)
Borderline range	1 (2.8%)	6 (13.6%)		1 (1.9%)
Clinical range	1 (2.8%)	1 (2.3%)		2 (3.8%)
Oppositional defiant problems				
Normal range	35 (97.2%)	40 (90.9%)	25 (92.6%)	50 (94.3%)
Borderline range	1 (2.8%)	4 (9.1%)	2 (7.4%)	3 (5.7%)
Conduct problems				
Normal range		44 (100%)		52 (98.1%)
Borderline range				1 (1.9%)

Moreover, we compared the clinical and obstetric variables between the two groups (women with PPD vs. women without PPD) in order to underline risk factors. Table 4 in the supplementary material summarizes the results of these analyses. We did not find any differences. The only exception was the rate of malformations: in women with PPD was statistically higher than non-depressed patients (15.8% vs. 3.3%, P = 0.005).

We performed a linear regression analyses and found an association among mothers' EPDS total score and children's CBCL global score (R-square = 0.056; P = 0.034), internalizing score (R-square = 0.067; P = 0.021), anxiety problems (R-square = 0.046; P = 0.05), affective problems (R-square = 0.061; P = 0.027) and withdrawn/depressed (R-square = 0.045; P = 0.05, Fig. 3 for broad-band significant scales).

The results of the multiple linear regression analyses, in order to evaluate the risk factors that most influence the probability of PPD, are not statistically significant.

3.3. Behavioural profile of children born to mothers with epilepsy vs. controls

Moreover, we compared CBCL scores of offspring of mothers with epilepsy to the control group. No statistical difference was found (Table 5 in the supplementary material).

Table 3
Comparison of CBCL scores between women without PPD and with PPD.

| CBCL (T score)	Without PPD n = 61 (76.2%)	PPD n = 19 (23.8%)	P	Effect size
Total score	**48.38 (10.51)**	**53.79 (7.39)**	**0.016**	**0.235**
Internalizing problems	**48.51 (10.93)**	**55.63 (10.32)**	**0.014**	**0.259**
Externalizing problems	48.39 (9.89)	49.89 (6.77)	0.458	0.079
Syndrome scales				
Anxious/depressed	53.52 (5.50)	56.74 (7.98)	0.099	0.180
Withdrawn/depressed	54.41 (6.39)	57.58 (9.09)	0.170	0.125
Somatic complaints	53.67 (5.96)	56.47 (5.77)	0.075	0.298
Emotionally reactive	53.13 (5.38)	53.60 (6.43)	0.860	0.062
Sleep problems	55.19 (9.25)	60.00 (19.18)	0.610	0.042
Social problems	54.83 (4.82)	54.21 (5.69)	0.710	0.082
Thought problems	55.00 (7.03)	54.57 (4.45)	0.836	0.139
Attention problems	55.61 (6.71)	55.74 (5.90)	0.940	0.057
Rule-breaking behavior	53.57 (4.39)	53.57 (5.50)	0.998	0.003
Aggressive behavior	53.18 (5.18)	53.32 (4.28)	0.918	0.163
DSM-Oriented Scales				
Affective problems	08 (6.57)	56.37 (6.20)	0.183	0.205
Anxiety problems	54.64 (6.11)	57.42 (6.75)	0.095	0.194
Somatic problems	**54.27 (6.08)**	**58.29 (6.17)**	**0.048**	**0.282**
Pervasive developmental problems	53.55 (5.95)	55.40 (8.96)	0.551	0.038
Attention deficit/hyperactivity (ADHD) problems	54.90 (6.14)	54.84 (5.56)	0.970	0.038
Oppositional defiant problems	53.02 (4.60)	53.47 (3.84)	0.696	0.170
Conduct problems	53.30 (4.04)	52.29 (3.71)	0.431	0.079
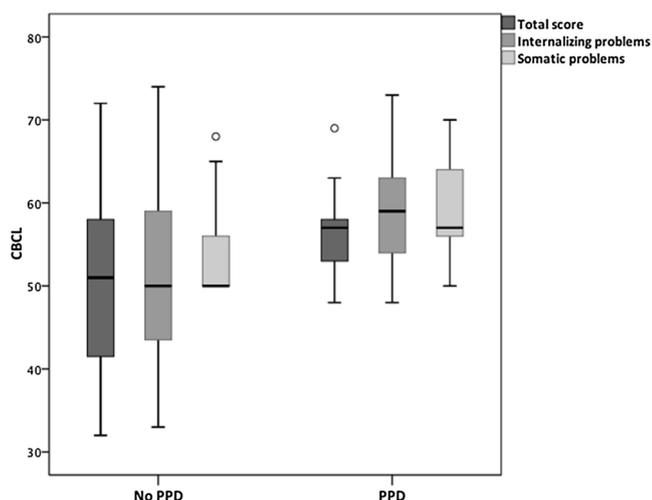
Fig. 2. CBCL's children of patients without PPD compared to patients with PPD. CBCL's children of patients without PPD (left side) compared to patients with PPD (right side) regarding the CBCL Total Score (P = 0.016, dark grey), internalizing problems (P = 0.014, medium grey) and somatic problems (P = 0.048, light grey)

4. Discussion

4.1. Epilepsy and PPD

The analysis of the EPDS scores in our sample of children exposed to AEDs revealed a high prevalence of PPD: 23.8% of women developed depressive symptomatology in accordance with previous research, showing a higher PPD rate in women with chronic epilepsy compared to the general population [5–8]. Bjørk et al demonstrated a similar finding relating to higher rates of PPD in women with epilepsy compared to controls and to women with other chronic diseases. These authors reported that women using AEDs during pregnancy were especially at risk for PPD regardless of AED type. The risk further increased with the use of multiple AEDs and with high doses and/or plasma levels [9].

According to our data, the only risk factor that seems to concur with PPD's onset is the presence of malformed children (P = 0.005). To our knowledge this is the first work to investigate the relationship between PPD in mothers with epilepsy and malformed offspring.

None of the most common risk factors such as type of epilepsy, type of AEDs, polytherapy or seizures during pregnancy were statistically significant in our sample [8,9].

Offspring of women exposed to AEDs had a higher frequency of malformations compared with those who were not exposed. Prospective registries and meta-analyses have better defined the risk of MCMs in offspring exposed to individual AEDs at different dose levels. Tomson and colleagues assessed the rates of major congenital malformations in 1402 pregnancies exposed to carbamazepine, 1280 on lamotrigine, 1010 on valproic acid, and 217 on phenobarbital. An increase in malformation rates with increasing dose at the time of conception was recorded for all anti-epileptic drugs. We found a malformation rate of 6.2%, which is in line with previous reports [17,18,31].

The teratogenicity of AEDs with regards to developing foetus has been a cause of concern for pregnant women, although they seemed to be able to face an identified medical problem with their doctor, assessing their point of view, and to discuss with neurologists about expectations and worries regarding epilepsy and AEDs [32].

Some well-controlled studies have emphasized that PPD predicted a delay in psychomotor development and language in children of women with PPD [14,15]. In a review analysis, Sohr-Preston and Scaramella reported that young children of depressed mothers are at risk for cognitive and language delays due to a wide variety of mechanisms, such as genetic risk, intrauterine environmental influences, reduced overall warmth and sensitivity, and qualitative and quantitative differences in a variety of specific maternal behaviours that shape early cognitive and language development. The frequency, severity, and duration of chronic depression may result in more profound cognitive and language impairments for children [15].

The effects of PPD on the child's cognitive profile appear to be more severe in males compared to females [14,15]. We did not find differences regarding gender; this probably reflects the fact that we have assessed the behavioural profiles without focusing on the cognitive outcomes.

4.2. PPD and behavioural/emotional profiles

The assessment of the CBCL scores in our sample of children revealed a high prevalence of behavioural/emotional comorbidities (27.8% and 22.7% in the preschool- and school-aged subgroups, respectively), in accordance with previous research [33,34]. Internalizing
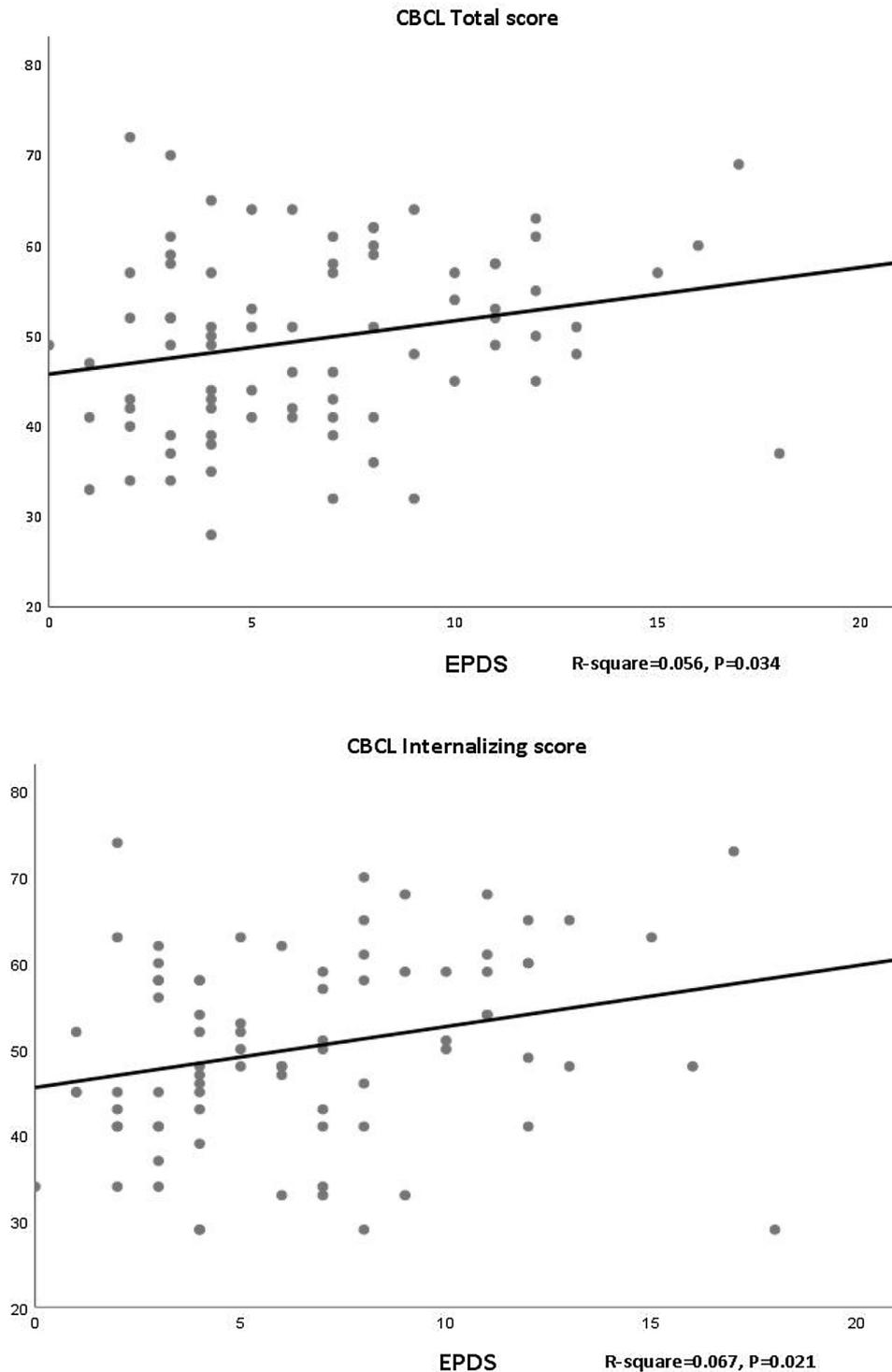
Fig. 3. Relationship between EPDS total score and CBCL Total score.
Linear regression analyses showed significant relationship between EPDS total score and CBCL global score (R-square = 0.056; P = 0.034) and internalizing score (R-square = 0.067; P = 0.021)

problems were more common than externalizing disorders. The association between PPD and the development of internalizing symptoms in children is well documented. Agnafors et al. found an association between PPD and externalizing problems [35]. Apter-Levy et al. analysed the impact of PPD in a population of children across the first 6 years of life with mothers with PPD, where 61.0% displayed axis I disorders, mainly anxiety and oppositional defiant disorders, compared with 15.0% of the children of non-depressed mothers [36].

In our study, there was a statistically significant difference in the

CBCL total score and internalizing problems between the children of women with PPD vs. those of non-depressed mothers, as it was reported in the studies of Verbeek, Park and Agnafors [33–37]. Another statistically significant difference observed between the two groups of children is the rate of somatic problems, which is still in line with the highest prevalence of internalizing disturbances.

Furthermore, our study is the first one, as far as we know, that has assessed PPD in children of women with epilepsy, previous works carried out this evaluation on the general population.

4.3. Children born to women with epilepsy vs. women without epilepsy

In our study, no statistically significant differences were found between CBCL results for children born to women with epilepsy compared to those born to women without epilepsy.

Vinten et al. examined the behaviour of 242 children, aged between 6 and 16, who have been exposed to VPA (mono and polytherapy) in utero [19]. The results of this study suggest that exposure to VPA in utero and the presence of a lowerered full scale IQ (FSIQ) are risk factors for the development of poorer adaptive behaviour and a higher rate of maladaptive disturbances.

Kjaer et al. reported that children prenatally exposed to AEDs tended to have more emotional problems compared to children of women without epilepsy [20].

4.4. Strengths and limitations

This study has an important strength: to our knowledge this is the first work that aims to investigate the influence of PPD in women with epilepsy on the behavioural development of offspring. Furthermore, a strong aspect of this study is the sample size examined and the presence of a control group matched by age and gender.

There are limitations to consider. First of all, we enrolled women retrospectively (EPDS evaluation), while children assessment (CBCL) was prospective, so other variables may have influenced the behavioural development of children in addition to PPD. Secondly, the questionnaire that we used (CBCL) was completed by the parents and none clinical evaluation was performed. This could affect the precision of our results, as mothers and fathers might tend to underestimate some aspects of their child and overestimate others. Thirdly, we did not have EPDS scores for mothers of the control group. Fourthly, we included in our analysis seven women with epilepsy with two children.

In conclusion, the follow-up of women with epilepsy during pregnancy should be extended to the postpartum period, considering the higher prevalence of PPD in these patients. In accordance with our results, it would be advisable to monitor women with epilepsy who have suffered from PPD and their children, as the latter are more at risk of internalizing problems.

Moreover, this issue needs to be more thoroughly investigated, although it is also evident that there is still a need for further studies on PPD in women with epilepsy and its influence on the behavioural development of offspring that may confirm our results.

Declaration of Competing Interest

None of the authors has any conflicts of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.10.018.

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