Newborns of preeclamptic mothers: Morbidity and mortality in a level 3 maternity hospital.

Ayari F*, Sdiri Y, Cherifi E, Belhaj Ammar W, Chourou H, Kacem S, Achour R

Department of Emergency, University Tunis El Manar, Tunis, Tunisia

Abstract

Background: Preeclampsia is a public health problem throughout the world, responsible for significant maternal and perinatal morbidity and mortality. The objective of our study was to describe the epidemiological, clinical and evolutionary profile of newborns born to preeclamptic mothers and to identify their risk factors for in-hospital mortality.

Method: Our study was retrospective, over a period of six months from July 1, 2020 to December 31, 2020. We included 95 newborns monitored at the neonatology department of the maternity and neonatology center of Tunis born to preeclamptic mothers.

Results: The prevalence of preeclampsia was 2.35% with severe and moderate prevalence being respectively 1.73% and 0.62%. The mean gestational birth age was 35.02 ± 3.15 weeks with 64.2% cases of prematurity. Intrauterine growth restriction was noted in 41% cases. Neonatal intensive care unit admissions were noted in 49.5% cases. The most frequent neonatal morbidities were neonatal respiratory distress, neonatal thrombocytopenia and hypocalcemia respectively registered in 22.1%, 25.3% and 11.6% cases. In-hospital mortality rate was 11.6% with a prematurity noted in 81.8% cases of death. In multivariate analysis, preeclampsia complicated by Hemolysis, Elevated Liver enzymes, Low Platelet count syndrome; HELLP (p=0.036), neonatal hypocalcemia (p=0.007) and newborn ventilation by Continuous Positive Airway Pressure (CPAP) (p=0.011) were identified as major risk factors independently associated with in-hospital mortality for newborns of preeclamptic mothers.

Conclusion: Strengthening antenatal care would allow an early screening of women with a high risk of preeclampsia and prevent the occurrence of subsequent complications.

Keywords: Newborn, Preeclampsia, Morbidity, Mortality.

Accepted on December 08, 2021

Introduction

Preeclampsia is a condition that affects 2%-8% of pregnant women. It is defined as gravidic hypertension associated with proteinuria greater than 0.3 g/24 hours. It is a public health problem throughout the world, responsible for significant maternal and perinatal morbidity and mortality. Perinatal morbidity is dominated by the hypoxic syndrome translated by Intrauterine Growth Retardation (IUGR), hypotrophy, in-utero death and premature delivery [1]. The prevention and treatment of this paroxysmal pregnancy event are not univocal throughout the world. Stopping the pregnancy remains the only etiological treatment. In Tunisia, as in countries with a low level of health care, the prognosis of the newborn (NN) of a preeclamptic mother (MPE) in the short and medium term remains to be improved by multidisciplinary management acting mainly on the factors of risk of morbidity and perinatal mortality [2]. With this in mind, the present study aims to establish the current epidemiological profile of newborns of pre-eclamptic mothers, to study the clinical and evolutionary profile of newborns of pre-eclamptic mothers and to identify the risk factors for neonatal mortality related to this condition.

Materials and Methods

This is a retrospective and descriptive study conducted over a period of 6 months from July 1 to December 31, 2020 in the department of medicine and neonatal resuscitation of the Tunis Maternity and Neonatology Center (CMNT), a level III neonatal care department. The gynecology-obstetrics departments of the CMNT are referral departments draining high-risk pregnancies. We included all live births of preeclamptic mothers followed in the gynecology-obstetrics departments "A" and "C" of the CMNT with a gestational age between 27 and 42 completed weeks of amenorrhea with a birth weight (BW) >700 grams.

Protocol for the management of preeclampsia

As soon as the diagnosis of pre-eclampsia has been made, hospitalization of parturients was indicated. An initial assessment of the impact on the mother was carried out, including a clinical examination with a blood pressure profile, a search for neurosensory signs or sharp osteotendinous reflexes, a search for oedemas, a weight measurement and a urine test: Blood group, rhesus, search for irregular agglutinin (RAI), blood count (NFS), haemostasis check-up, renal function (creatinemia), uricemia, liver check-up (transaminases, LDH, bilirubin) and 24 hour proteinuria. And fetal: Measurement of uterine height, recording of fetal heart rate, obstetrical ultrasound to assess fetal biometry, amniotic fluid index, umbilical doppler ± cerebral doppler and uterine doppler. General measures were indicated with hospitalization, bed rest

and a normo-sodium diet. At the end of the workup, the course of action varied according to the severity of the preeclampsia.

Data collection

The information was collected from the medical records of each observation and then transcribed on an individual form including different variables and sub-variables concerning maternal characteristics, the course of the pregnancy (pregnancy pathology, antenatal corticosteroid therapy), the course of the perinatal period, the characteristics of pre-eclampsia, characteristics of the newborns, intra-hospital morbidities, therapeutic management and evolutionary modalities.

Statistical study

The data were entered and analyzed using the statistical package for the social.

A descriptive study

For categorical variables, we calculated simple frequencies and relative frequencies (percentages) if the number of people was greater than or equal to 30.

For quantitative variables, we calculated means, medians and standard deviations and determined their range (extreme values: minimum and maximum).

An analytical study

Comparisons of two means on independent series were made using the student's t-test for independent series and in case of small numbers by the non-parametric Mann Whitney test. Comparisons of two percentages on independent series were made using the Pearson chi^2 test and in case of invalidity by the Fisher exact test. Quantitative variables were transformed into two-modality qualitative variables [3].

To define the threshold at which to "cut off" the quantitative variable, the ROC (Receiver Operating Characteristics) curve was constructed. After checking that the area under the curve is significantly greater than 0.05, we chose as the threshold the value of the variable that corresponds to the best "sensitivity-specificity" pair.

A comparative study was performed between two groups of patients. The first group involved NN who did not die of MEP while the second group involved NN who died of MEP [4].

The search for risk factors was carried out by calculating the Odds Ratio (OR) which represented the number of times by which the probability (risk) of an event (death of NN) was multiplied in case of exposure to a factor compared to non-exposure. The OR was given for each variable with their 95% confidence intervals (95% CI).

In all statistical tests, the significance level (p) was set at 0.05.

Multivariate study

In order to identify the risk factors independently linked to the event, we conducted a multivariate analysis using top-down stepwise logistic regression.

In the first step, we introduced the variables whose "p" was lower than 0.20 in the univariate study and the risk factors known in the literature to be related to the event even if their "p" in the univariate study was higher than 0.05.

Then, step by step, we removed the factor whose "p" was least significant. A low p-value ($p<0.05$) led to the rejection of the hypothesis of independence and the assumption of a significant relationship between the factors studied.

The multivariate analysis made it possible to calculate adjusted Odds Ratios determining the specific role of each factor with their 95% confidence intervals (CI 95%). In all statistical tests, the significance level (p) was set at 0.05.

Results

During the period of our study, we counted 4038 live births. Of these NN, 1263 were admitted to the neonatal intensive care unit.

The most common reasons for hospitalization were respiratory distress, prematurity and infection. In our study, 95 EPM were included. The prevalences of EP, severe and moderate EP were 2.35%; 1.73% and 0.62% respectively.

The mean maternal age was 31.44 ± 5.71 years with extremes of 20 and 43 years. The majority of parturients were between 25 and 30 years of age. Mothers older than 30 years were noted in 58.9% of cases. A family history of

hypertension was reported in 47.3% of cases (n=45). A family history of PE was noted in 4.2% of cases (n=4). Maternal medical history was reported in 15.8% of cases (n=15).

The mean gravidity was 2.12 ± 1.39 with extremes of 1 and 8. The average parity was 1.78 ± 1.11 with extremes of 1 and 5.

The mothers were primigravida in 46.3% of the cases and primiparous in 56.8% of the cases. A history of EP in previous pregnancies due to prematurity was noted in 29.5% (n=28) and 18.9% (n=18) respectively.

The pregnancy was spontaneous in all cases and multiple in 2 cases. Pregnancy follow-up was considered good in 27.4% (n=26) and was essentially done in the private sector in 35 cases (36.8%).

Follow-up was mainly done by a gynecologist in 64 cases (67.4%). Pregnancy-related pathologies were essentially represented by pregnancy-related hypertension in 29 cases, i.e. a rate of 30.5%, and gestational diabetes in 16 women, i.e. 16.8% of cases where screening was performed. The latter was achieved in 51.5% (n=49) (Table 1).

Table 1. *Gyneco-obstetrical history of parturients.*

Gyneco-obstetrical history	Number of cases	Percentage (%)
Pregnancy-induced hypertension	27	28,4
Preeclampsia	28	29,5
Gestational diabetes	10	10,5
Fetal death	1 6	16,8
HELLP syndrome	3	3,2
IUGR	1 3	13,7
LBW	2 0	21
Prematurity due to EP	1 8	18,9
Death before 7 days of life	3	3,2
History of hospitalization in intensive care unit	0	0
The current pregnancy		
Compliant pregnancy monitoring	26	
Monofetal pregnancy	94	98,9
Oligohydramnios	14	14,7
PMR over 12 h	7	7,4
Pregnancy-induced hypertension	29	30,5
Gestational diabetes	16	16,8
HRP	5	5,3

Twenty-nine parturients presented with High Blood Pressure (HBP). The mean term of discovery of HBP was 30.24 ± 3.76 weeks of gestation with extremes of 23 and 36 weeks of gestation. the treatments received by the parturients were anti-hypertensive treatment associated with acetylsalicylic acid in 6 cases and Low Molecular Weight Heparin (LMWH) in 4 cases. Obstetrical ultrasound was performed in 86 cases (90.5%). Obstetrical ultrasound was pathological in 2.1% of cases for Trimester 1 (T1) ultrasound, in 4.2% of cases for Trimester 2 (T2) ultrasound and in 12.6% for Trimester (T3) ultrasound. Doppler ultrasound was performed in 68 cases (71.6%). Doppler ultrasound of the umbilical artery was pathological in 20 cases (29.4%). Doppler ultrasound of the uterine artery was pathological (notch) in 8 cases (11.7%). Fourteen cases of oligohydramnios were noted in 14.7% of cases. Intrauterine growth retardation was recorded in 24 cases (25.3%). A vaginal delivery was performed in 9 cases (9.5%). The number of deliveries by caesarean section was 86 (90.5%) of deliveries. Caesarean section was performed as an emergency in 84 cases and electively in 2 cases, either 97.7% and 2.3% of the total number of caesarean sections respectively. The indications for caesarean delivery varied. They were essentially dominated by severe EP in 48 cases, either 50% of cases, followed by acute fetal distress in 15.6% of cases and HRP in 5 cases. The delivery was complicated by acute fetal distress in 15 NN (15.8%) and the Fetal Heart Rate (FHR) recording was pathological in 14 cases (14.7%). Delivery was complicated by acute fetal distress in 15 NN (15.8%) and Fetal Heart Rate (FHR) recording was pathological in 14 cases (14.7%).

Characteristics of preeclampsia

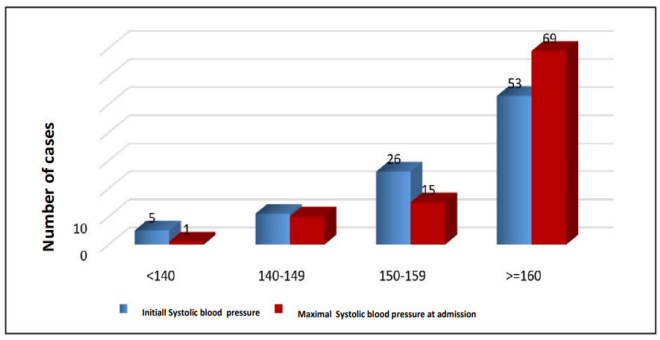
The mean gestational age at the onset of EP was 34.38 ± 3.27 weeks of gestation with extremes of 27 and 39 weeks of gestation. It occurred between 32 and 37 weeks of amenorrhea in 59 cases. The reason for hospitalization of parturients was mainly high blood pressure in 85 cases (89.5%). Elsewhere, severe EP and no diastole were the reasons for hospitalization in 6 and 3 cases respectively. The mean systolic blood pressure on admission was 158 ± 16.3 mmHg with extremes of 110 and 210 mmHg. The mean maximum systolic blood pressure on monitoring was 163.3 ± 15.3 mmHg with extremes of 130 and 200 mmHg. The mean diastolic blood pressure on admission was 97.3 ± 10.26 mmHg with extremes of 70 and 120 mmHg.

The mean maximum diastolic blood pressure on monitoring was 101.74 ± 10.98 mmHg with extremes of 80 and 140 mmHg. The mean proteinuria measured by urine strips was 1.89 ± 1.04 crosses with extremes of 0 and 4 crosses .The mean proteinuria measured by urine strips during admission was 1.94 ± 1.03 crosses with extremes of 0 and 4 crosses. The distribution of baseline systolic and diastolic blood pressures and proteinuria and their changes on admission. 24-hour proteinuria was performed in 26 cases with a mean of 1.33 ± 1.56 g/24 hours and extremes of 0 and 5.13 g/24 hours. EP was severe in 73.7% of cases (n=70). Eighty-six parturients had obstetrical ultrasound on admission. BIAPD, CA and LF measurements were $<3^{rd}$ percentile in 3, 17 and 9 cases respectively. The evolution of EP was marked by the occurrence of complications in 30.5% of cases. HELLP syndrome was the most frequent complication in 19 cases

(20%), followed by retroplacental hematoma in 5 cases (5.3%), renal failure in 3 cases and disseminated intravascular coagulation (DIC) in 2 cases.

Antihypertensive treatment was prescribed as follows: a calcium channel blocker, a beta-blocker and a central antihypertensive (methyldopa) in 90, 54 and 21 cases respectively, i.e. in 94.7%, 56.8% and 22.1% of cases. The anti-hypertensive treatment received by the parturients during their hospitalization was in the form of triple therapy in 10.5% of cases .The average stay in hospital was 5.57 ± 4.95 days, with extremes of 1 and 24 days. Four of the parturients were admitted to the intensive care unit. No maternal deaths were reported (Figure 1).

Figure 1: *Systolic blood pressure, diastolic blood pressure and initial proteinuria measured by urine dipstick in parturients and their evolution on admission.*



Characteristics of newborns

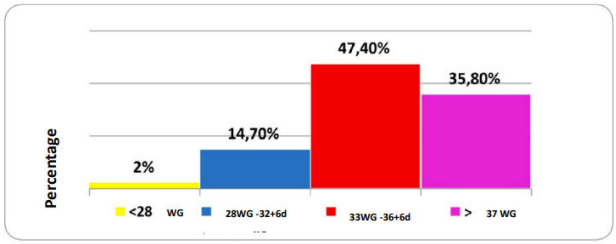
There was a female predominance with a gender ratio (M/F) of 0.73. The mean gestational age was 35.02 ± 3.15 weeks of gestation with extremes of 27 and 39 weeks of gestation. Preterm NN were noted in 61 cases (64.2%). The mean birth weight was 2164.8 ± 829.6 g with extremes of 710 g and 5330 g. The mean height was 43.4 ± 4.3 cm with extremes of 35 and 53 cm. The mean PC was 31.36 ± 2.2 cm with extremes of 25 and 34.5 cm. Fifty-one NN were eutrophic (in 53.7% of cases). IUGR was noted in 39 NN (41.05%). The distribution of newborns according to gestational age, birth weight and trophicity. The mean Apgar score at 1 minute was 7.62 ± 1.97 with extremes of 1 and 9. The mean Apgar score at 5 minutes was 8.42 ± 1.95 with extremes of 1 and 10. Poor adaptation to extrauterine life with an Apgar score of less than 7 at 5 minutes was observed in 15 cases (15.8%), of which 12 cases were born by caesarean section and 3 cases by vaginal delivery. Perinatal asphyxia (PNA) was noted in 3 cases (3.2%). Apparent death with an Apgar score less than 3 at one minute was noted in 6 cases (6.3%). Delivery Room Resuscitation (DRR) was used in 24 cases (25.3%). Two NN were intubated in 2.1% of cases. Forty-seven newborns were admitted to the neonatal intensive care unit, i.e. 49.5% of cases. The most frequent reason for admission was prematurity in 27 cases (57.4%) followed by neonatal respiratory distress and perinatal asphyxia in 23 cases (48.9%). The in-hospital evolution was burdened with co-morbidities dominated by respiratory distress and sepsis (Table 2 and Figure 2).

Table 2: *Distribution of newborns by in-hospital co-morbidities.*

In-hospital co-morbidities	Number of cases
Seizures	3
Intra-ventricular hemorrhage>Grade II	4
PVLM	1
Bilateral ROP stage II	1
Transient respiratory distress	10
Respiratory distress syndrom	6
Infectious alveolitis	4
Meconium inhalation	1
PAH	2
Hemodynamic disorders	10
Materno-fetal infection	25
Nosocomial infection	11
Necrotinzing enterocolitis	10
Hypoglycemia	7
Hypocalcemia	11
Jaundice	28

Anemia	10
Thrombocytopenia	24
Neutropenia	15
Polycythemia	9

Figure 2: *Distribution of NN by gestational age, birth weight and trophicity.*



Twenty-four NN benefited from ventilatory support, i.e. 25.3% of cases. CPAP (Continuous Positive Airway Pressure) was the most frequent ventilatory mode used in 15 cases with a mean duration of use of 1.76 ± 1.26 days with extremes of 2 hours and 5 days. 8 NN were on artificial Ventilation (VA). Peripheral venous access was the most frequent route used in 45 cases (47.4%). A broviac catheter was used in 10 cases. Twenty-one NN were put on antibiotics for suspected Materno Fetal Infection (MFI) and 11 NN for suspected nosocomial infection. Vasoactive drugs were used in 10 cases, i.e. in 21.3% of cases hospitalized in NICU. The average length of hospitalization for NN was 10.87 ± 9.05 days with extremes of 1 and 44 days. Survival rate was noted in 88.4% of cases. Intra-hospital death was observed in 11 cases (11.6%). The mean survival age of the deceased NN was 10.09 ± 11.98 days with extremes of 2 and 44 days. Prematurity was noted in 9 cases of the deceased newborns, i.e. 81.8% of the deceased cases, 66.6% of which were very premature (<32 weeks of gestation).

Low birth weight was noted in 7 of the deceased babies, i.e. 63.6% of the deaths. IUGR was observed in 6 of the deceased babies, i.e. 54.5% of the deaths.The most frequent direct cause of death was fulminant ulcerative colitis in 5 cases followed by severe sepsis and Hypoxic-ischemic encephalopathy.

Risk factors for in-hospital neonatal mortality

The comparative study carried out between the two groups of NN (G1=NN of non-deceased MPEs and G2=NN of deceased MPEs) concluded that there was no difference in maternal data (maternal age, gestation, parity and pathological ATCDs) as well as in the course of the pregnancy and delivery.

The characteristics of NN in group G1 were comparable to those of NN in group G2 for gender.

The study of the relationship of maternal epidemiological characteristics, maternal history, pregnancy characteristics, EP characteristics, newborn characteristics with in-hospital mortality of MEP NN is summarized (Table 3).

Table 3: *Relationship of maternal characteristics to mortality of newborns of preeclamptic mothers.*

Risk factors	G1	G2	P	Odds ratio	CI (95%)
Features maternal epidemiology					
Average socio-economic conditions	57	8	1000	1,26	[0,31-5,14]
Married Mothers	81	9	0,367	0,33	[0,03-3,55]
Housewife	42	4	0,395	0,57	[0,15-2,09]
Smoking	6	1	0,590	1,30	[0,14-11,93]
Background maternals					
Family history of hypertension	40	5	0,892	0,92	[0,26-3,24]
History of high blood pressure	23	4	0,205	1,52	[0,41-5,66]
History of severe preeclampsia	24	4	0,726	1,43	[0,38-5,33]
Fetal death history	12	1	0,101	0,11	[0,01-1,39]
History of death before 7 days of life	1	2	0,093	20	[0,85-471,57]
Congenital heart disease	23	4	0,502	1,52	[0,41-5,66]

Primiparity	49	5	0,739	0,71	[0,19-2,65]
Primigravida	84	5	1000	1,15	[0,31-4,28]
Characteristics of the pregnancy					
Incorrect monitoring of the pregnancy	61	7	0,502	0,66	[0,17-2,46]
IUGR on ultrasound	1	5	0,138	2,85	[0,78-10,38]
Oligohydramnios	12	2	0,663	1,33	[0,25-6,94]
Fetal distress	13	1	1000	0,55	[0,06-4,64]
Delivery by caesarean section	76	10	1000	1,05	[0,12-9,32]
Characteristics of the PE					
Term of occurrence of the EP ≤ 32 weeks of gestation	16	6	0,017	5,1	[1,38-18,82]
Severe EP	61	9	0,722	1,69	[0,34-8,45]
Moderate EP	23	2	0,722	0,59	[0,12-2,94]
Delivery by caesarean section	76	10	1000	1,05	[0,12-9,32]
HELLP syndrome	13	6	0,007	6,55	[1,74-24,68]
Anti-hypertensive treatment					
Monotherapy	27	2	0,494	0,47	[0,09-2,32]
Dual therapy	50	6	0,756	0,82	[0,23-2,89]
Tritherapy	7	3	0,089	4,13	[0,88-19,16]

The study of the relationship of NN characteristics with in-hospital mortality of MEP NN is summarized in (Table 4).

Table 4: *Relationship of characteristics of newborns of preeclamptic mothers to their in-hospital mortality.*

Risk factors	**G1**	**G2**	**P**	**Odds ratio**	**CI (95%)**
Characteristics of the newborns at the birth					
Male gender	36	4	0,756	0,76	[0,21-2,80]
Gestational age ≤ 30 weeks of gestation	8	5	0,006	7,92	[1,96-31,86]
Gestational age: 30S+1d - 36 weeks of gestation +6d	40	4	0,481	0,63	[0,17-2,31]
Gestational age: ≥ 37 weeks of gestation	36	2	0,190	0,29	[0,06-1,45]
Birth weight <1500 (g)	14	7	0,002	8,75	[2,25-33,95]
Birth weight: 1500-2000 (g)	17		0,454	0,37	[0,04-3,06]
Birth weight: 2000-4000 (g)	50	3	0,056	0,25	[0,06-1,03]
IUGR	33	6	0,516	1,82	[0,51-6,45]
Dysharmonic IUGR	27	5	0,503	1,69	[0,47-6,063]
Harmonious IUGR	7	1	1000	1,07	[0,12-9,64]
Apgar at 1 minute ≤ 7	22	7	0,031	4,93	[1,32-18,48]

Stay in NICU ≥ 3 days	27	8	0,022	4,8	[1,18-19,46]
Apgar at 5 minutes ≤ 8	27	9	0,002	9,5	[1,92-47,08]
Apparent state of death	5	1	0,532	1,58	[0,16-14,92]
Neonatal morbidities	16	5	0,061	3,54	[0,96-13,70]
Respiratory distress syndrom	2	4	0,001	23,43	[3,63-151,19]
Infectious alveolitis	31	1	0,394	2,7	[0,25-28,49]
Congenital heart disease	1	2	0,035	18,22	[1,50-221,36]
Necrotizing enterocolitis	2	8	<0,001	109,33	[15,85-753,9]
Hemodynamic disorder	1	9	<0,001	373,5	[30,75-4536,79]
Intraventricular hemorrhage	2	2	0,065	9,11	[1,14-72,73]
Materno fetal infection	17	8	0,001	10,51	[2,52-43,90]
Nosocomial infection	5	6	<0,001	18,96	[4,26-84,27]
Jaundice	24	4	0,726	1,43	[0,38-6,33]
hypocalcemia	6	5	0,003	10,83	[2,54-46,11]
hypoglycemia	6	1	0,590	1,30	[0,14-11,93]
Anemia	6	4	0,015	7,43	[1,68-32,72]
Thrombocytopenia	18	6	0,027	4,4	[1,20-16,08]
Leukopenia	12	3	0,372	2,25	[0,52-9,69]
Polycythemia	7	2	0,279	2,44	[0,44-13,69]
CPAP Ventilation	9	6	0,002	10	[2,53-39,49]
Invasive ventilation	1	7	<0,001	145,25	[14,23-1482,64]
Hospital stay in NICU ≥ 3 days	30	8	0,024	4,8	[1,18-19,46]

Multivariate study

In order to identify the independent factors related to hospital mortality in MEP NN, we conducted a multivariate analysis using stepwise descending logistic regression. The variables chosen were those with p values less than 0.05 in the univariate study. We selected 10 of the 19 significant variables obtainedin the univariate analysis. Table V summarizes the variables used in the multivariate study. In this multivariate analysis, three risk factors independently related to in-hospital mortality in MEP NN were identified.

Table 5: *The variables used in the multivariate study.*

Risk factors	**G1**	**G2**	**P**	**Odds ratio**	**CI (95%)**
Onset of PE ≤ 32 WG	16	6	0,017	5,1	[1,38-18,82]
HELLP syndrome	13	6	0,007	6,55	[1,74-24,68]
Gestational age ≤ 30 WG	8	5	0,006	7,92	[1,96-31,86]
Birth weight<1500 (g)	14	7	0,002	8,75	[2,25-33,95]
Apgar at 5 minutes ≤ 8	27	9	0,002	9,5	[1,92-47,08]
Neonatal hypocalcemia	6	5	0,003	10,83	[2,54-46,11]
Anemia	6	4	0,015	7,43	[1,68-32,72]
Thrombocytopenia	18	6	0,027	4,4	[1,20-16,08]
CPAP Ventilation	9	6	0,002	10	[2,53-39,49]
Stay in NICU ≥ 3 days	30	8	0,024	4,8	[1,18-19,46]

The risk factors for in-hospital mortality of BEP NNs and the risk factors independently related to in-hospital mortality of BEP NNs based on the multivariate study (Table 6).

Table 6: *Risk factors for in-hospital mortality in newborns of pre-eclamptic mothers.*

Univariate study	**P**	**Odds ratio**	**IC (95%)**
Onset of PE ≤ 32 WG	0,017	5,1	[1,38-18,82]
HELLP syndrome	0,007	6,55	[1,74-24,68]
Gestational age ≤ 30 WG	0,006	7,92	[1,96-31,86]
Birth weight<1500 (g)	0,002	8,75	[2,25-33,95]
Apgar at 1 minute ≤ 7	0,031	4,93	[1,32-18,48]
Apgar at 5 minutes ≤ 8	0,002	9,5	[1,92-47,08]
MMH	0,001	23,43	[3,63-151,19]
Congenital heart disease	0,035	18,22	[1,50-221,36]
Necrotizing enterocolitis	<0,001	109,33	[15,85-753,9]
Hemodynamic disorder	<0,001	373,5	[30,75- 4536,79]
Materno fetal infection	0,001	10,51	[2,52-43,90]
Nosocomial infection	<0,001	18,96	[4,26-84,27]
Neonatal hypocalcemia	0,003	10,83	[2,54-46,11]
Anemia	0,015	7,43	[1,68-32,72]
Thrombocytopenia	0,027	4,4	[1,20-16,08]
CPAP Ventilation	0,002	10	[2,53-39,49]
Invasive ventilation	<0,001	145,25	[14,23-1482,64]
Vasoactive drugs	<0,001	373,5	[30,75- 4536,79]
Length of stay in NICU ≥ 3 days	0,024	4,8	[1,18-19,46]
Multivaried study	P	Odds ratio	IC (95%)
EP complicated by HELLP syndrome	0,036	7,42	[1,14 - 48,19]
Neonatal hypocalcemia	0,007	16,80	[2,16 – 130,56]
Use of CPAP ventilation in NN	0,011	10,59	[1,7 – 66,05]

The risk factors independently associated with in-hospital mortality for NN of pre-eclamptic mothers are summarized (Table 7).

Table 7: *The risk factors independently associated with in-hospital mortality for NN of pre-eclamptic mothers.*

Risk factor	**p**	**OR**	**IC (95%)**
EP complicated by HELLP syndrome	0,036	7,42	[1,14-48,19]
Neonatal hypocalcemia	0,007	16,80	[2,16-130,56]
Use of CPAP ventilation in NN	0,011	10,59	[1,7-66,05]

Discussion

Preeclampsia is a frequent pathology responsible for a significant maternal and neonatal morbidity and mortality [5]. To date, few studies have assessed the impact of this condition and the quality of its management on neonatal prognosis in our country. The objective of our study was to describe the epidemiological, clinical and evolutionary profile of newborns of preeclamptic mothers and to identify their risk factors for

hospital mortality [6]. Our study was retrospective, monocentric over a period of 6 months from July 1 to December 31, 2020 and included 95 live births of preeclamptic mothers initially managed in the "A" and "C" obstetrics gynecology departments of the CMNT [7]. We excluded fetal death, NN with a PN birth weight lower than 700 grams and/or less than 27 weeks of gestation. The prevalence of EP was 2.35% with a prevalence of severe and moderate forms that were respectively 1.73% and 0.62%. Although the overall prevalence of EP in our study is similar to that of developed countries, we note that it differs in the preponderance of preponderance of severe EP compared to moderate EP [8]. Indeed, a longitudinal study in Canada over 24 years on a large database that included 1.9 million births and 68010 cases of EP, the incidences of moderate and severe EP were respectively 2.57% and 0.89%. The mean maternal age was 31.44 ± 5.71 years and 59.1% of parturients were older than 30 years [9]. Our results are consistent with those who found respectively for this age group 71.3% and 69.8% of the two populations studied, with an average age of 28.5 years and 31.5 years. This age range represents in our socio-cultural context the age of marriage and maximum procreation. Indeed, according to the

Multiple Indicator Cluster Survey (MICS) of Tunisia was conducted in 2018 by the National Institute of Statistics in collaboration with the Ministry of Development Investment and International Cooperation (MDICI) under the global program of MICS 6 surveys [10]. Women aged between 30 and 34 years have the highest fertility rate and to a lesser extent those aged between 25 and 29 years. Parental consanguinity was noted in 29.5% of cases. This rate is close to that reported in the literature [11]. In a study published in 2007, conducted in Monastir, to determine the prevalence of consanguinity and its effects on fertility and mortality in Tunisia, 1741 live births from 1989 to 1991, consanguinity in the Tunisian population was 24.8%. Studies on the effect of consanguinity on EP are contradictory [12]. In a review of the literature, which aimed to study the consequences of inbreeding on reproduction,the authors noted that in some studies that inbreeding does not seem to increase the risk of but on the contrary decrease it. Other studies have shown that there was no association between inbreeding and EP, nor on the development of maternal-fetal complications [13]. In a study in Holland, which aimed to analyze the relationship of family aggregation and consanguinity with EP and IUGR for 106 women in a genetically isolated area in Holland, the percentage of women born of a consanguineous marriage was higher in women with a history of EP compared to the control group [14]. The authors observed that the co-segregation of EP and IUGR supports a common genetic etiology and that the high rate of parental consanguineous marriages suggests the possibility of an underlying recessive genetic mutation. 56.8% of mothers were primiparous. Parturients reported a family history of hypertension and PE in 47.3% and 4.3% of cases, respectively [15]. A personal history of maternal pathology was noted in 27.4% of cases. Maternal pathologies were dominated by chronic hypertension, diabetes, asthma and hypothyroidism and were noted in 6.3%, 6.3%, 5.3% and 4.2% of cases respectively. A history of PE and fetal death was reported in 70% and 40% of the multiparous women respectively. Primiparity was noted in 56.8% of parturients. During the gestational period, gestational hypertension was noted in 30.5% of cases, 55.2% of which occurred before 34 weeks' gestation. Gestational diabetes was observed in 16.8% of parturients. Our results are consistent with those of the literature [16]. The literature states that multiparous patients with a history of EP, MFIU or other complications of EP represent a population at high risk of developing a second episode of EP, especially in its severe forms that can be identified early in pregnancy [17]. Thus, a history of EP has been shown to be a significant risk factor in many studies with a recurrence rate that varies between 14 and 50% according to the publications [18]. A retrospective German study, including 647, 392 pregnancies from the German Perinatal Quality Registry, aimed to examine the relationship between gestational diabetes and EP after controlling for common risk factors. The authors found that the risk of EP was increased in women with gestational diabetes with an adjusted Odds Ratio (OR): 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, occupational status, smoking, parity, multiple pregnancy and weight gain during pregnancy [19]. A retrospective German study, including 647,392 pregnancies from the German Perinatal Quality Registry, aimed to examine the relationship between gestational diabetes and EP after controlling for common risk factors. The authors found that the risk of EP was increased in women with gestational diabetes with an adjusted Odds ratio (aOR): 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, occupational status, smoking, parity, multiple pregnancy and weight gain during pregnancy [20]. In a systematic review of the literature, which included 149 controlled studies, it was found that a family history of EP triples the risk of EP, that nulliparity triples the risk of EP, and that mothers with a history of this disease have a sevenfold increased risk of developing EP.

The mean gestational age of discovery of EP was 34.38 ± 3.27 weeks of gestation. EP was late and early respectively in 69.5% and 30.5% of cases [21]. For perinatal outcome, the studies noted a high incidence of fetal growth restriction resulting in low birth weight in the EP NNs; almost one third of them had weight below the 10^{th} percentile for their gestational age. There was also a higher rate of perinatal mortality [22]. Our results are consistent with the literature. Indeed, a significant association was found between hospital mortality and NN of mothers whose EP occurred before 32 SA (p=0.017). Severe EP was most frequent in 73.7% of cases and moderate in 26.3% of cases. Our results differ from the literature in the distribution of EP severity [23]. The high prevalence of severe EP in our study can be explained by the fact that the Tunis maternity center recruits mainly high-risk pregnancies subject to both maternal and neonatal complications [24]. The high prevalence of severe EP in our study can be explained by the fact that the Tunis maternity center recruits essentially high-risk pregnancies and subject to both maternal and neonatal complications [25]. The evolution of EP was marked by the occurrence of complications in 30.5% of cases. HELLP syndrome was the most frequent

complication in 20% of cases. In a systematic review of the literature, HELLP syndrome complicates 10 to 20% of severe EP and develops in 50% of cases before 34 weeks' gestation. Perinatal morbidity and mortality is significantly higher in NN of mothers with HELLP syndrome. The perinatal mortality rate of HELLP syndrome varies between 7.4% and 34% and depends mainly on the gestational age at delivery. Our results are consistent with those of the literature with a statistically significant association between hospital mortality and NN of MEPs with HELLP syndrome (p=0.007) and a neonatal mortality of 32% for the latter. In our study, a female predominance was noted with a gender ratio (M/F) of 0.73. Our results are in agreement with those of the literature.

In our study, the mean gestational age was 35.02 ± 3.15 SA with extremes of 27 and 39 SA. The number of preterm NN was 64.2%. This rate was higher than that found in the literature. A study conducted in the United States from 1990 to 2004 on 57 million newborns showed that hypertensive disorders of pregnancy (gestational hypertension and EP) are associated with a greater risk of stillbirth and neonatal mortality and that the risk of prematurity is multiplied by 4 in mothers with EP compared to those with normotension [26]. In our study, prematurity with gestational age ≤ 30 weeks of gestation was significantly associated with in-hospital mortality (p=0.006). In our study, 23.2% of NN had a weight less than or equal to 1500 g. They were eutrophic in 53.7% of cases. IUGR was noted in 41% of the cases, it was considered disharmonious and severe respectively in 82% and 38.5% of the IUGR cases. The relationship between EP and IUGR is well studied in the literature. Indeed, EP is present as a result of abnormal placentation that can lead to delayed placental development, lack of oxygenation and nutrition of the fetus responsible for IUGR. EP affects the placental blood supply, resulting in IUGR and may lead to preterm delivery [27]. It is estimated that there are 30 million newborns with IUGR in low-and middle-income countries, with one in seven births associated with EP. The mean Apgar scores at 1 and 5 minutes were 7.62 ± 1.97 and 8.42 ± 1.95, respectively. The Apgar scores at 1 and 5 minutes were considered low in 15.8% and 13.7% of cases, respectively. In a univariate study, we found a significant association between a low Apgar score and in-hospital mortality in NN, with a score less than or equal to 7 at 1 minute (p=0.031) and less than or equal to 8 at 5 minutes (p=0.002).

These results are in line with the data demonstrated by the study with a lower Apgar score more frequent in NN of mothers with severe EP and associated with maternal complications. Among the intra-hospital comorbidities, we noted in our study a statistically significant association between the occurrence of respiratory distress syndrome (p=0.001). Among the in-hospital comorbidities, there was a statistically significant association between the occurrence of respiratory distress syndrome (p=0.001), congenital heart disease (p=0.036), SIMF (p=0.001), nosocomial infection (p<0.001), neonatal anemia and thrombocytopenia (p=0.015 and p=0.027), neonatal hypocalcemia in univariate and multivariate analysis (p=0.003 and p=0.007), and in-hospital mortality in NN of EP mothers [28]. The literature has largely focused on the study of the involvement of these risk factors identified in our study, in this sense, it contains divergent opinions on the effect of EP of occurrence or not of respiratory distress. In a Chinese study, on a large cohort of 185,687 live births, aiming to determine the association between maternal hypertension and EP with DRNN, that EP is a risk factor for the occurrence of DRNN and infectious alveolitis not only for preterm newborns but also for those born at term. In a Canadian study, which included 1,942,072 newborns, which aimed to determine the risk of congenital heart disease in newborns of EPM, the risk of EP is more frequent in newborns of EPM with a prevalence of 16.7/1000 births.

The authors found that there was a significant association between EP and the occurrence of non-severe congenital heart disease and that early EP was associated with severe congenital heart disease. The authors also noted that ductus arteriosus persistence is more common in NN of EP compared to those of normotensive mothers. In a systematic review of the literature, aimed at studying the long-term infectious morbidity of children of MEP, although severe EP is associated with a higher risk of infectious morbidity in these children. This association is thought to be due to prematurity and mode of delivery by caesarean section rather than the EP itself. In a 3-year retrospective study in the USA to determine the association between EP and necrotizing enterocolitis, 4.6% necrotizing enterocolitis in newborns of EPM and concluded that EP is a risk factor for necrotizing enterocolitis in newborns of EPM, especially those with IUGR. Neonatal neutropenia is a common hematological disorder in newborns withMEP, especially in preterm infants. It is often of short duration but can be prolonged and severe. This type of neutropenia during the first week after birth potentiates the subsequent risk of infection, especially for preterm infants. The literature contains conflicting opinions on the effect of magnesium sulfate on neonatal calcium levels. Some studies report a significant correlation between the total dose of magnesium sulfate and neonatal serum calcium [29]. The management of newborns of EP mothers allowed us to identify a number of risk factors for mortality related to the use of invasive mechanical ventilation (p<0.001) and CPAP (p=0.002) and the use of vasoactive drugs (p<0.001). Our results are in line with the literature. In a retrospective study in India, during 20 months, aiming to study the neonatal complications of MEP NN, 13% of MEP NN had received mechanical ventilation, 10% CPAP ventilation and 25% Hood oxygen therapy [30]. None of the newborns of normotensive mothers received mechanical ventilation or CPAP. Similarly, it has been reported in the literature that the use of vasoactive drugs is associated with greater neonatal mortality after adjustment for gender, gestational age and 5-minute Apgar score.

A statistically significant association was found between the duration of hospitalization in NICU greater than 3 days and in-hospital mortality of BEP (p=0.024). In this sense, a statistically significant relationship between the duration of hospitalization in NICU and the NN of BEP with a longer duration in the NN of BEP with a positive correlation between

neonatal complications especially neonatal mortality and the duration of hospitalization in NICU. In our study, in-hospital mortality was 11.6% of total cases [31]. The mean survival age of deceased NN was 10.09 ± 11.98 days with extremes of 2 and 44 days. Prematurity was noted in 81.8% of the deceased cases, of which 66.6% were very premature. Low birth weight was noted in 63.6% of the deceased NN. IUGR was noted in 54.5% of the deceased cases. necrotizing enterocolitis was the most frequent direct cause of death of the newborns in 45.5% of cases. The relationship between prematurity and low birth weight is well studied in the literature. In fact, in a study carried out in Holland, the aim was to evaluate the neonatal morbidity and mortality in newborns of mothers with early onset of PE and to compare it with that of newborns of the same gestational age [32]. Newborns with EP had higher perinatal (13% *vs*. 7%) and infant (16% *vs.* 9%) mortality compared to the control group. The authors noted that preterm infants with MEP were twice as likely to have low birth weight compared to preterm infants of similar gestational age born to non-pre-eclamptic mothers. They also concluded that low birth weight is a risk factor for perinatal mortality in EPM NN. Neonatal mortality in our study is higher than that reported in BEP NNs from developed countries but less than that from developing countries [33]. This is consistent with the data in the literature. Indeed, infant mortality is 3 times higher in NEPs in low- and middle-income countries than in developed countries. EP can cause up to 12% of low birth weight in newborns and 20% of prematurity. In the World Health Organization (WHO) WHO Multicountry Survey (WHOMCS), which included 308,392 pregnancies from 29 different countries and aimed to determine the risk of perinatal mortality in mothers with severe pregnancy complications, the authors concluded that for live births, NN of EP had a perinatal mortality rate of 7.2% which is higher than that of NN of non-preeclamptic mothers.

Conclusion

Pre-eclampsia is a frequent pathology responsible for a significant maternal and neonatal morbidity and mortality. To date, few studies have assessed the impact of this condition and the quality of its management on neonatal prognosis in our country. The objective of our study was to describe the epidemiological, clinical and evolutionary profile of newborns of preeclamptic mothers and to identify their risk factors for hospital mortality.

In univariate analysis, we found a significant association between in-hospital mortality of MEP NN and the following variables: EP complicated with HELLP syndrome (p=0.007); term of discovery of EP ≤ 32SA (p=0.017); gestational age of birth of NNs ≤ 30 SA (p=0.006); birth weight <1500g (p=0.002); Apgar score at 1 minute (p=0.031); Apgar score at 5 minutes (p=0.002); respiratory distress syndrome (p=0.001); congenital heart disease (p=0.035), hemodynamic disorders (p<0.001), ECUN (p<0.001); neonatal anemia (p=0.015); neonatal thrombocytopenia (p=0.027); neonatal hypocalcemia (p=0.003); healthcare-associated infection (p<0.001); suspected maternal-fetal infection (p=0.001); use of vasoactive drugs (p<0.001); use of antibiotics (p=0.001); use of CPAP ventilation in NN (p=0.002); use of invasive ventilation in NN (p<0.001) and hospital stay in NN in NICU ≥ 3 days (p=0.024). On multivariate analysis, EP complicated with HELLP syndrome (p=0.036), neonatal hypocalcaemia (p=0.007) and use of CPAP ventilation in NN (p=0.011) were identified as risk factors independently related to in-hospital mortality in NN of BEP.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' Contribution

Sdiri Y and Cherifi E have given substantial contributions to the conception and the design of the manuscript, Ayari F and Kacem S to acquisition of the data, Belhaj Ammar W and Chourou H to analysis and interpretation of the data.

References

1. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170:1-7.
2. American College of obstetricians and gynecologists. Hypertension in pregnancy. Washington, DC. 2013.
3. Ibn Khadija N. Management of severe preeclampsia: About 140 cases. Medicine: Tunis; 2010;88.
4. Ben Slimene M. Newborn of preeclamptic mother. Medicine: Tunis. 2004;69.
5. Benjelloun AT, Benchrifi Y, Mahdaoui S, et al. Epidemiology of preeclampsia in the greater Casablanca region. Pan Afr Med J. 2020;2:11.
6. Kerkeni E, Monastiri K, Seket B, et al. Interplay of socio-economic factors, consanguinity, fertility, and offspring mortality in Monastir, Tunisia. Croat Med J. 2007;48:701-707.
7. Oniya O, Neves K, Ahmed B, et al. A review of the reproductive consequences of consanguinity. Eur J Obstet Gynecol Reprod Biol. 2019;232:87-96.
8. Berends AL, Steegers EA, Isaacs A, et al. Familial aggregation of preeclampsia and intrauterine growth restriction in a genetically isolated population in Netherlands. Eur J Hum Genet. 2008;16:1437-42.
9. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. Br Med J. 2005;330:565.
10. Weissgerber TL, Mudd LM. Preeclampsia and Diabetes. Curr Diab Rep. 2015;15:579.
11. Schneider S, Freerksen N, Rohrig S, et al. Gestational diabetes and preeclampsia--similar risk factor profiles? Early Hum Dev. 2012;88:179-84.
12. Roberts D, Brown J, Medley N, et al. Antenatal corticosteroids for accelerating fetal lung maturation for

women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3.

13. Sharma N, Jayashree K, Nadhamuni K. Maternal history and uterine artery wave form in the prediction of early-onset and late-onset preeclampsia: A cohort study. Int J Reprod Biomed. 2018;16:109-14.
14. Pettit F, Mangos G, Davis G, et al. Pre-eclampsia causes adverse maternal outcomes across the gestational spectrum. Pregnancy Hypertens. 2015;5:198-204.
15. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre- eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145:1-33.
16. Thiam, M Mbaye, AA Diouf, et al. Epidemiological, prognostic and therapeutic aspects of PRH in a rural referral maternity hospital. Pan Afr Med J. 2014;17:1-4.
17. Khader YS, Batieha A, Al-njadat RA, et al. Preeclampsia in Jordan: Incidence, risk factors, and its associated maternal and neonatal outcomes. J Matern Fetal Neonatal Med. 2018;31:770-76.
18. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4:97-104.
19. Chaiworapongsa T, Chaemsaithong P, Yeo L, et al. Pre-eclampsia part 1: Current understanding of its pathophysiology. Nat Rev Nephrol. 2014;10:466-80.
20. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. Semin Perinatol. 2009;33:130-37.
21. Sirenden H, Sunarno I, Arsyad MA, et al. Birth weight, Apgar score, and fetal complications in mothers with severe preeclampsia. Enfermeria Clin. 2020;30:533-36.
22. Susilo SA, Pratiwi KN, Fattah ANA, et al. Determinants of low APGAR score among preeclamptic deliveries in Cipto Mangunkusumo Hospital: A retrospective cohort study in 2014. Med J Indones. 2015;24:183-89.
23. Uddin MN, Allen SR, Jones RO, et al. Pathogenesis of pre-eclampsia: Marinobufagenin and angiogenic imbalance as biomarkers of the syndrome. Transl Res. 2012;160:99-113.
24. Harrison RK, Palatnik A. The association between preeclampsia and ICD diagnosis of neonatal sepsis. J Perinatol. 2020;1-8.
25. Perger L, Mukhopadhyay D, Komidar L, et al. Maternal pre-eclampsia as a risk factor for necrotizing enterocolitis. J Matern Fetal Neonatal Med. 2016;29:2098-103.
26. Cetinkaya M, Ozkan H, Koksal N. Maternal preeclampsia is associated with increased risk of necrotizing enterocolitis in preterm infants. Early Hum Dev. 2012;88:893-98.
27. Root AW, Diamond FB. Disorders of mineral homeostasis in the newborn, infant, child, and adolescent. In: Sperling M.A. ed. Pediatric Endocrinology. Elsevier. 2008;686-769.
28. McKenzie KA, Trotman H. A retrospective study of neonatal outcome in preeclampsia at the University hospital of the West Indies: A resource-limited setting. J Trop Pediatr. 2019;65:78-83.
29. Bursal Duramaz B, Bilgin L, Salihoglu O, et al. Neonatal outcomes of preterm infants born to preeclamptic mothers. Marmara Med J. 2017;30:8-13.
30. Afrasiabi N, Mohagheghi P, Kalani M, et al. The effect of high risk pregnancy on duration of neonatal stay in neonatal intensive care unit. Iran J Pediatr. 2014;24:423-28.
31. Vogel JP, Souza JP, Mori R, et al. Maternal complications and perinatal mortality: Findings of the World Health Organization multicountry survey on maternal and newborn health. Int J Obstet Gynaecol. 2014;121:76-88.
32. Ben Hamida Nouaili E, Chaouachi S, Ben Said A, et al. Determinants of neonatal mortality in a Tunisian population. Tunis Med. 2010;88:42-45.
33. Esch JJA van, Heijst AF van, Haan AFJ de, et al. Early-onset preeclampsia is associated with perinatal mortality and severe neonatal morbidity. J Matern Fetal Neonatal Med. 2017;30:2789-94.

*Correspondence to

Dr. Ayari F

Department of Emergency

University Tunis El Manar

Tunis

Tunisia

E-mail: ayarifeirouz@yahoo.fr