Original Article

Pheochromocytoma associated with pregnancy: unexpected favourable outcome in patients diagnosed after delivery

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Objective: The objective of this study is to present the clinical findings and outcome of a large cohort of pregnant women with pheochromocytoma (PHEO) with the aim to contribute to the better recognition, detection and management of pregnancy-related PHEO in the population of pregnant patients with hypertension.

Methods: This is a longitudinal follow-up of a single cohort of 15 patients aged 19–40 years with PHEO associated with pregnancy. Urinary catecholamines and vanillylmandelic acid (VMA) were analysed. *Ret* proto-oncogene, *SDHB* and *VHL* mutations were determined in germline DNA from seven women using PCR followed by direct sequencing.

Results: During pregnancy, all women presented typical features of catecholamines excess. Nevertheless, biochemical diagnosis was performed only in four out of 15 cases during pregnancy and postpartum in the remaining 11. Paroxysmal hypertension was the predominant pattern. Urinary catecholamines and/or VMA were increased in all patients. Tumours were adrenal in 13 patients and extraadrenal in two. Mutations in the *Ret* proto-oncogene were found in four patients, in the *VHL* gene in one and in the *SDHB* gene in one. Antihypertensive treatment resulted in effective control of blood pressure and all women survived. In the group of women diagnosed postpartum, one foetus demised. Newborns from mothers receiving adequate treatment survived. One woman left the hospital after caesarean section but before PHEO surgery became pregnant again and this gestation ended with maternal-foetal dead.

Conclusion: A high index of suspicion in all pregnant women presenting hypertension mainly paroxystic during any gestational phase and/or a history of familial PHEO are the keys to disclose this important diagnosis.

Keywords: catecholamines, hypertension, paraganglioma, pheochromocytoma, pregnancy

Abbreviations: CT, computed tomography; HPLC-ED, high performance liquid chromatography with electrochemical detection; MEN, multiple endocrine neoplasia; MIBG, metaiodobenzylguanidine; PGL, paraganglioma; PHEO, pheochromocytoma; SDHB, succinate dehydrogenase B; VHL, von Hippel Lindau; VMA, vanillylmandelic acid

INTRODUCTION

Hypertension is a common medical complication in pregnancy [1]. Less than 1–2% of the cases are caused by endocrine disorders [2]. Pheochromocytoma (PHEO) is a catecholamine-secreting tumour that is a rare but important cause of hypertension in pregnant women and it may be responsible for morbidity and mortality to both mother and foetus [3].

A diagnosis of PHEO during pregnancy is difficult because it may mimic other more frequent problems such as preeclampsia [4,5]. It has an estimated prevalence of one in 50 000 to one in 15 000 term pregnancies [4,6]. Its clinical features are similar to those in nonpregnant women. Most patients have hypertension either sustained or paroxysmal accompanied or not by a wide variety of other signs and symptoms [7].

It has been reported that a high foetal mortality (26–55%) and high maternal mortality (17–48%) are associated with unrecognized PHEO during pregnancy [4,8]. Due to the improvement in early detection and management, these figures decreased to 4–12% for maternal mortality and 10–17% for foetal mortality in the last two decades. All this information arises from case reports extensively reviewed by different authors and are the basis for physicians' best practice [4,7,9].

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This work presents the clinical findings and outcome of a large cohort of pregnant women with PHEO with the aim to contribute to the better recognition, detection and management of PHEO in the population of pregnant patients with hypertension.

MATERIALS AND METHODS

Fifteen pregnant women with PHEO (aged 19–40 years, median age 27 years) were included in this study.

Diagnosis was established by analysis of 24-h urinary excretion of catecholamines and vanillylmandelic acid (VMA) and confirmed by tumour histology.

Urinary epinephrine and norepinephrine were determined by fluorometric method [10] or by high performance liquid chromatography with electrochemical detection (HPLC-ED) [11]. VMA was measured by a spectrophotometric technique [12].

The diagnosis of PHEO was performed during pregnancy in four patients and after the delivery in the remaining 11. One patient had two pregnancies while carrying the tumour; so a total of 16 gestations were considered.

Imaging studies employed to localize the tumour during pregnancy included ultrasound scan, MRI or both. In addition, postpartum imaging included computed tomography (CT) and/or metaiodobenzylguanidine (^{131}I-MIBG) scan.

Molecular genetic analysis could be performed in seven patients. According to clinical and biochemical characteristics and/or family history, we screened exons 8,10,11,13–15 of the proto-oncogene *RET*, exons 1–3 of *VHL* gene and 1–7 of the succinate dehydrogenase B (*SDHB*) gene using PCR in DNA obtained from peripheral blood samples, followed by automatic direct sequencing [13].

The study protocol was approved by the Ethical Committee of de Hospital de Niños Ricardo Gutiérrez and written informed consent was obtained from all patients.

RESULTS

Table 1 summarized the data from the patients studied.

In most women (11/15), PHEO appeared during the first pregnancy. Hypertension was present in all patients. Five of them presented a medical history of arterial hypertension, although in 10 women hypertension developed during the gestational period. In this latter group, remarkably, hypertension appeared after the 20th week of pregnancy ($n = 9$). Only one patient became hypertensive at 8 weeks of gestation. Different patterns of blood pressure were observed. The predominant was paroxysmal hypertension, presented by half of the patients, followed by sustained hypertension as well as paroxysmal crisis presented by five patients. Only three patients had sustained hypertension.

Blood pressure showed wide variations, ranging between 170 and 310 mmHg for systolic, and 100–180 mmHg for diastolic.

In most patients, hypertension was associated with a variety of symptoms and signs, the most frequent being headache, diaphoresis and palpitations (Table 2). The classic triad of hypertension, headache and sweating occurred in only three out of 15 pregnancies, while the triad of palpitations, headache and diaphoresis associated with hypertension occurred more frequently (five out of 15).

Despite the presence of the mentioned clinical manifestations, the PHEO was not suspected in most cases and the biochemical diagnosis was performed during the course of pregnancy only in four out of 15 women. The predominance of paroxysmal crisis in women whose PHEO was diagnosed after delivery was noticeable (Fig. 1).

The levels of urinary epinephrine, norepinephrine and VMA are summarized in Table 3. The combined measurement of urinary catecholamines and VMA was performed in 13 out of 15 patients. In one patient, only the data of urinary catecholamines were available, although in another only urinary VMA was measured. The amine more frequently increased was norepinephrine, which was found elevated

TABLE 1. Data on patients with pheochromocytoma associated with pregnancy

Patient	Age	Parity	Time of presentation (weeks)	Hypertension pattern	Tumour site	Genetic	Time of delivery weeks	Mode of delivery	Maternal outcome	Foetal outcome
Diagnosis antepartum										
1	31	1	Pregest	S	B	MEN 2A	38	C	A	A
2	21	1	24	Px	B	MEN 2A	32	C	A	A
3	30	1	Pregest	S + Px	R	MEN 2A	32	C	A	A
4	26	6	25	S + Px	R	–	37	C	A	A
Diagnosis postpartum										
5	19	1	24	Px	L	VHL	24	–	A	D
6	22	1	Pregest	S + Px	EA	PGL 4	36	C	A	A
7	23	1	37	Px	R	–	37	C	A	A
8	24	1	24	Px	R	–	38	V	A	A
9	26	1	20	Px	L	–	32	C	A	A
10	27	2	24	S + Px	R	–	38	V	A	A
11	29	2	Pregest	Px	R	MEN 2A	36	C	A	A
12	29	1	27	S	EA		27	C	A	A
13	30	1	Pregest	S	B	–	36	C	A	A
14	32	2	8	Px	L	–	32	C	A	A
15	40	1	20	S + Px	R	–	36	C	A	A

A, alive; B, bilateral; C, caesarean; D, dead; EA, extraadrenal; L, left; MEN 2A, multiple endocrine neoplasia type 2A; PGL 4, familial paraganglioma type 4; Pregest, pregestational; Px, paroxysmal crises; R, right; S, sustained hypertension; V, vaginal; VHL, von Hippel Lindau disease.

TABLE 2. Symptoms and signs ($n = 15$)

Hypertension	15	Oedema	1
Headache	12	Nausea/vomiting	1
Diaphoresis	11	Chest pain	1
Palpitations	8	Diarrhoea	1
Visual symptoms	4	Sialorrhoea	1
Warmth	4	Epigastric pain	1
Anxiety	3	Dizziness	1
Orthostatic hypotension	3	Acrocyanosis	1
Pallor	3	Tremor	1
Flushing	3	Back pain	1
Insomnia	1	Seizures	1

in 13 out of 14 patients, while epinephrine was increased in eight out of 14 patients. The urinary metabolite VMA was abnormally high in 12 out of 14 cases. It should be noted that in all patients (15/15), at least one of these analytes was found above the normal range.

All imaging methods used succeeded in localizing the tumour. There was a clear predominance of adrenal tumours ($n = 13$). Ten of them were unilateral (seven in the right and three in the left gland) and three bilateral. The remainder two were paraaortic abdominal paragangliomas.

As mentioned before, genetic studies could only be performed in seven patients. Four of them presented mutations in the exon 11, codon 634 of the RET proto-oncogene (Cys634Tyr in two cases and Cys634Phe, Cys634Arg in one patient each). In two of these patients, the clinical diagnosis of MEN 2A had been performed before pregnancy.

Two patients showed mutations in the *VHL* and *SDHB* genes, thus constituting cases of von Hippel-Lindau disease and familial paraganglioma type 4 (PGL4), respectively. In the remaining one, no genetic abnormalities could be detected. None of these patients presented other clinical signs of disease.

Patients were treated with different antihypertensive drugs. Normal blood pressure was achieved in all patients treated. The treatments included alpha blockers (doxazosin, prazosin), beta blockers (atenolol), alpha-methyl-dopa, calcium antagonists (amlodipine) and vasodilators (nitroglycerin and nitroprusside).

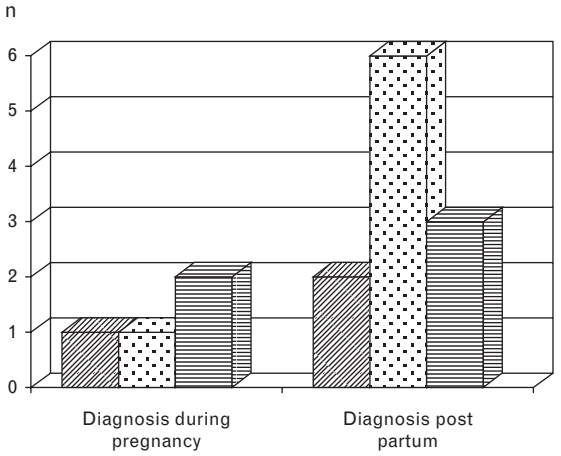

FIGURE 1 Frequency of hypertension patterns according to PHEO diagnosis: during or after pregnancy. ▨, sustained hypertension, ⬚, paroxysmal hypertension, ▤, sustained and paroxysmal crises.

TABLE 3. Individual values of urinary epinephrine, norepinephrine and vanillylmandelic acid

Patient	E	NE	VMA
Diagnosis antepartum			
1*	121	304	31.2
2	9	1008	70.4
3	48	112	17.7
4	140	98	32.7
Diagnosis postpartum			
5	0	2840	45.8
6	3	457	ND
7	44	172	8.5
8*	87	958	34.5
9*	116	149	20.5
10*	110	571	21.8
11	ND	ND	19.2
12	18	732	20.3
13	0	130	9.9
14*	0	1111	62.6
15*	63	213	6.2

Methods – normal values: fluorometric (*) E: 0–8.5 μg/24 h. NE: 18.5/100 μg/24 h, HPLC E: 0–21 μg/24 h NE: 18–110 μg/24 h. VMA: 1.8–8.5 mg/24 h. 0: below the detection limit. ND: not done.

In the group of women in whom the diagnosis of PHEO was performed during pregnancy, there were no maternal or foetal deaths. All these patients underwent caesarean section between 27 and 38 weeks of pregnancy. Surgical treatment of the tumour was performed at different times. One patient (#1) who had the diagnosis of MEN 2A became pregnant during the planned PHEO preoperatory period. She was adrenalectomized at week 12 of pregnancy and caesarean was performed at week 38.

In another patient (#2) who also had the pregestational clinical diagnosis of MEN 2A, PHEO diagnosis was made at 24 weeks of gestation and bilateral tumours were removed simultaneously with caesarean section at 32 weeks of pregnancy. In the remaining two patients, PHEO was diagnosed but not removed antenatally. Delivery was by caesarean section at 32 and 36 weeks, respectively. In the first one (#3 MEN 2A), the tumour was resected 3 months after delivery. The remaining patient (#4) left the hospital after successful delivery by caesarean section but without performing PHEO surgery. This latter patient did not receive any medical care; she became pregnant again (seventh gestation) 1 year later and this pregnancy ended in maternal-foetal death.

It should be noted that all 11 pregnant women in whom the diagnosis and treatment of PHEO was not performed during pregnancy continued symptomatic after delivery. All remained hypertensive and five required urgent hospitalization due to causes associated with PHEO: hypertensive crisis (two patients), hypertensive encephalopathy (one patient), electrocardiographic abnormalities (one patient) and seizures (one patient).

One of the 11 patients (#5) suffered intrauterine foetal demise at 6 months of gestation. Ten women continued their pregnancies and surgery of the PHEO was performed at variable times after delivery. Eight of them had caesarean section on week 27–37 of gestation. The remaining two women had normal delivery in week 38 of gestation.

Prematurity was a major morbidity associated with PHEO in pregnancy. In 10 out of 14 cases, the newborns

had less than 37 weeks of gestational age, two out of four in the group of PHEO diagnosed antepartum and eight out of 10 in the group of PHEO diagnosed postpartum. All newborns were normal and their weight was appropriate for gestational age.

DISCUSSION

The age of our patients at the time of PHEO presentation was similar to that described in the last systematic reviews [4,7,8]. PHEO causes similar symptoms in both pregnant and nonpregnant patients, but the diagnosis is often missed because they produce signs and symptoms that mimic other forms of hypertension such as preeclampsia [4], gestational hypertension and other hypertensive syndromes [2,14]. It is noticeable that in our group of patients, 73% were diagnosed postpartum.

Even when PHEO may appear at any time during pregnancy, data from the literature show that most women presented PHEO symptoms during the second or third trimester of pregnancy, predominantly during the last trimester [9]. In accordance with the previous report, in our group of patients, hypertension was identified in the great majority of women after week 20. Only those patients who had a previous diagnosis of hypertension, or MEN 2A, were diagnosed in early pregnancy. Noticeable one PHEO patient with no previous history of hypertension developed arterial hypertension before 20 weeks of pregnancy.

Similarly to what has been previously described [4,7–9], in our cohort, hypertension was the most constant clinical feature, predominantly the pattern of paroxysmal hypertension, followed in order of frequency by sustained as well as paroxysmal hypertension and less often by sustained hypertension.

The wide range of variation in blood pressure is noteworthy, with high values of both diastolic and systolic pressure. Hypertension was associated with a variety of symptoms such as those previously described. If we consider the presence of the classic triad of hypertension, headache and sweating, it was less frequently found than in nonpregnant patients with PHEO, as described [2].

As with PHEO cases that are unrelated to pregnancy, the diagnosis was made on the basis of the quantification of catecholamines and their metabolites [2,14–16], which in our case were urinary epinephrine, norepinephrine and VMA. At least one of these analytes was increased in all of our patients. Previous reports have shown that the levels of norepinephrine and epinephrine are normal in normotensive pregnant women and preeclamptic patients, and therefore, the levels of catecholamines do not correlate with blood pressure [17]. There is a general agreement in that elevated blood pressure observed in preeclampsia is not caused by increased circulating catecholamines. However, in rare cases, elevated catecholamines have been reported in preeclampsia [9,18,19]. Lately, metanephrines determination has been proposed as the test of choice for detecting PHEO [19]. Nevertheless, diagnosis of PHEO in pregnant women has been successfully achieved measuring 24-h urinary catecholamines in all the previous studies. Altogether, this information points out that measurement of catecholamines allows for discrimination between preeclampsia and PHEO in the vast majority of patients and is a valuable diagnostic tool.

Regarding the imaging methods used, both ultrasound and MRI proved to be useful during pregnancy. Although ultrasound is a safety procedure, the pregnant uterus may limit its use and become less helpful to identify extraadrenal tumours [14]. MRI is the method of choice because of its high sensitivity (95%) and safety during pregnancy [5,14]. In our patients diagnosed postpartum, there were also effective other common methods such as CT and scintigraphy with ^{131}I-MIBG, procedures that are contraindicated during pregnancy because of the risk of foetal exposure to ionizing radiation [8,14]. The location of the tumours showed a clear majority of adrenal PHEOs (87%), with a predominance of unilateral adrenal tumours (77%). Only two were extra-adrenal (13%). Although data in the literature mention a predominance of adrenal location, a higher frequency of extra-adrenal neoplasms is reported (21–32%) [4,8].

At least 10 genes have been associated with PHEO. Proto-oncogene *RET*, *NF1*, *VHL* and *SDHB* are the ones classically described and are quite well studied; the syndromes they produce are well characterized and these genes are routinely analysed in clinical practice when the typical phenotype is present and this was the case for our patients. Although other PHEO/PGL-susceptible genes have been described – *SDHA*, *SDHC*, *SDHD*, *SDHAF$_2$*, *TMEM127* and *MAX* – patients show clinical characteristics that were not present in our cohort [20,21].

Although the number of patients in whom the genetic test was available is small, the predominant hereditary syndrome was MEN 2A, with a lower incidence of VHL and PGL 4. It is noticeable that in all patients but one who underwent the genetics study, this was positive. Previous data reported 18–30% of mothers having genetic mutations [8,9]. These figures are much lower than the results of the present report; six out of seven patients were positive. In fact, even if we consider the remaining patients negative (in whom the study was not performed), syndromic presentation would increase to 40%.

MEN 2A has rarely been found in pregnancy. Until now, 15 cases have been reported in the literature [22–25]. Although it has been reported that in these cases tumours are more likely to be bilateral [13,24], a recent review on this subject reports that 50% of these patients had bilateral PHEO [23], in agreement with our findings. It is remarkable that in our series, three out of the four patients in whom the tumour was identified during pregnancy had the diagnosis of MEN 2A, and the tumour could be removed before or simultaneously with caesarean in two of them.

PHEO has also been reported in pregnant women with VHL disease [26–29]. Maternal VHL disease related complications have been reported to occur in 17% of pregnancies, being PHEO a quarter of these lesions [27]. In our study in only one woman, VHL disease was diagnosed. She was the one who presented intrauterine foetal demise. Both the biochemical diagnosis of PHEO and VHL genetic test were performed after it. The urinary norepinephrine values were the highest found in the whole group in contrast to undetectable levels of epinephrine. This is consistent with the property of VHL-associated PHEOs [5]. She did not present any other manifestation of disease after 20 years

of follow up; therefore, she can be classified as VHL type 2C [30].

PHEOs due to *SDHB* mutations are even more infrequent [9,31]. Carriers of the *SDHB* mutation develop mainly extra-adrenal tumours and are at an increased risk for malignant disease [13]. However, our patient who had an abdominal paraganglioma remains free of disease after 10 years of follow up.

On the basis of these findings, and considering the importance of antepartum diagnosis, the PHEO should be sought as soon as pregnancy is confirmed in any patient with a proved or suspected mutation in the genes related to familial PHEO or a history of having previously suffered the tumour [2].

Recently, a constant increase in the rate of antepartum diagnosis of PHEO in pregnancy from 25% in 1969 to 83% in 1998 has been reported, decreasing to 70% between 1998 and 2008 [4,7,8]. In contrast, in the present study, the antenatal diagnosis of PHEO continued to be infrequent. Despite the advances in diagnostic techniques, 6.7% of PHEOs in pregnant women remain undiagnosed and correspond to cases identified postmortem [8].

There is a general agreement in systematic reviews conducted to date that the most important factor to reduce maternal and foetal mortality is the diagnosis during pregnancy [4,7–9]. However, in our patients, despite the predominant late diagnosis, the outcomes were uneventful when properly treated. All women with a good control of their blood pressure during pregnancy survived. In the group of women diagnosed postpartum, only one foetus was lost. We registered only one maternal-foetal dead. This was the case of the woman who was not operated for PHEO, became pregnant again and did not receive any medical care during that gestation.

Although the patients received different antihypertensive drugs, all women achieved effective control of their blood pressure. It is possible that this fact had a decisive impact on the evolution of the patients.

Surgical treatment of PHEO was performed at different times. Several factors have to be taken into account such as gestational age, clinical response to treatment, access to the tumour and the presence or absence of foetal distress. In our patients when the diagnosis was performed in early pregnancy, the tumour was successfully removed before or simultaneously with caesarean section as recommended [14,32].

Most of our patients ended their pregnancy by caesarean. There is consensus regarding the benefit of caesarean section instead of vaginal delivery. A mortality of 31% in the vaginal delivery versus 19% in the caesarean section has been reported [33]. It is considered that vaginal delivery can induce an increased release of catecholamines from the tumour by unknown mechanisms probably mechanical [7]. The only two women of our series who had vaginal delivery did not experience adverse outcomes.

Catecholamines adverse effects on pregnant women health have been extensively studied and clinical outcome has improved greatly over the time. However, the role of catecholamine excess on foetal development has been the subject of fewer studies. A case of PHEO during pregnancy in which catecholamine levels in the umbilical cord blood were very low has been described, despite the simultaneous increase in maternal values. This has been attributed to the high activity of placental monoamine oxidase and catechol-O-methyltransferase, which results in metabolic inactivation of maternal catecholamines [34]. The intracellular uptake of catecholamines in placental cells also contributes to the high clearance of epinephrine and norepinephrine observed in the foetus [35].

The fact that all but one of the newborns of this study have evolved normally could be attributed to the above-mentioned characteristics of placental metabolism of catecholamines.

A five-fold higher concentration of VMA in cord blood of a foetus than in the peripheral blood of his mother was found in humans, confirming that the placenta is a major source for degradation of catecholamines.

In conclusion, a high index of clinical suspicion is the key to disclose PHEO diagnosis in pregnancy. On the basis of the clinical features found in this important cohort of patients, we stress the importance of looking for PHEO in all pregnant women presenting hypertension, mainly paroxysmal crises developed during any gestational phase. Another significant issue to be considered is the maintenance or worsening of hypertension after caesarean or natural delivery. It is also necessary to find out a medical history of genetic diseases associated with PHEO. An individualized approach to treatment to prevent serious maternal and foetal complications is recommended. Remarkably, a strict control of maternal blood pressure has a critical role for a favourable maternal-foetal outcome in PHEO-related pregnancy.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Referee 1

In this interesting paper Salazar-Vega *et al*. evaluated a large cohort of pregnant patients with pheochromocytoma (PHEO). PHEO and paraganglioma (PGL) are rare tumors of neuroectodermal origin, occurring in 0.1–0.2% of hypertensive patients, while incidence arises to 4–5% in patients with incidentally-discovered adrenal mass. The finding of PHEO/PGL is an important and relevant event in clinical practice that requires extreme care; this paper adds important considerations about it, because case reports and limited series with inherent limitations are the only sources of information on which to base best practice.

Referee 2

This case series reports on pheochromocytoma in pregnancy. The number of patients is relatively large. Nevertheless little information is added to the reviews and case series cited by the authors. The paper also does not tackle the question of what are abnormal levels of catecholamines and vanillymandelic acid in pregnancy and the more commonly used dosage of metanephrines (be it in plasma or urine). In its absence, it may be difficult to assess the missed cases (false negative) and their prognosis.