Paraganglioma in pregnancy: A case series and review of the literature

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Abstract

Context: Pregnancies complicated by a phaeochromocytoma or paraganglioma are very rare, being estimated to occur in 0.007% of all pregnancies. Both the wellbeing of the mother and fetus need to be considered, and management can be challenging. The optimal management of women with a phaeochromocytoma or paraganglioma in pregnancy is not well established.

Objective: To assess whether there is a difference in fetal or maternal mortality between phaeochromocytomas and paragangliomas in pregnancy.

Design: We present an experience of eight pregnancies in four *SDHB* germline mutation positive women with sympathetic paragangliomas, followed by a systematic review of the literature to compare the outcome of paragangliomas to that of phaeochromocytomas occurring in pregnancy.

Results: In our case series favourable fetal and maternal outcomes were seen in all eight pregnancies. From the systematic review, maternal and fetal mortality were lower in women with paragangliomas, at 3.6 and 12% respectively, compared with 9.8 and 16% in women with phaeochromocytomas.

Conclusion: Pregnant women with paragangliomas may be at a lower risk of adverse outcome than those with phaeochromocytomas but both maternal and fetal mortality rates are still higher than that of the general obstetric population.

Introduction

Pregnancies complicated by a phaeochromocytoma or paraganglioma (PGL) are very rare, estimated to occur in 0.007% of all pregnancies0. Due to the rarity of phaeochromocytomas and PGLs in pregnancy, the recommended management for the mother and baby is based on case reports, small case series and expert opinion.

Improving maternal and fetal mortality in patients with a phaeochromocytoma/PGL in pregnancy have been published since the initial case reports of the 1950s. In the 1960s, maternal and fetal mortality in phaeochromocytoma/PGL were reported as 48% and 55% respectively[2]. In the period between 1980 and 1987, maternal and fetal mortality in these conditions were cited as being 17 and 26%, respectively[3]. These respective mortalities in pregnancy-associated phaeochromocytoma/PGL decreased further to 12 and 17% in cases reported from 1998-2008[4]. The diagnosis of phaeochromocytoma/PGL is increasingly being recognised in the antenatal period, resulting in 12% fetal mortality (and 0% maternal mortality), compared to 29% fetal and maternal mortality when the diagnosis is made during labor or immediately postpartum[5].

Current recommendations for the management of a phaeochromocytoma/PGL discovered in pregnancy are that if the condition is diagnosed in the first 24 weeks gestation the tumor should be removed, preferably by a laparascopic approach in the second trimester[6]. Whereas, when a phaeochromocytoma/PGL is discovered in the third trimester surgical excision should be delayed until the fetus is viable and able to be delivered with the tumour being removed either immediately following delivery or at a later date[6]. Due to historical data, in which fetal mortality from vaginal delivery was much higher, caesarean section is the recommended mode of delivery of the baby[7]. For imaging, MRI is recommended for phaeochromocytoma/PGL in pregnancy due to the associated risk of fetal exposure to ionising radiation with CT imaging. Preoperative alpha receptor blockade should be given as for non-pregnant patients (although a target blood pressure has not been established),

along with increased salt and fluid intake[6]. Phenoxybenazmine does cross the placenta and may cause neonatal hypotension and respiratory depression[8].

PGLs are extra-adrenal chromaffin cell tumours which, in a recent review of their incidence in pregnancy, were reported to comprise only 19% of chromaffin cell tumours whereas the majority were phaeochromocytomas[5]. The clinical and biochemical patterns of phaeochromocytomas may differ when compared to PGLs. Differences in tumor size, catecholamine content and secretion may result in differential haemodynamic effects. As a result, the maternal and fetal risk may vary according to tumour site (adrenal vs extra-adrenal).

We report our experience of eight pregnancies in four women with *SDHB*-related PGLs. In addition, we conducted a systematic review of the literature to analyse maternal and fetal outcomes in pregnant women with phaeochromocytomas compared to PGLs. The aim of the review was to assess whether there was a difference in fetal or maternal mortality between phaeochromocytomas and PGLs in pregnancy.

Subjects and Methods

We conducted a systematic literature review of articles published over the 15 year period between 1998 and 2013. OVID MEDLINE and Pubmed search engines were used to identify relevant articles. The keywords “pheochromocytoma”, “paraganglioma”, “extraadrenal pheochromocytoma” were used. A separate search was performed to identify articles specifically related to PGL and phaeochromocytoma in pregnancy, using the keywords “pregnancy” or “pregnant”. All articles published in the period between 1998 and 2013 were included. Non-English articles were identified and translated. Cases were also included if the diagnosis of phaeochromocytoma/PGL was made within 6 months of delivery.

A total of 190 articles were identified. Thirty-five articles contained inadequate information or did not describe a case and were excluded. Two additional papers were excluded as the cases had previously been reported by another author. A total of 117 articles were included in the review comprising 143

cases of chromaffin cell tumours in pregnancy (112 adrenal phaeochromocytomas, 28 extraadrenal PGLs, and three patients who had synchronous phaeochromocytomas and PGLs). Data was collected on maternal and fetal mortality, symptoms, fold elevation in urinary or plasma catecholamines or metanephrines, genetic testing, and stage of pregnancy at which diagnosis was made. Confidence intervals were calculated using the modified Wald method. The process whereby articles were selected for the systematic review is shown in Figure 1.

Case Series (summarised in Table 1).

Case 1

A 26-year old Cook Island Māori woman presented in her third pregnancy to another centre with an incidental finding of a right perirenal mass on obstetric ultrasound scan. An MRI scan performed at 30 weeks gestation demonstrated a complex 81 x 77 x 76mm retroperitoneal mass, (with T2 enhancement and central necrosis), in close proximity to the right kidney. This mass was initially reported as consistent with a retroperitoneal sarcoma. Labor was induced at 38 weeks and she had an uncomplicated normal vaginal delivery. A subsequent biopsy of the tumour was suggestive of a PGL. Twenty-four hour urine catecholamines demonstrated elevated dopamine and noradrenaline levels of 3482 nmol/24 hours (reference range [RR] 400-2600) and 979 nmol/24 hours (RR 70-500), respectively. Repeat MRI imaging post partum demonstrated a second mass in the right presacral region. Following alpha blockade the masses were resected without complication. Histology confirmed the diagnosis of paragangliomas. Genetic testing demonstrated a germline missense mutation (*R46Q*) in exon 2 of the *SDHB* gene.

The patient re-presented two years later during her fifth pregnancy following a first trimester miscarriage one year previously. Her plasma normetanephrine level was mildly elevated at 1130 pmol/L (RR <900pmol/L) with a normal plasma metanephrine level. She was treated with alpha blockade (doxazosin) and remained normotensive with no hyperadrenergic symptoms during the pregnancy. An uncomplicated elective caesarean section was performed at 38 weeks gestation, delivering a healthy male infant weighing 3450g. A sixth pregnancy in 2010 was complicated by

placenta previa and recurrent vaginal bleeding. Further MRI imaging showed two lesions, both 2.2cm in maximum diameter lesions, one to the left of aorta and one between the superior mesenteric artery and aorta. Plasma normetanephrine levels were elevated at 1860pmol/L (RR 0-900). She was monitored as an inpatient from 31 weeks, and required an emergency caesarean section at 32 weeks for bleeding. Her baby required a prolonged admission to the new born unit for respiratory distress. A seventh pregnancy was electively terminated and she did not present again until 20 weeks into her eighth pregnancy. She had been offered multiple endocrinology clinic appointments but did not attend for follow-up.

During the eighth pregnancy she remained asymptomatic and normotensive. Plasma normetanephrines were three-fold elevated. Widespread metastatic PGL was evident on imaging. Doxazosin was commenced. She developed obstetric cholestasis, and due to concerns about fetal wellbeing she underwent elective caesarean section at 38 weeks gestation giving birth to a live healthy female infant weighing 3050g.

The family of the index patient underwent predictive testing for the *R46Q* mutation (Figure 2). Her father and three of her four sisters were identified as carriers. Two siblings declined testing.

Case 2

Patient 2, a sister of the index case, presented in the third trimester of her third pregnancy at age 23. She had a history of two previous normal vaginal deliveries. The most recent delivery had occurred after her genetic testing confirmed she was an *SDHB* mutation carrier, but prior to any biochemical testing, as she had failed to attend her scheduled specialist appointments. She delivered the second baby without complications by vaginal delivery. During the third pregnancy she was normotensive and treated with doxazosin as an inpatient from 33 weeks gestation, and remained normotensive with blood pressures between 100/50 and 116/50mmHg. MRI imaging demonstrated a 13mm lesion with high signal on T2-weighted imaging in the para-aortic region near the left renal hilum. Plasma metanephrines were normal with a normetanephrine of 382 pmol/L (RR 0-900) and a metanephrine of <100pmol/L (RR 0-500). The chromogranin A was mildly elevated at 65 U/L (RR 0-20U/L). On the

basis of the normal plasma metanephrines and the non-specific nature of the lesion seen on MRI, the decision was made to allow a trial of normal vaginal delivery under close monitoring. This occurred without complication.

After delivery of the baby, she underwent an FDG-PET scan. This confirmed two lesions: one adjacent to the right carotid body, and a second lesion adjacent to the inferior vena cava posterior to the caudate lobe of the liver. She was re-commenced on doxazosin and had the two lesions resected without complication although it was noted during resection of the abdominal lesion there was haemodynamic changes with tumour handling suggesting that indeed the para-aortic tumour was secretory. Follow-up plasma metanephrines remained normal. Histology was consistent with both of these lesions being paragangliomas.

Case 3

Patient 3, another sister of the index case, was identified as carrying the *R46Q SDHB* germline mutation in 2008 when aged 17. She had an extensive history of non-attendance at the clinic, and was first assessed by the endocrine service at age 21 when 14 weeks gestation into her third pregnancy. Two previous vaginal deliveries had been uncomplicated. At assessment, plasma free metanephrines were normal (normetanephrine 342pmol/L [RR 0-900], metanephrine 104pmol/L [RR 0-500]) but a plasma 3-methoxytyramine level was markedly elevated at 10,115pmol/L (RR <110pmol/L). Chromogranin A was elevated at 135U/L (RR 0-20U/L). An MRI of the abdomen showed a large retroperitoneal mass surrounding the mesenteric vessels and encasing the superior mesenteric artery. Due to the isolated dopamine hypersecretion she was considered at low risk of a hypertensive crisis, and trial of normal vaginal delivery was offered under close monitoring. She had an uncomplicated normal vaginal delivery of a health male infant weighing 3100g. She was normotensive throughout the labour and delivery. Resection of the tumour was discussed with multiple endocrine and gastrointestinal surgeons however the patient was not considered a suitable surgical candidate. Further treatment options are being explored.

Case 4

Patient 4, the youngest sister of the index patient, presented at age 17 in the second trimester of her first pregnancy. Plasma normetanephrine was significantly elevated at 7770pmol/L (RR <900pmol/L), with normal metanephrine of 102pmol/L and a chromogranin A of 31U/L (RR 0-20U/L). She was commenced on phenoxybenzamine, and remained normotensive throughout the pregnancy maintaining an average blood pressure of 100/60. An MRI scan revealed a 3.5x2.2cm lesion behind the uncinate process of the pancreas compressing the inferior vena cava. She had an elective caesarean section under an epidural anaesthetic at 38 weeks and gave birth to a healthy baby boy. She failed to attend her scheduled follow-up appointments to discuss surgical resection.

She represented two years later during her second pregnancy. The plasma normetanephrine level again was significantly elevated at 7680pmol/L (RR <900). Plasma metanephrine and 3-methoxytyramine levels were normal. The patient was commenced on phenoxybenzamine at 37 weeks gestation. She was monitored as an inpatient for three days prior to surgery, and remained normotensive. Her phenoxybenzamine dose was uptitrated to 20mg twice daily with no significant postural hypotension. She was commenced on a high salt diet and fluid loaded for 24 hours prior to surgery. She underwent an uncomplicated elective lower segment caesarean section followed by resection of the para-caval lesion under general anaesthesia at 39 weeks gestation. Her baby required intubation for two hours post-delivery and newborn unit admission due to sedation at delivery, thought to be due to the combination of phenoxybenzamine and fentanyl, but was well on discharge after a three day admission. On direct inspection a placental mass was noted. Histologically the para-caval tumour was subsequently confirmed to be a PGL and the placental lesion to be a chorangioma, (a benign tumour found in approximately 1% of placentas)[9]. Chorangioma has not previously been reported in association with phaeochromocytoma or PGL. The patient's postoperative plasma metanephrines were normal.

Results

Results of the systematic review are shown in Table 2. A total of 117 articles were included in the review comprising 143 cases of chromaffin cell tumours in pregnancy (112 adrenal phaeochromocytomas, 28 extraadrenal paragangliomas, and three patients who had synchronous phaeochromocytomas and paragangliomas).

The overall maternal mortality rate was 9.8% (95% CI 0.054-0.17) in phaeochromocytomas, and 3.6% in paragangliomas (95% CI <0.0001-0.19). Fetal mortality was calculated after excluding those pregnancies which resulted in elective termination. Fetal mortality in women with phaeochromocytomas was 16% (95% CI 0.1-0.24), compared to 12% (95% CI 0.032-0.3) for those with paragangliomas. The diagnosis was made antenatally in 84% of patients with paragangliomas, and 80.3% of those with phaeochromocytomas. When we add our case series of eight pregnancies, of which seven were secretory paragangliomas, overall maternal mortality for PGLs decreased to 2.8% (95% CI <0.001-0.15) and fetal mortality to 8.8% (95% CI 0.023-0.24). Of those women reported to have bilateral phaeochromocytomas there was no maternal mortality reported, however fetal mortality occurred in 3/15 of these cases (0.2, CI 0.063-0.46)[10-12]. There were three cases of phaeochromocytoma with Cushing's syndrome[13-15]. There was no fetal or maternal mortality in these cases.

The degree of elevation in the urinary/plasma catecholamines or metanephrines was documented in 54.8% of cases in the literature. In those cases in which catecholamine levels were documented there did not appear to be a correlation between the degree of elevation in the catecholamines and fetal or maternal mortality. There was also no clear correlation between the size of the lesions and the probability of fetal or maternal mortality but again only incomplete data was available for tumour size.

Cardiovascular collapse, pulmonary oedema or fatal arrhythmia was the cause of death in 6 of the 11 maternal deaths[1, 16-20]. One patient died of multiorgan failure [21], and another suffered from a subarachnoid haemorrhage[22]. The cause of death was not reported in three cases[14, 23, 24]. There was one

maternal death in a woman with a paraganglioma. The cause of death was reported as cardiovascular collapse resulting in a VF arrest[25].

Hypertension was the most common presenting feature in pregnancy, reported in 87% of phaeochromocytomas, and 86% of PGLs. Hypertensive crises were more commonly seen in patients with phaeochromocytomas, occurring in 27 women (0.24, CI 0.17-0.33) compared to four women with PGLs (0.14, 95% CI 0.051-0.32). Patients with PGLs were more likely to be asymptomatic than those with phaeochromocytoma (10/36 vs 5/112). Of particular note, in our case series all four women were asymptomatic and normotensive throughout the eight pregnancies.

Discussion

Pregnancies complicated by a PGL or phaeochromocytoma are extremely rare, estimated to occur in 1 in 15000 pregnancies[1]. PGLs are less common than phaeochromocytomas in pregnancy. In a recent review of phaeochromocytoma in pregnancy extra-adrenal lesions accounted for only 14 (19%) of the cases described[5].

Based on our experience from our case series we hypothesized that the risk of hypertensive crisis during delivery may be less in patients with functioning PGLs compared to phaeochromocytomas. Our review of the literature indicates that maternal mortality may be lower in patients with PGLs compared to those with phaeochromocytomas. Fetal mortality also may be lower in patients with PGLs compared to those with phaeochromocytomas.

In addition, there is a lower rate of hypertensive crises reported in patients with PGLs, 4 patients (0.14, 95% CI 0.051-0.32) compared to 27 patients (0.27, 95% CI 0.19-0.36). This may relate to less effective catecholamine secretion compared to phaeochromocytomas. Phaeochromocytomas and PGLs can have diverse biochemical phenotypes. It is recognised that PGLs may exhibit different biochemical behaviour from phaeochromocytomas. PGLs secrete noradrenaline and/or dopamine whereas phaeochromocytomas may secrete either noradrenaline or adrenaline. The total tissue concentrations of catecholamines are highest in adrenaline-secreting tumours[26]. Tumours related to an

underlying genetic abnormality (*VHL*, *NF1*, *MEN2*, *SDHB* and *SDHD*) show different catecholamine secretory profiles[26]. In patients with *SDHB* mutations, the tumour catecholamine concentration is lower than in tumours caused by other genetic mutations and noradrenaline-secreting tumours where a mutation has not been identified[27]. Catecholamine secretion rates into plasma were higher in the non-hereditary noradrenaline secreting tumours and in those with VHL compared to other hereditary syndromes (MEN2, NF1, *SDHB* and *SDHD*)[26]. In our review of the literature, the degree of epinephrine or metanephrine level elevation was reported in 19/29 (67%) patients with phaeochromocytomas who developed a hypertensive crisis. There were six maternal deaths where no catecholamine level was reported and the type or degree of catecholamine excess was not reported in four cases. Mixed noradrenaline and adrenaline elevation was reported in 13 patients. Isolated noradrenaline elevation was reported in two cases, isolated adrenaline elevation in two cases, and VMA alone in two cases. There were four cases of hypertensive crisis reported in patients with paragangliomas. In these four patients, there was one maternal death[25], and one fetal death in a different patient[28].

The management of blood pressure in pregnant woman with phaeochromocytoma is a careful balance between providing adequate catecholamine blockade in order to reduce the risk of catecholamine excess, while not compromising placental blood flow by lowering the blood pressure excessively. In non-pregnant patients, a preoperative target blood pressure of <130/80 sitting but >80/45 standing has been recommended[29]. It has been suggested that excessive blood pressure lowering in pregnancy may result in uteroplacental insufficiency and intrauterine growth restriction, with a 176g decrease in fetal weight with a 10mmHg decrease in mean arterial pressure in pregnant mothers without phaeochromocytoma/PGLs[30]. In the context of pregnant women without phaeochromocytomas, the threshold for treatment of hypertension in pregnancy varies depending on which guideline is used, but treatment is only suggested if the BP is >140-159 mmHg systolic, or 90-109mmHg diastolic[31]. However, the issue with phaeochromocytoma/PGL patients is the potentially labile blood pressure with the risk of severe peaks of blood pressure if no alpha blockade is given. Women with phaeochromocytoma or PGLs are at risk of placental abruption and fetal loss[7]. In our series of

patients, the women were normotensive in all of the pregnancies described. This is unusual given that 82% (23 women) were hypertensive in 31 cases of PGL reported in the literature. Despite the normotension we did use low dose alpha blockade in combination with a high salt diet to try to prevent marked blood pressure fluctuations. As demonstrated by Patient 2, normal plasma free metanephrine levels does not necessarily mean that the lesion is non-secretory particularly with manipulation at the time of surgery, and low dose alpha blockade should be considered in these cases.

The choice of specific alpha blockade needs to be carefully considered in management of phaeochromocytoma/PGL in pregnancy. Phenoxybenzamine is an irreversible alpha-adrenergic antagonist and has previously been suggested as the treatment of choice in women with phaeochromocytoma or PGL[32]. Phenoxybenzamine has a half-life of 24 hours and the clinical effects may continue for up to a week following discontinuation[33]. Phenoxybenzamine has been shown to cross the placenta and accumulate in the fetus[8] potentially leading to neonatal respiratory depression and hypotension. As such, it has been recommended that neonates of women who have taken phenoxybenzamine in pregnancy are monitored for hypotension and respiratory depression in the first few days of life[34]. It is theorised that the respiratory depression observed in these babies may result from an element of cardiac failure due to the large proportion of alpha adrenergic receptors in the fetal heart[34]. Despite no teratogenic effects of phenoxybenzamine having been reported in animal testing, there are no well-controlled studies in pregnant woman. In the United States and the United Kingdom, phenoxybenzamine is a pregnancy category C, indicating that the pharmacological effects of the drug may cause harm to the fetus or neonate without causing malformation. Doxazosin is a competitive alpha-1 selective alpha adrenergic blocker with a plasma half-life of 20 hours[33]. There have been no reports of adverse effects on the neonate with the use of doxazosin in pregnant women with phaeochromocytoma or paragangliomas. In our series of patients doxazosin was used in 4/8 pregnancies. For patient 1 doxazosin was used in the sixth pregnancy. This baby was born prematurely at 32 weeks, and experienced respiratory depression requiring neonatal unit admission. Given the premature delivery it is difficult to determine what extent the doxazosin may have contributed to the respiratory depression. Doxazosin was used without complication in three of the

remaining eight pregnancies. Phenoxybenzamine was used in the two pregnancies of patient 4. Despite low blood pressure, she delivered appropriate-for-gestational age babies in both cases. In gestational hypertension, prazosin, another selective alpha-1 blocker, has been suggested as a possible second-line antihypertensive during pregnancy[35], and its use is reported in cases of phaeochromocytoma and PGL in pregnancy without adverse effects. However, prazosin has a much shorter half-life of only 2-3 hours meaning that multiple daily dosing regimen is required[33]. In our systematic review of the literature, phenoxybenzamine was the alpha blocker most commonly used. In the 62 cases of phaeochromocytoma where the type of alpha blockade was specified, there were 36 cases (58%) of phenoxybenzamine use, 18 cases of prazosin use (26%), and 8 (12.9%) cases in which doxazosin was used. There were 17 cases of PGL where the type of alpha blockade was specified. Phenoxybenzamine was the most commonly reported (15 cases, 88%), and two cases reported use of doxazosin (12%). Based on the literature review, doxazosin appears to be the least commonly used of these three alpha blockers. However, if no additional safety concerns are identified, due to its more favourable duration of action, doxazosin may become the alpha blocker of choice for these women during pregnancy.

Traditionally it has been recommended that vaginal delivery is best avoided in pregnant women with phaeochromocytomas or paragangliomas[36]. There is a potential risk of precipitating a hypertensive crisis from active labour. There have been cases reported in the literature of successful normal vaginal deliveries without maternal or fetal mortality[37-43]. However, in a case reported by Lyman the post partum period was complicated by pulmonary oedema in the mother[41]. In our series, three of the eight neonates were delivered by vaginal delivery. In one of these cases the delivery was performed elsewhere prior to the diagnosis of PGL. In the other two, one was purely dopamine-secreting (patient 3) so deemed to be at low risk of hypertensive crisis. The third case (Patient 2) had normal plasma free metanephrine levels but in retrospect likely did have a secretory lesion as the later intraoperative behaviour was consistent with a functioning tumour at the time of surgical manipulation. Despite her normal plasma free metanephrines she was pre-treated with alpha blockade, salt and fluid loading and an uncomplicated vaginal delivery was undertaken with close monitoring.

Following the diagnosis of PGL or phaeochromocytoma in pregnancy a multidisciplinary approach is essential. It is important that the mother with phaeochromocytoma/PGL deliver in a tertiary hospital with an experienced obstetric, anaesthetic and endocrine service, as well as a neonatal intensive unit. The delivery can be performed under a spinal anaesthetic. Spinal anaesthetic may have a theoretical advantage of reducing neural stimulation to the adrenal glands, and sympathetic chain if the block is high enough. It is also important to remember to avoid medications in these women which may precipitate a crisis, in particular agents such as metoclopramide[33]. Ondansetron was successfully used in our case series without haemodynamic instability and has previously been reported to be used without adverse effects in metastatic phaeochromocytoma[44].

One limitation of this review is that it is vulnerable to publication bias given that centres with more favourable pregnancy outcomes may be more likely to publish their case reports, however it would be expected that this should pertain to both pregnancies with phaeochromocytoma as well as those with PGL. It is also possible that additional pregnancies had unrecognised synchronous tumours however due to the varied locations it would be expected that PGLs are more likely to have been missed than phaeochromocytomas.

In conclusion, pregnant women with PGLs may be at a lower risk of adverse outcome than those with phaeochromocytomas but both maternal and fetal mortality rates are still higher than that of the general obstetric population and a multidisciplinary approach with careful monitoring is recommended.

Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contributions

LAW – study design, data collection and analysis, drafting the article, approval of the final version

JVC – study design, revising article for important intellectual content, and approval of the final version

GYMR – conception of the study, revising the article for important intellectual content, approval of the final version

MSE – study design, interpretation of data, revising article for important intellectual content, and approval of the final version

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Figure Legends

Figure 1. Figure 1. Schematic of articles included in the systematic review

PGL = paraganglioma

Figure 2. Family pedigree,

Arrow indicates index case, patient 1.

Figure 3. Selected imaging of our case series patients

A: Patient 1 - 30/40 MRI scan- 81 x 77 x76mm retroperitoneal mass with central necrosis, and presacral lesion

B: Patient 2 - FDG-PET demonstrating right carotid body and abdominal PGLs (post partum)

C: Patient 3 - MRI scan showing large retroperitoneal mass encasing the mesenteric vessels

D: Patient 4 - post partum FDG-PET demonstrating the abdominal PGL

Table 1. Summary of our case series

Case	Pregnancy	Lesion	CA excess	Normet	Other	CgA	Alpha blocker	Delivery	Fetal outcome
1	2006	PGL	Yes	ND	Plasma NA 2-fold increase	ND	Nil	NVD	Healthy
	2008	PGL	Yes	1.3-fold increase			Doxazosin	Elective LSCS	Healthy
	2010	PGL	Yes	2-fold increase			Doxazosin	Emerg LSCS	NICU Resp depression
	2010	PGL	Yes	ND			Nil	Termination	
	2013	Met PGL	Yes	3-fold increase			Doxazosin	Emerg LSCS	Healthy
2	2010	HNPGL PGL	Yes*	Normal		65	Doxazosin	NVD	Healthy
3	2013	PGL	No	Normal	Plasma 3-MT 92-fold increase	138	Nil	NVD	Healthy
4	2010	PGL	Yes	8.6-fold increase		31	PBZ	Elec LSCS	Healthy
	2013	PGL	Yes	4.5-fold increase		9	PBZ	Elec LSCS	NICU admission

PGL = paraganglioma; HNPGL = head & neck paraganglioma; NVD = normal vaginal delivery; ND = not done; CA = catecholamine: Normet = normetanephrine; MT = methoxytyramine; CgA = chromogranin A; NA = noradrenaline; Emerg LSCS = emergency lower segment caesarean section; elec LSCS = elective lower segment caesarean section; NICU = newborn intensive care unit; PBZ = phenoxybenzamine

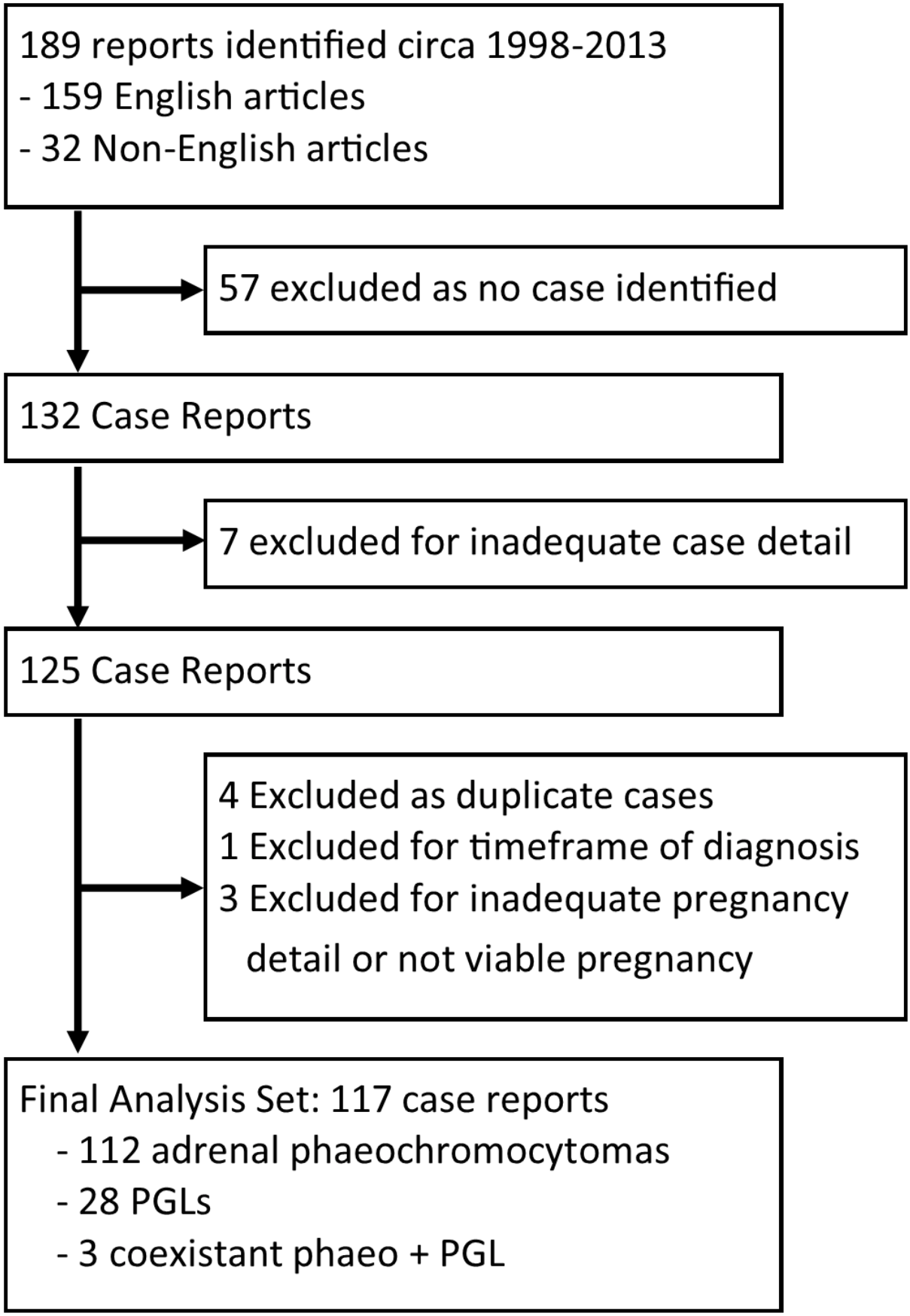
*This case was likely secretory based on haemodynamic changes during tumour handling at the time of later tumour resection but plasma free metanephrine levels were not elevated on serial samples

Table 2. Summary of findings from the systematic review

	Phaeochromocytoma N=115	Paraganglioma N=31
Hypertension		
- **Unilateral/isolated**	83 (0.85, CI 0.76-0.91)	23 (0.82, CI 0.64-0.93)
- **Bilateral**	11 (0.73, CI 0.48-0.90)	
- **Concurrent PGL**	3 (1, CI 0.38-1)	
Hypertensive crisis	29 (0.27, CI 0.19-0.36)	4 (0.14, CI 0.051-0.32)
Mode of delivery		
- **Caesarean**	62 (0.70, CI 0.60-0.79)	22 (0.92, CI 0.73-0.99)
- **Vaginal delivery**	26 (0.3, CI 0.21-0.40)	2 (0.083, CI 0.12-0.27)
Maternal mortality	11 (0.098 (CI 0.054-0.17)	1 (0.036, CI <0.0001- 0.19)
Fetal mortality		
- **Unilateral/isolated**	17 (0.16, CI 0.10-0.24)	3 (0.12, CI 0.032-0.30)
- **Bilateral**	3 (0.2, CI 0.063-0.46)	
- **Concurrent PGL**	1 (0.5, CI 0.095-0.91)	

Confidence intervals calculated using the Modified Wald method.

PGL = paraganglioma


189 reports identified circa 1998-2013
- 159 English articles
- 32 Non-English articles
57 excluded as no case identified
132 Case Reports
7 excluded for inadequate case detail
125 Case Reports
4 Excluded as duplicate cases
1 Excluded for timeframe of diagnosis
3 Excluded for inadequate pregnancy detail or not viable pregnancy
Final Analysis Set: 117 case reports
- 112 adrenal phaeochromocytomas
- 28 PGLs
- 3 coexistant phaeo + PGL

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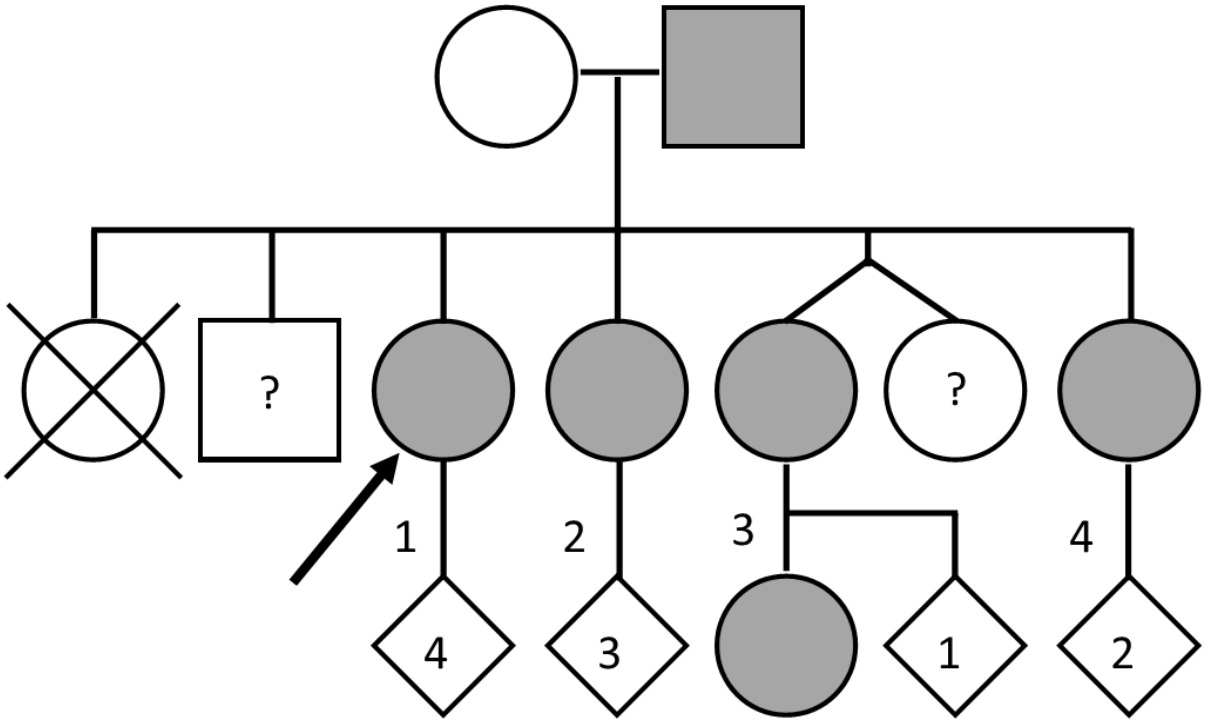

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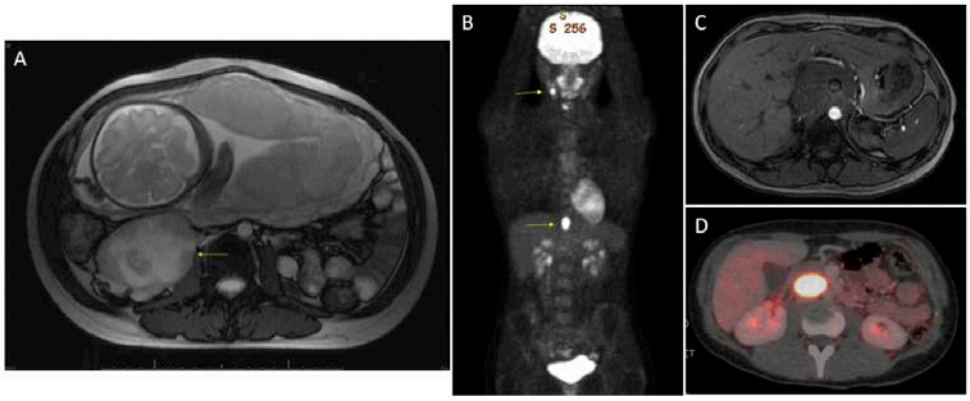

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