Maternal and fetal outcomes in phaeochromocytoma and pregnancy: a multicentre retrospective cohort study and systematic review of literature

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Summary

Background Phaeochromocytoma or paraganglioma (collectively known as PPGL) in pregnant women can lead to severe complications and death due to associated catecholamine excess. We aimed to identify factors associated with maternal and fetal outcomes in women with PPGL during pregnancy.

Methods We did a multicentre, retrospective study of patients with PPGL and pregnancy between Jan 1, 1980, and Dec 31, 2019, in the International Pheochromocytoma and Pregnancy Registry and a systematic review of studies published between Jan 1, 2005, and Dec 27, 2019 reporting on at least five cases. The inclusion criteria were pregnancy after 1980 and PPGL before or during pregnancy or within 12 months post partum. Eligible patients from the retrospective study and systematic review were included in the analysis. Outcomes of interest were maternal or fetal death and maternal severe cardiovascular complications of catecholamine excess. Potential variables associated with these outcomes were evaluated by logistic regression.

Findings The systematic review identified seven studies (reporting on 63 pregnancies in 55 patients) that met the eligibility criteria and were of adequate quality. A further 197 pregnancies in 186 patients were identified in the International Pheochromocytoma and Pregnancy Registry. After excluding 11 pregnancies due to potential overlap, the final cohort included 249 pregnancies in 232 patients with PPGL. The diagnosis of PPGL was made before pregnancy in 37 (15%) pregnancies, during pregnancy in 134 (54%), and after delivery in 78 (31%). Of 144 patients evaluated for genetic predisposition for phaeochromocytoma, 95 (66%) were positive. Unrecognised PPGL during pregnancy (odds ratio 27·0; 95% CI 3·5–3473·1), abdominal or pelvic tumour location (11·3; 1·5–1440·5), and catecholamine excess at least ten-times the upper limit of the normal range (4·7; 1·8–13·8) were associated with adverse outcomes. For patients diagnosed during pregnancy, α-adrenergic blockade therapy was associated with fewer adverse outcomes (3·6; 1·1–13·2 for no α-adrenergic blockade *vs* α-adrenergic blockade), whereas surgery during pregnancy was not associated with better outcomes (0·9; 0·3–3·9 for no surgery *vs* surgery).

Interpretation Unrecognised and untreated PPGL was associated with a substantially higher risk of either maternal or fetal complications. Appropriate case detection and counselling for premenopausal women at risk for PPGL could prevent adverse pregnancy-related outcomes.

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See Online for appendix

Introduction

Phaeochromocytoma and paraganglioma (collectively known as PPGL) are tumours that can secrete catecholamines.[1] The release of catecholamines potentially leads to severe clinical consequences, such as hypertensive crisis, stroke, and even death. Germline pathogenic variants are identified in 40–50% of individuals with PPGL.[2] Case detection programmes for individuals genetically predisposed to PPGL use biochemical and imaging techniques to detect these tumours early in an attempt to decrease PPGL-related morbidity and mortality.[3] Nevertheless, the majority of cases of PPGL are still discovered incidentally on imaging done for another reason or on the basis of symptoms related to catecholamine production, rather than through case detection testing.[4]

For a pregnant woman, an unrecognised PPGL can be devastating because uncontrolled catecholamine action can alter both maternal and fetal physiology, leading to severe complications or death.[5–10] Only a few small retrospective studies have reported on the presentation, management, and outcomes of pregnant women with PPGL.[5–9,11,12] Therefore, determining predictors of favourable outcomes and making strong conclusions about optimal management is challenging. A systematic exploration of pregnancy-associated PPGL is needed, especially given the considerable advances made over the last decade in the genetic classification, clinical characterisation, and anaesthetic and therapeutic approaches for PPGL.[3,13–20] As such, we sought to describe the clinical characteristics and outcomes of women with PPGL during pregnancy, to

Research in context

Evidence before this study

We screened PubMed for studies on the epidemiology of adrenal tumours, using the terms "pheochromocytoma", "paraganglioma", "phaeochromocytoma", or "adrenal mass" combined with "pregnancy", "pregnancy complication", or "pregnancy outcome". We considered all studies published before Dec 27, 2019, in any language. The majority of previous studies were case reports, small studies (<10 cases) from endocrine referral centres, or narrative reviews. Previous reviews of case reports and small case series suggest that maternal and fetal mortality have decreased over time, and previously published data on non-fatal maternal complications are scarce.

Added value of this study

We did a large retrospective study of 197 patients with phaeochromocytoma or paraganglioma (PPGL) and pregnancy enrolled through an international multicentre collaboration of 25 countries and 52 patients from a systematic review of the literature published between 2005 and 2019. The large sample size of our cohort allowed us to identify factors associated with adverse maternal and fetal outcomes in women with PPGL and pregnancy. We characterised the association of adverse outcomes with known genetic predisposition, metastatic disease, antepartum medical and surgical management, degree of catecholamine excess, and the location of the tumour.

Implications of all the available evidence

We found that severe maternal complications of catecholamine excess or maternal or fetal death occurred in 14% of pregnancies, all with a concomitant unrecognised or suboptimally treated functioning PPGL. We found that adverse outcomes were more likely in patients with abdominal or pelvic PPGL and in patients with a higher degree of catecholamine excess. α-adrenergic blockade therapy was associated with better outcomes. We found that patients with metastatic PPGL experienced no pregnancy-related cardiovascular adverse outcomes of catecholamine excess. We did not find that antepartum surgery was associated with better outcomes. Based on our findings, we recommend evaluation for PPGL before conception or as soon as possible during pregnancy in women with a known predisposing germline pathogenic variant or who could be carriers of a heritable PPGL disorder. α-adrenergic blockade therapy alone can be considered in women diagnosed with PPGL during pregnancy.

identify factors associated with maternal and fetal outcomes, to determine the best approach to management of PPGL during pregnancy, and to develop recommendations for women with a known genetic predisposition for PPGL who are contemplating pregnancy.

Methods

Study design and participants

Considering the low incidence of PPGL, we followed the framework by Lin and colleagues,[21] which recommends combining an original observational study with a systematic review of the literature that identifies additional non-overlapping cases. Therefore, we combined an international, retrospective, multicentre study based on the newly founded International Pheochromocytoma and Pregnancy Registry of patients with PPGL and pregnancy occurring between Jan 1, 1980, and Dec 31, 2019, and a systematic review of studies published between Jan 1, 2005, and Dec 27, 2019 (appendix pp 2–14). A comprehensive search of databases (MEDLINE, Embase, Cochrane Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus) was done by an experienced librarian with input from the study's principle investigator, IB (appendix pp 7–9). Case reports and case series with fewer than five patients were excluded. Individual patient data collection from the included studies was done independently and in duplicate by two investigators and any discrepancies were resolved by IB. The methodological quality of studies was assessed using a previously reported method.[22]

For both the systematic review and observational study, any patient with pregnancy after 1980 and meeting one of the following inclusion criteria was eligible: known PPGL during pregnancy, discovered before or during pregnancy; PPGL discovered within 12 months post partum. If a patient had more than one pregnancy and untreated PPGL, each pregnancy was recorded separately with corresponding fetal and maternal outcomes.

The multicentre study was done in accordance with the local ethical committees or institutional review boards for all participating centres. All patients provided either written informed consent or a consent waiver was used, depending on the local requirements.

Procedures

For all patients included via the observational study or systematic review, we recorded patient characteristics (demographics, germline pathogenic variant, follow-up data), PPGL characteristics (type of PPGL, tumour size, number of tumours, presence of metastases, biochemical profile [noradrenergic, adrenergic, or dopaminergic], and type of therapy), and pregnancy-related data (age at pregnancy, timing of PPGL diagnosis in relation to pregnancy, maternal symptoms of catecholamine excess during pregnancy, pregnancy outcome, including type and time of delivery, potential termination of pregnancy, complications during delivery, and maternal and fetal complications). Severe cardiovascular complications of catecholamine excess included death or any cardiovascular event requiring intensive care or leading to permanent sequelae occurring any time during pregnancy or up to

	Patients (n=232)
Pregnancies	249
Pregnancies per patient	
One	220 (93%)
Two	10 (4%)
Three	1 (<1%)
Six	1 (<1%)
Age at pregnancy, years*	29 (15–46)
Year of pregnancy* (n=199)	2012 (1980–2019)
Type of disease (n=230)	
Phaeochromocytoma	
Unilateral	142 (62%)
Bilateral	19 (8%)
Paraganglioma	
Head and neck	5 (2%)
Thoracic	6 (3%)
Abdominal or pelvic	27 (12%)
Multiple primary PPGL	11 (5%)
Metastatic PPGL	20 (9%)
Genetic predisposition	
RET	28 (12%)
SDHB	27 (12%)
VHL	18 (8%)
SDHD	8 (3%)
NF1	5 (2%)
MAX	2 (1%)
SDHC	2 (1%)
SDHA	1 (<1%)
FH	1 (<1%)
CDKN2B	1 (<1%)
Carney triad	2 (1%)
Tested, not identified	49 (21%)
Not tested	88 (38%)
Family history of PPGL (n=194)	
Yes	49 (25%)
No	145 (75%)

(Table 1 continues in next column)

(Continued from previous column)

Tumour diameter, mm (n=190)	53 (13–310)
Catecholamine excess (n=232)	
Functioning	220 (95%)
Noradrenergic	103 (47%)
Adrenergic	91 (41%)
Dopaminergic	3 (1%)
Unknown subtype	23 (10%)
Non-functioning	12 (5%)
Degree of catecholamine excess in functioning tumours (n=178)	
2×ULN	34 (19%)
5×ULN	29 (16%)
10×ULN	26 (15%)
>10×ULN	89 (50%)
Surgery for PPGL (n=231)	
During pregnancy	42 (18%)
Gestation week	20 (10–35)
After pregnancy	161 (70%)
Weeks post partum (n=151)	8 (0–224)
No surgery	28 (12%)

Data are n, n (%), or median (range). For categories with missing data, the number of patients with available data is indicated. ULN=upper limit of normal. PPGL=phaeochromocytoma or paraganglioma. *Reported once for each patient, at the time of first pregnancy.

Table 1: **Clinical presentation and treatment of patients with PPGL**

3 days post partum. When tested and present, PPGL germline pathogenic variants included PPGL susceptibility genes *RET* (causing multiple endocrine neoplasia type 2), *VHL* (von Hippel-Lindau disease), *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2* (paraganglioma syndromes type 1–5, pathogenic variants of the succinate dehydrogenase subunit genes, *SDHx*), and other familial PPGL caused by pathogenic variants of the genes *TMEM127* and *MAX*.[13,14,23,24] Neurofibromatosis type 1 was diagnosed in accordance with the US National Institutes of Health (NIH) consensus criteria.[25]

Outcomes

Outcomes of interest were maternal or fetal death and maternal severe cardiovascular complications of catecholamine excess that occurred during pregnancy, at the time of delivery, or within 3 days post partum.

Statistical analysis

Pregnancy-related maternal and fetal outcomes were analysed only for pregnancies with known outcomes, pregnancies that were not electively terminated, and only for patients with functioning PPGL. Descriptive data are presented as frequencies for categorical variables and medians with ranges for continuous variables. Subgroup comparisons were done with use of χ^2 tests for categorical variables and the Kruskal-Wallis test for continuous variables. We predefined the following variables for analysis of association with maternal and fetal outcomes: timeline for PPGL discovery in relation to pregnancy (during or after *vs* before pregnancy); year of pregnancy (before *vs* after median year of pregnancy in our cohort); location of PPGL (abdominal or pelvic *vs* other); degree of catecholamine excess (≥10-times upper limit of normal [ULN] *vs* <10-times ULN); antepartum surgery; α-adrenergic blockade for at least 2 weeks; caesarean section versus vaginal delivery; presence of genetic predisposition for PPGL; and metastatic PPGL. Variables possibly associated with maternal and fetal outcomes were evaluated using logistic regression and expressed as odds ratios (ORs) with 95% CIs. Multivariable analysis was not done. We did additional subgroup analyses of the outcomes of patients enrolled through the multicentre collaboration versus patients from the systematic review, and of the outcomes of patients enrolled systematically through the search of electronic databases

	Pregnancies (n=249)
Age at pregnancy, years*	28 (15–46)
Year of pregnancy* (n=214)	2012 (1980–2019)
Time of PPGL discovery*	
Before pregnancy	37 (15%)
During pregnancy	134 (54%)
Gestation week (n=129)	24 (2–38)
After pregnancy	78 (31%)
Weeks post partum (n=54)	6 (0–52)
Signs and symptoms of catecholamine excess during pregnancy*	
Yes	206 (83%)
No	43 (17%)
Management during pregnancy*	
Surgery	42 (17%)
Gestation week	20 (10–35)
α-adrenergic blockade	104 (42%)
Duration, weeks	8 (0–40)
Type of delivery*	
Caesarean section	146 (59%)
Gestation week	36 (25–41)
Vaginal	76 (31%)
Gestation week	38 (28–41)
Unknown, live birth	3 (1%)
Gestation week	38 (36–39)
Emergent induced vaginal	1 (<1%)
Gestation week	20†
Elective abortion	8 (3%)
Gestation week	9 (3–22)
Miscarriage or intrauterine fetal loss	11 (4%)
Gestation week, median (range)	18 (8–37)
Pregnancy ongoing	2 (1%)
Gestation week	25, 26†
Autopsy	2 (1%)
Gestation week	28, unknown†
Maternal adverse outcomes related to catecholamine excess‡ (n=230)	
Death	3 (1%)
Severe cardiac complications	15 (7%)
None	212 (92%)
Fetal adverse outcomes related to catecholamine excess‡ (n=230)	
Death	20 (9%)
None	210 (91%)

Data are n (%) or median (range), unless otherwise indicated. For categories with missing data, the number of patients with available data is indicated. PPGL=phaeochromocytoma and paraganglioma. *Reported for each pregnancy. †Values for individual pregnancies are given instead of median (range). ‡Reported for each pregnancy, after excluding non-functioning PPGL, pregnancies terminated through elective abortion, and ongoing pregnancies.

Table 2: **Clinical presentation and outcomes of pregnancy in women with PPGL**

versus centres with a non-systematic, non-consecutive enrolment process. p values of less than 0·05 were considered to be statistically significant. Statistical analysis was done using the R programming environment.

For more on **R software** see https://www.r-project.org

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, or data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The systematic review identified 1481 studies, of which 1394 were excluded during screening. 87 full-text articles were assessed for eligibility, of which 79 were excluded because they did not meet the eligibility criteria. Eight studies reporting on 73 pregnancies in 65 patients with PPGL were included in the qualitative synthesis (appendix pp 10–13). Seven of eight studies (reporting on 63 pregnancies in 55 patients) were found to be of adequate quality and individual patient data were extracted (appendix p 14).

An additional 197 pregnancies in 186 patients were identified in the International Pheochromocytoma and Pregnancy Registry. After excluding 11 pregnancies due to potential overlap (appendix p 3), the final cohort included 232 patients and 249 pregnancies (197 pregnancies from the observational study and 52 from the systematic review). 220 patients had a single pregnancy, ten patients had two pregnancies, one patient had three pregnancies, and one patient had six pregnancies. At the time of pregnancy, 180 (78%) of 230 patients had a single PPGL (phaeochromocytoma in 142 [62%], paraganglioma in 38 [17%]), 30 (13%) had multiple primary PPGL (bilateral phaeochromocytoma in 19 [8%], other multiple primary PPGL in 11 [5%]), and 20 (9%) patients had metastatic PPGL (table 1). Median tumour diameter was 53 mm (range 13–310). The majority of patients (220 [95%]) presented with a functioning PPGL, with a noradrenergic profile in 103 patients (47%), adrenergic in 91 (41%), purely dopaminergic in three (1%), and an unknown profile in 23 (10%).

Among 194 patients with available data, 49 (25%) reported a family history of PPGL at the time of pregnancy. 144 patients were tested for a predisposing germline pathogenic variant (or had a documented clinical diagnosis of neurofibromatosis type 1 or Carney triad); of these, 95 (66%) were positive (*RET* in 28 [29%] patients who tested positive, *SDHB* in 27 [28%], *VHL* in 18 [19%], *SDHD* in eight [8%], *NF1* in five [5%], and other syndromes in nine [9%]; table 1).

PPGL was discovered during pregnancy in 134 (54%) pregnancies at a median of 24 weeks of gestation (range 2–38; table 2). In 78 (31%) pregnancies, PPGL was not recognised during pregnancy but was discovered at a median of 6 weeks (0–52) after delivery (figure 1). Of 37 (15%) pregnancies with known PPGL before pregnancy, 17 (46%) had metastatic PPGL not amenable to surgery, and 20 (54%) had not had surgery for a resectable PPGL. Patients reported symptoms and signs of catecholamine excess during

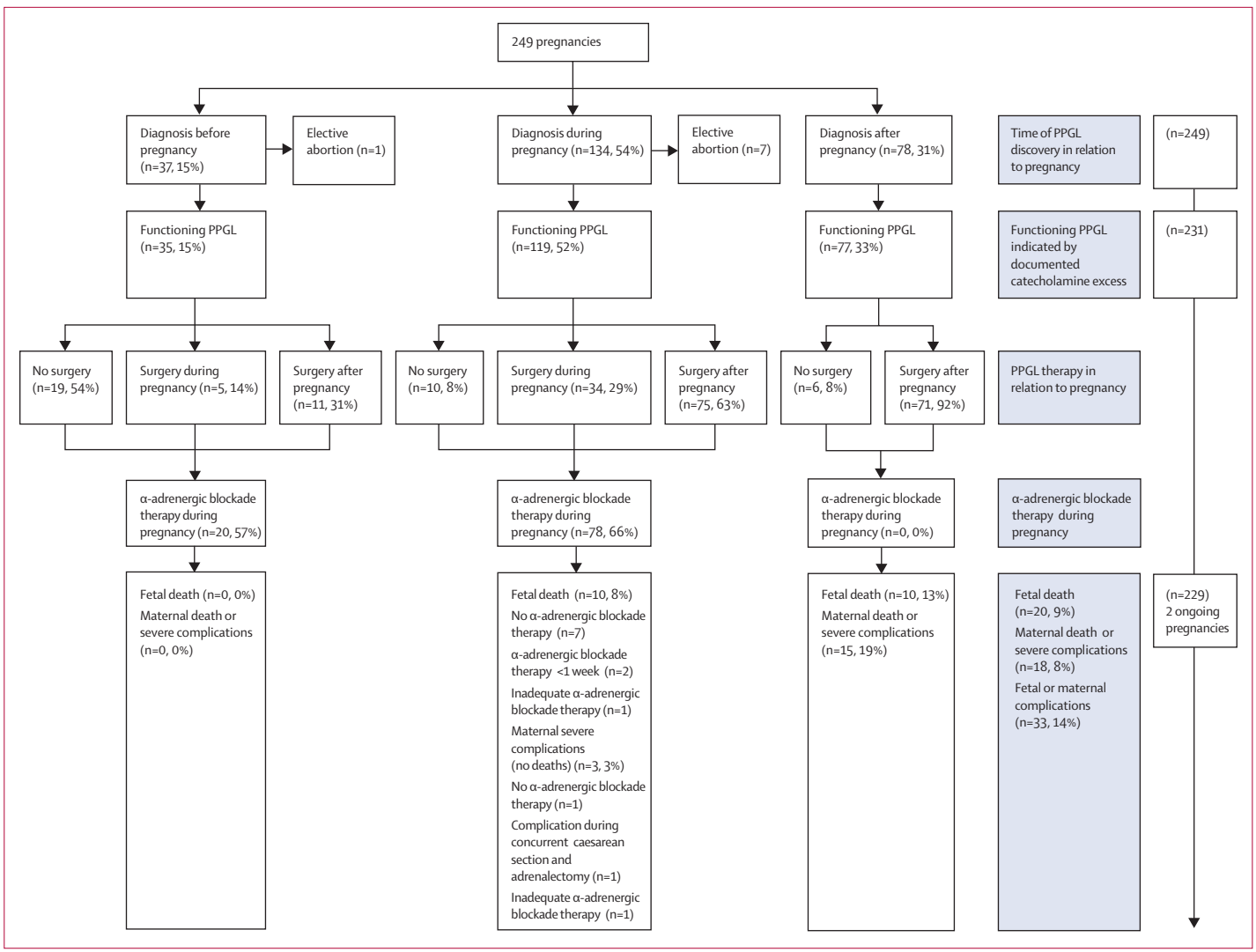

Figure 1: **Outcomes of pregnancies in patients with PPGL based on the time of PPGL discovery**
PPGL=phaeochromocytoma and paraganglioma.

206 (83%) pregnancies (table 2). Of these, the most common was hypertension (191, 93%), followed by palpitations (117, 57%), headaches (102, 50%), and diaphoresis (87, 42%).

Elective termination was done in eight (3%) pregnancies at a median of 9 weeks of gestation (range 3–22), all in women with recognised PPGL before or during pregnancy. Miscarriage or intrauterine fetal loss occurred in 11 (4%) pregnancies at a median of 18 weeks of gestation (8–37), in six pregnancies with unrecognised PPGL during pregnancy, and in five pregnancies in which PPGL was discovered within a median of 2 weeks (0–10) before pregnancy loss. Two (1%) pregnancies were confirmed at autopsy. Two pregnancies were ongoing at the time of manuscript submission. Of the other 226 pregnancies, 168 (74%) were carried to term (>36 weeks of gestation) and delivered by caesarean section (94, 56%), vaginal delivery (71, 42%), or an unknown method of delivery (three, 2%). An additional 58 (26%) pregnancies were delivered preterm (median 32 weeks of gestation [20–35]) by caesarean section (52, 90%) or vaginal delivery (six, 10%). Seven fetal deaths occurred during or shortly after delivery (six in preterm deliveries and one in a term delivery). In patients with PPGL diagnosed before or during pregnancy, caesarean section was more common if the patient had symptoms of catecholamine excess (86% *vs* 64% for vaginal delivery, p=0·014) and a high degree of catecholamine excess (catecholamine >10-times ULN in 52% *vs* 13% for vaginal delivery, p=0·0023; appendix p 16).

Patients were treated with surgery (203, 88%) or other therapies or observation (28, 12%). Of 42 (18%) patients who underwent removal of PPGL during pregnancy, 40 had functioning PPGL, treated with surgery at a median of 20 weeks of gestation (range 10–35; table 1).

	No complications (n=197)	Complication or death (n=33)	p value
Age at pregnancy, years	29 (15–46)	29 (19–40)	0·40
Year of pregnancy (n=195)	2012 (1980–2019)	2006 (1982–2019)	0·043
Time of PPGL discovery			
Before pregnancy	35 (18%)	0	0·0001
During pregnancy	106 (54%)	12 (36%)	..
Gestation week	26 (6–38)	25 (10–28)	..
After pregnancy	56 (28%)	21 (64%)	..
Location of PPGL			
Abdominal or pelvic	169 (86%)	33 (100%)	0·021
Other locations	28 (14%)	0	..
Time of delivery or miscarriage (n=228)			
<32 weeks	15 (8%)	19 (59%)	<0·0001
≥32 weeks	181 (92%)	13 (41%)	..
Type of delivery in term pregnancies (n=156)			
Vaginal	62 (42%)	2 (22%)	0·24
Caesarean section	85 (58%)	7 (78%)	..
Tumour size, mm (n=186)	51 (13–310)	51 (20–158)	0·67
Degree of catecholamine excess (n=187)			
2×ULN	33 (20%)	2 (8%)	0·0027
5×ULN	31 (19%)	2 (8%)	..
10×ULN	26 (16%)	1 (4%)	..
>10×ULN	72 (44%)	20 (80%)	..
Metastases present during pregnancy			
No	172 (87%)	33 (100%)	0·030
Yes	25 (13%)	0	..
Positive for genetic disease (n=149)			
No	36 (29%)	12 (52%)	0·026
Yes	90 (71%)	11 (48%)	..

Data are n (%) or median (range). Data are reported for each pregnancy, after excluding non-functioning PPGL, pregnancies terminated through elective abortion, and ongoing pregnancies. For categories with missing data, the number of patients with available data is indicated. PPGL=phaeochromocytoma and paraganglioma. ULN=upper limit of normal.

Table 3: **Factors associated with adverse maternal and fetal outcomes in pregnancy with PPGL**

PPGL surgery during pregnancy was done with α-adrenergic blockade in 33 (83%) of 40 patients with functioning PPGL (median duration of α-adrenergic blockade 4 weeks [0·1–21]). In 161 (70%) patients, surgery for PPGL was done after delivery, at a median of 8 weeks post partum (0–224). The remaining 28 patients who did not have surgery were treated with post-partum iodine-131 metaiodobenzylguanidine therapy, lutetium-177-labelled somatostatin analogue, or external radiation therapy, or they were observed.

Pregnancy-related maternal and fetal outcomes were analysed for 230 (92%) pregnancies (eight elective terminations, one ongoing pregnancy managed without antepartum surgery, and ten patients with non-functioning PPGL were excluded from this analysis). Maternal or fetal complications of catecholamine excess (or both) were observed in 33 (14%) pregnancies; fetal death occurred in 15 (7%) pregnancies, severe maternal complications or death occurred in 13 (6%) pregnancies, and both maternal and fetal complications occurred in five (2%) pregnancies. Three women had long-term sequelae from the catecholamine-related complications, including myocardial infarction in one patient and cerebral vascular accident in two patients (appendix pp 17–20).

All adverse outcomes occurred in patients with functioning PPGL diagnosed during or after pregnancy (table 3, figure 1). No complications occurred in patients diagnosed with PPGL before pregnancy, possibly due to a lower degree of catecholamine excess (appendix p 21). Unrecognised PPGL during pregnancy was strongly associated with adverse maternal and fetal outcomes (OR 27·0; 95% CI 3·5–3473·1 for PPGL diagnosis after *vs* before pregnancy; figure 2, appendix p 22). PPGL location (abdominal or pelvic *vs* other) was also associated with adverse outcomes (11·3; 1·5–1440·5). In a subset of patients for whom the degree of catecholamine excess was documented, a level of at least 10-times the ULN was associated with adverse outcomes (4·7; 1·8–13·8). For patients diagnosed during or before pregnancy, an absence of α-adrenergic blockade therapy was associated with adverse outcomes (3·6; 1·1–13·2 for no α-adrenergic blockade *vs* α-adrenergic blockade for ≥2 weeks). Surgery during pregnancy was not associated with better outcomes (0·9; 0·3–3·9 for no surgery *vs* surgery during pregnancy; figure 2). Of 39 patients with functioning PPGL treated with surgery during pregnancy, three (8%) adverse outcomes occurred (two fetal deaths and one severe cardiovascular maternal complication). Maternal age, year of pregnancy, tumour size, and type of delivery were not associated with outcomes (table 3, figure 2). Patients without a known PPGL syndrome or pathogenic variant were more likely to have adverse pregnancy outcomes compared with those with a pathogenic variant (2·7; 1·1–6·6). Patients with no metastatic disease were more likely to experience adverse pregancy outcomes compared with those with metastases during pregnancy (9·9; 1·3–1267·7; figure 2, appendix pp 22–24).

Subgroup analysis of outcomes in patients enrolled through the multicentre collaboration versus patients from the systematic review showed similar rates of adverse fetal and maternal outcomes (appendix p 25). Subgroup analysis of outcomes in patients enrolled systematically versus non-systematically showed similar rates of adverse maternal outcomes, but lower rates of adverse fetal outcomes in patients enrolled non-systematically, possibly due to a more recent period of enrolment (appendix p 26).

Discussion

In this international, multicentre study and systematic review, we describe the presentation, management, and outcomes of women with PPGL during pregnancy.

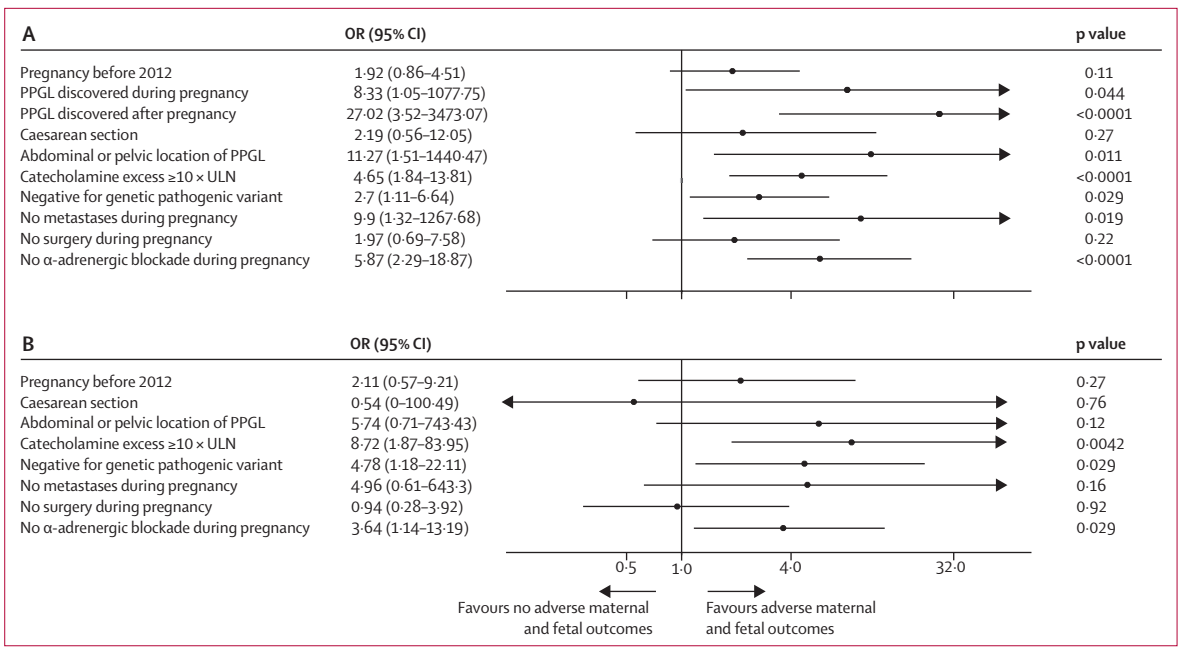

Figure 2: **Factors associated with adverse maternal and fetal outcomes**
(A) All pregnancies with functioning PPGL (n=230). (B) Pregnancies with PPGL diagnosed before or during pregnancy (n=153). The variables analysed were: year of pregnancy (<2012 *vs* ≥2012), time of PPGL discovery (during *vs* before and after *vs* before), type of delivery (caesarean *vs* vaginal), location of PPGL (abdominal or pelvic *vs* other locations), degree of catecholamine excess (≥10-times ULN *vs* <10-times ULN), genetic pathogenic variant (negative *vs* positive), metastatic PPGL (*vs* non-metastatic), surgery during pregnancy (*vs* no surgery), and use of α-adrenergic blockade during pregnancy (*vs* no α-adrenergic blockade). OR=odds ratio. PPGL=phaeochromocytoma and paraganglioma. ULN=upper limit of normal.

Overall, we found that maternal and fetal outcomes were good when catecholamine excess was treated. However, several severe and fatal events occurred, mainly in patients with unrecognised PPGL.

We found that severe maternal complications of catecholamine excess occurred in 7% of pregnancies with a concomitant functioning PPGL, and maternal death occurred in 1%. By contrast, a review of the literature summarising 89 cases and published in 1971 reported a much higher maternal mortality of 48%.[26] Subsequently, several reviews have described lower rates of maternal death of 5–17%.[10,27,28] A more recent systematic review from 2013 reporting maternal mortality of 8%,[29] which was still higher than that found in our study (1%), possibly indicating a publication bias. Similarly, we found an overall fetal mortality of 9% (including miscarriage, intrauterine fetal loss, and death at delivery), whereas it was 54% in the review from 1971,[26] 14–26% in subsequent studies,[10,27,28] and 17% in the review from 2013.[29] Of note, all previous studies were case reports, small case series, or reviews of literature. In addition to the selection and publication biases contributing to higher rates of adverse outcomes in previous studies, the decrease in both maternal and fetal adverse outcomes probably reflects overall improvements in obstetric care and surgical expertise, advances in anaesthesia care, and a higher rate of PPGL discovery based on presymptomatic case detection or incidental diagnosis on imaging, and the availability of α-adrenergic blockade.[4,17,20,30]

Adverse outcomes occurred more frequently in patients with abdominal or pelvic PPGL compared with other locations, probably due to compression of the tumour by the gravid uterus or the higher degree of catecholamine release in patients with abdominal or pelvic PPGL. However, tumour size was not associated with a higher risk of complications at delivery in patients with pregnancies carried to term. The type of delivery was not associated with adverse outcomes, although caesarean section was two-times more common than vaginal delivery and usually reserved for patients with a higher degree of catecholamine excess. Although it is difficult to make a specific recommendation for the type of delivery, our data suggest that natural labour could be safe in appropriately selected patients with PPGL.

Adverse outcomes occurred in 8% of pregnancies when surgery for PPGL was done during pregnancy. Of note, surgery during pregnancy was not associated with better outcomes. Therefore, the choice of intervention during pregnancy depends on the availability of surgical expertise, particularities of the PPGL disease, the trimester of gestation, and anticipated tolerance and compliance with medical therapy.

Surprisingly, we found that patients with metastatic PPGL experienced no pregnancy-related cardiovascular adverse outcomes of catecholamine excess. As we previously reported, many patients with metastatic PPGL have an indolent course of disease.[31,32] The absence of fatal or severe cardiovascular adverse events of

catecholamine excess in our cohort of patients with metastatic PPGL was probably related in part to the indolent nature of PPGL disease in patients choosing to become pregnant, including a lower burden of disease and a lower degree of catecholamine secretion. In addition, patients with metastatic disease are more likely to be aggressively monitored, allowing for sufficient time to plan PPGL management before and during pregnancy. Indeed, as we show in our data, most patients with metastatic PPGL were diagnosed with PPGL before pregnancy (appendix p 21). Of note, in one patient with metastatic PPGL, management was difficult and required hospitalisation (appendix pp 17–20).

We observed that patients with a known syndromic PPGL were less likely to have adverse outcomes, possibly due to earlier diagnoses of PPGL during pregnancy. PPGL in a young woman of childbearing age is likely to be related to a predisposing germline pathogenic variant.[2] Indeed, we found that of patients tested, 66% carried a predisposing pathogenic variant. Thus, it is imperative for syndromic carriers to undergo clinical, radiological, and biochemical evaluation for a possible PPGL before planning a pregnancy.

When the diagnosis of PPGL was made before or during pregnancy, medical management with α-adrenergic blockade was associated with good outcomes. Optimal α-adrenergic blockade and compliance probably contributed to favourable outcomes, although the retrospective design makes this difficult to assess. Our data do not allow us to conclude on the dose or type of α-adrenergic blockers that should be used. It is reasonable to choose either a non-selective α-adrenergic blocker (eg, phenoxybenzamine) or an α-1-selective shorter-acting α-adrenergic blocker (eg, doxazosin) and to individualise the dose with the goal of sufficient α-adrenergic blockade to prevent hypertension during pregnancy. Intensification of α-adrenergic blockade 1 week before surgery or vaginal delivery could be considered.

The main strength of this study is that it represents the largest known cohort of pregnant women with PPGL. We also systematically searched multiple databases and obtained published data on individual patients not included in the registry, therefore presenting the most complete evidence base to date and providing more generalisable inferences. To address potential differences in outcomes of patients enrolled through the multicentre collaboration versus patients from the systematic review, we did a subgroup analysis, which showed similar rates of adverse fetal and maternal outcomes (appendix p 25). The limitations of our study include the retrospective design, the inclusion of a convenient sample of patients, non-systematic reporting of data, selection, and information bias. A prospective study on PPGL in pregnancy is not feasible due to the rarity of disease, especially in young women. We were not able to ascertain or adjust for all potential confounders. Several important variables had missing data, and the sample size for some analyses was small. To address potential differences in outcomes of centres that enrolled systematically (electronic search of databases) versus centres with non-systematic enrolment, we did a subgroup analysis, which showed similar rates of adverse maternal outcomes but lower rates of adverse fetal outcomes in centres enrolled non-systematically, possibly due to a more recent period of enrolment (appendix p 26). The period of enrolment for this study spans several decades, during which considerable advances in both obstetric care and the understanding of PPGL occurred. However, a subgroup analysis of patients diagnosed in the first 20 years of the study did not identify significant differences when compared with patients treated in the last 20 years of the study (appendix p 27). Given the differences between assays and changes in assays over time, a comparison of catecholamine excess assessment was not possible. Geographical differences in the approaches to PPGL and pregnancy care, as well as higher PPGL expertise of participating centres, could have influenced the results of this study. Given the international design, the findings of this study are likely to be generalisable to most tertiary centres in the world, but not to community settings. Lastly, selection, publication, and reporting bias are clearly concerning in a body of evidence that consists of case series, and the estimates provided in this study might not have valid denominators.

In conclusion, the majority of pregnancies in women with PPGLs had good outcomes, even in women with metastatic or functional disease. PPGL diagnosed before or during pregnancy allowed for appropriate management, which probably improved maternal and fetal outcomes. PPGL surgery during pregnancy was generally safe, but it was not associated with favourable outcomes, and medical management with α-adrenergic blockade alone during pregnancy can be considered. By contrast, unrecognised and untreated PPGL was associated with a much higher risk of either maternal or fetal complications. Thus, we recommend biochemical or imaging evaluation for PPGL in patients at high risk of the disease, ideally before conception or as soon as pregnancy is confirmed. PPGL should be suspected in patients with a family history of PPGL or those who carry a PPGL susceptibility gene.

Contributors

IB, CE, WFY Jr, and HPHN conceptualised the study. IB and HPHN contributed to study design. All authors collected or reviewed the data. IB and EA did the analysis. IB drafted the article. All authors contributed to critical revision and final approval of the article.

Declaration of interests

IB reports advisory board participation with Corcept, CinCor, and HRA Pharma, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Statistical code and de-identified datasets are available upon request.

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