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DOI:

[10.1111/1471-0528.14918](https://doi.org/10.1111/1471-0528.14918)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Quartermaine, G., Lambert, K., Rees, K., Seed, P. T., Dhanjal, M. K., Knight, M., ... Williamson, C. (2017). Hormone-secreting adrenal tumours cause severe hypertension and high rates of poor pregnancy outcome: a UKOSS study with case control comparisons. *BJOG*. <https://doi.org/10.1111/1471-0528.14918>

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Hormone-secreting adrenal tumours cause severe hypertension and high rates of poor pregnancy outcome; a UKOSS study with case control comparisons

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.14918

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Abstract

Objective

To examine the management and outcomes of adrenal tumours in pregnancy.

Design

A national observational, cohort study over four years using the UK Obstetric Surveillance System (UKOSS).

Setting

Consultant led obstetric units

Patients

Women with pheochromocytoma, primary aldosteronism or Cushing's syndrome diagnosed before or during pregnancy.

Methods

Clinical features of UKOSS cases were compared to those of women with adrenal tumours reported from 1985-2015. Nested case-control comparisons involving the UKOSS cases as well as those identified in the literature were performed for pregnancy outcome data using UKOSS controls with uncomplicated singleton (n= 2250) pregnancy and data from the Office of National Statistics (ONS).

Main Outcome measures

Incidence, management and frequency of adverse maternal and offspring outcomes of adrenal tumours in pregnancy.

Results

Fifteen pregnant women met the inclusion criteria: ten pheochromocytoma, three primary aldosteronism and two Cushing's syndrome. All of the tumours had an incidence rate <2 per 100,000 pregnancies. Clinical symptoms were similar to those in non-pregnant women due to the hormones released. All women had severe hypertension in pregnancy, and in those diagnosed during pregnancy there was a more marked elevation of blood pressure than in women diagnosed prior to conception. There was a significantly increased risk of adverse pregnancy outcomes in affected women, with increased rates of stillbirth, preterm labour and operative delivery.

Conclusions

Adrenal tumours are associated with increased risks for pregnant women and their babies. Data on these tumours to inform practice are limited and international collaborative efforts are likely to be needed.

Funding

Sparks; National Institute of Health Research.

Key words:

pregnancy, adrenal, tumour

Tweetable Abstract

Study of hormone secreting adrenal tumours in pregnancy linked with high BP and high rates of fetal morbidity

Introduction

Phaeochromocytoma, primary aldosteronism and adrenal Cushing's syndrome are rare, but due to the secretion of excess catecholamines, mineralocorticoids, and glucocorticoids can result in serious morbidity and mortality.

The presenting features of phaeochromocytoma (hypertension, headache, sweating and palpitations) [1] are similar to non-pregnant women, but may be ascribed to pre-eclampsia, or to pregnancy. If phaeochromocytoma remains undiagnosed, maternal and fetal mortality can be as high as 40-50% [2]. Patients treated with alpha-adrenergic blockade have a lower maternal and fetal mortality [3]. Decisions about timing of surgery are made by a multidisciplinary team on a case by case basis. However, this is usually laparoscopic and may be undertaken during pregnancy, at the time of caesarean section or postnatally [3].

Primary aldosteronism (PA) presents with hypertension and hypokalaemic alkalosis due to autonomous production of aldosterone and secondary renin suppression [4]. The commonest management strategy during pregnancy is to use potassium supplements and antihypertensive drugs with deferral of surgery until after delivery.

Cushing's syndrome diagnosed in pregnancy is more commonly caused by an adrenal rather than a pituitary tumour [2]. Classical symptoms and signs of hypercortisolism, (central weight gain, edema, moon face, abdominal striae and hypertension) may occur in women with uncomplicated pregnancy and therefore the diagnosis of Cushing's syndrome can be difficult [2]. Pregnancy complicated by Cushing's syndrome can result in uncontrolled hypertension, associated with an increased risk of adverse outcomes for mother and fetus.

We aimed to undertake a prospective, national cohort study of the incidence, monitoring, management and outcomes of hormone-secreting adrenal tumours in pregnant women.

Methods

A national, prospective, observational cohort study was undertaken over four years (March 2011 to February 2015) using the UK Obstetric Surveillance System (UKOSS). UKOSS is a prospective monthly case collection scheme that includes all 202 consultant-led obstetric units in the UK. Women are not contacted directly and no personally identifiable information is collected. As all women with symptomatic adrenal tumours should have consultant-led care, we anticipate that the study is likely to have covered all cases within the entire UK birth cohort. The study was approved by the Riverside Ethics Committee, London (09/H0706/78).

Additional case ascertainment

The study was advertised at the UK Society for Endocrinology Annual Conference and all UK endocrinologists were contacted via email and by post to ask them to inform the study team of any pregnant women with adrenal tumours during the study period. No extra cases were identified.

Case definition

Cases were defined as women with a functioning hormone secreting endocrine adrenal tumour, including women diagnosed pre-pregnancy who had not undergone surgery to remove the tumour. Inclusion criteria specified any woman with the diagnosis of pheochromocytoma, primary aldosteronism or Cushing's syndrome due to an adrenal tumour; exclusion criteria included women with non-functioning adrenal tumours. Cases were only included if the diagnosis had been confirmed by a consultant endocrinologist.

Data collection

Cases that met the criteria for the study were identified by the obstetrician or endocrinologist responsible for their care. On reporting a case, the clinician was asked to complete a data collection form. Anonymized data were collected about adrenal tumour diagnosis, monitoring and management before pregnancy and antenatally, as well as maternal demographics, obstetric and medical history, delivery and perinatal outcomes. Cases were excluded if they did not meet the entry criteria (n=16)

(these cases included nine that were reported in error, three that were surgically treated prior to the reported pregnancy, two duplicates, one was not confirmed by an endocrinologist and for one the reporter was unable to locate the hospital notes) or a data collection form was not returned (n=2) (Figure 1). Clinical features of women with specific tumour types were compared with those reported in case reports or case series from the English language literature from 1985 to 2015, identified using a PubMed search (search terms: pheochromocytoma, primary aldosteronism, Cushing's syndrome, endocrine tumours and pregnancy). When the data from previous systematic reviews were used, two separate researchers (GQ and KR) reviewed all articles, and individual cases common to more than one report were identified and excluded in order to ensure no individual case was compared twice. The majority of pheochromocytoma cases were captured in two systematic reviews [1, 5] as well as in three additional case reports [6-8], providing a total of 123 additional pheochromocytomas for comparison. For primary aldosteronism there was one systematic review [11] as well as 15 individual cases [10-24] resulting in 34 cases for comparison. For Cushing's syndrome, there were two systematic reviews [25, 26] as well as two individual cases [8, 27] (142 cases in total).

Demographic features of the adrenal tumour cases (maternal age, body mass index (BMI) and ethnic group) were compared to 2250 women in an established UKOSS database of pregnant controls, as previously described [28]. To establish whether adverse pregnancy outcome occurs more commonly in pregnancies complicated by adrenal tumours, two control groups were used for comparison (Figure 1). The first was the UKOSS control group of 2250 women that was used for demographic comparisons. A second comparison group was obtained using information from the Office of National Statistics (ONS) in England for the years of the study. The ONS control group enabled comparison of the rates of rarer pregnancy outcomes in a large sample set. As the number of pregnancies complicated by adrenal tumours is small, these comparisons used outcome data from all cases in the literature from 1985-2015 in addition to pregnancy outcome data from the UKOSS adrenal tumour cases.

Statistical analyses

Statistical analysis was performed using Stata 12.1. P values were considered significant if ≤ 0.05 . For comparison of cases to UKOSS controls, the data relating to multiple pregnancies were removed.

However, for ONS control data it was not possible to remove multiple pregnancies from the dataset.

Incidence rates were estimated with 95% CI. Adjustment for variables such as maternal age or occupation was not possible due to small numbers. For categorical data, unadjusted risk ratios (RR) were used with Fisher's exact p values (more appropriate than chi-square for smaller sample sizes).

Results

During the four-year study period there were 15 cases of hormone-secreting adrenal tumours in pregnancy (Figure 1). There were 2,852,099 normal pregnancies from 2011 to 2015, giving an overall incidence of hormone-secreting adrenal tumours in the UK of 0.53 per 100,000. The incidence rate for each individual tumour was: pheochromocytoma 0.32 per 100 000, primary aldosteronism 0.11 per 100 000 and Cushing's syndrome 0.07 per 100 000. There were no significant differences in the age or BMI of women with any of the sub-types of adrenal tumours compared to controls (Table S1). The clinical features of each tumour type were considered in turn.

Phaeochromocytoma

The most common presenting features in the UKOSS pheochromocytoma cases were palpitations (40%, 95% CI 12.2- 73.7), headaches (20%, 95% CI 2.5- 55.6) and hypertension (20%, 95% CI 2.5- 55.6). The previously reported cases [11-14] had similar findings; palpitations affected 29.3% (95% CI 21.4- 38.1) and headache affected 34.1% (95% CI 25.8- 43.2). However, while the most noticeable feature in the previously reported cases was hypertension (73.9%, 95% CI 65.3- 81.5), blood pressure control varied in the UKOSS cohort of women with pheochromocytoma in pregnancy. The two cases that had been diagnosed prenatally had good control of blood pressure in pregnancy. Those diagnosed in pregnancy all had severe hypertension at the time of diagnosis with systolic levels

ranging from 140-190 mmHg and diastolic 96-120 mmHg. Two women were diagnosed soon after delivery, and in these women the majority of blood pressure measurements during pregnancy were normal.

The most commonly administered medication to the women in whom phaeochromocytoma was diagnosed in pregnancy was phenoxybenzamine (70%, 95% CI 19.4- 99.4) (Table S2), and four were also prescribed a beta-blocker. One woman was treated with propranolol alone; this woman had poorly-controlled, severe hypertension in the third trimester and was diagnosed as having a phaeochromocytoma at the time of delivery. Hence, use of a beta-blocker in isolation occurred before the diagnosis was made. In the literature, the most commonly administered medication was also phenoxybenzamine (62.1%, 95% CI 49.3- 73.7), followed by atenolol (15.2%, 95% CI 7.5- 26.1) and labetalol (15.2%, 95% CI 7.5- 26.1) (Table S2).

The timing of surgery for the UKOSS cases was primarily post-partum (60%, 95% CI 23.3- 83.2).

However, in the literature, surgery occurred at more varied times (16% in the 2nd trimester, 15% in the third trimester, 21% simultaneously with caesarean section and 35% post-partum). One of the 10 UKOSS cases had a previous diagnosis of medullary thyroid carcinoma and multiple endocrine neoplasia type 2a.

Delivery outcomes were reported for six women from the UKOSS cohort (two cases had terminations of pregnancy and in two cases the outcomes were not reported). When combined with the cases in the literature, the mode of delivery was significantly more likely to be a caesarean section for women with phaeochromocytoma (RR 3.2, CI 2.81- 3.64, $p < 0.001$) compared to controls (Table 1).

The mean gestational age at delivery for the UKOSS phaeochromocytoma cases was 35.7 weeks, (range 31-39 weeks' gestation). This was higher than the average gestational age at delivery of the women reported in the combined literature review which was 32.1 weeks.

There was an increase in the rate of preterm delivery in women with phaeochromocytoma compared to UKOSS (RR 8.7, CI 6.9- 10.9, $p < 0.001$) and ONS (RR 8.2, CI 6.9- 9.7, $p < 0.001$) controls (Table 1). There was also a significantly higher rate of stillbirth compared to both UKOSS (RR 25.8, CI

12.1- 54.9, $p < 0.001$) and ONS (RR 26.8, CI 16.7- 43.0, $p < 0.001$) controls. Furthermore, four of the eight women with pheochromocytoma were admitted to the Intensive Care Unit (ICU) (50%, 95% CI 15.7- 84.2), all of whom had surgery postpartum, and three of six infants were admitted to the neonatal ICU (50%, 95% CI 11.8- 88.2).

Primary Aldosteronism

There were three UKOSS cases of primary aldosteronism and, in all cases, serum aldosterone was high and plasma renin levels were low. Two women had hypokalaemia ($K^+ < 3.4$ mmol/L) prior to pregnancy as well as in their first trimester.

Presenting symptoms in the UKOSS cases included headache, dizziness and intermittent numbness of the hands and feet. In previously reported cases [9-24] the symptoms included headache, palpitations, muscle weakness, oedema, fatigue and nausea. All UKOSS cases had hypertension in the first trimester with systolic values ranging from 146-175 mmHg and diastolic from 100-113 mmHg. One case had proteinuria (0.9g/24hr). All three cases were treated with anti-hypertensive medication. One case was treated with amiloride and by the third trimester had a normal blood pressure and serum potassium concentration. The other two cases continued to have elevated blood pressure despite 3-5 different anti-hypertension treatments. These findings are consistent with cases reported in the literature with 88% presenting with blood pressures above 140/90 mmHg.

When combined with the cases identified in the literature the most commonly prescribed medications for primary aldosteronism in pregnancy were methyldopa (55.6%, 95% CI 30.7- 78.4) and labetalol (50%, 95% CI 26.1- 73.9) in conjunction with a potassium supplement (55.6%, 95% CI 30.7- 78.4) (Table S3).

None of the UKOSS cases had surgery during pregnancy. From the literature review, 40% (95% CI 16.3- 67.7) of cases had surgery during the second trimester. Of the women that had surgical intervention, five proceeded to successful delivery at an average of 36 weeks' gestation. One woman in the literature suffered an intrauterine fetal death in the early third trimester, several weeks post-

laparoscopic adrenalectomy. The remainder had surgery either post-partum (47%, 95% CI 21.2- 73.4) or not at all (13%, 95% CI 1.6- 40.4).

Of the three UKOSS cases with primary aldosteronism, two planned to have vaginal births and one had a caesarean section. The two cases that had planned vaginal deliveries were induced at 39 and 40 weeks' gestation due to raised blood pressure. When all cases in the literature and UKOSS cases were compared to UKOSS controls, women with primary aldosteronism were significantly more likely to have a caesarean section (RR 1.6, CI 1.08- 2.5, $p < 0.001$) (Table 2).

Women with primary aldosteronism in pregnancy also had increased rates of adverse pregnancy outcomes compared to the UKOSS controls and ONS controls (Table 2). The mean gestational age at delivery was 36 weeks compared to a mean gestational age of 39.6 weeks in the UKOSS control group. Preterm deliveries were significantly more common in these women than both the UKOSS controls (RR 8.03, CI 5.6-11.5, $p < 0.001$) and ONS controls (RR 7.5, CI 5.4-10.4, $p < 0.001$). In the literature, there were two stillbirths recorded among women with primary hyperaldosteronism, a significantly higher rate than both UKOSS (RR 11.68, CI 2.7-50.8, $p = 0.016$) and ONS (RR 12.2, CI 3.2- 46.7, $p = 0.012$) controls.

Cushing's syndrome

There were two UKOSS cases of adrenal Cushing's syndrome; both presented with pregnancy-induced hypertension, headache and oedema. The commonest clinical features reported in the literature were hypertension (68.3%, 95% CI 59.9- 75.8) followed by diabetes mellitus (25%, 95% CI 11.9- 25.2).

The UKOSS cases had severe hypertension with maximum systolic levels of 183-197mmHg and diastolic pressures of 95-108 mmHg; one case had proteinuria. Both patients were administered anti-hypertensive drugs but these appeared to be relatively ineffective. However, while the most common medication used in the literature was metyrapone followed by ketoconazole, the UKOSS cases only received anti-hypertensive medication (Table S4).

Both UKOSS cases had laparoscopic unilateral adrenalectomy: one had it was performed 4 weeks post-miscarriage while the other occurred at 28 weeks' gestation.. In the literature, 4.9% (95% CI 2.0-9.8) had a bilateral adrenalectomy and 16.9% (95% CI 11.1- 24.1) had a unilateral adrenalectomy during pregnancy. Although the specific timings of the surgery were not given, there was an 87% live birth rate from the cases that had unilateral or bilateral adrenalectomy.

One of the UKOSS cases had a successful pregnancy outcome delivering a 36 week-old infant by induced labour. The other case had a fetal loss prior to surgery. When combined with the literature and compared to both control groups, women with Cushing's syndrome had a significantly higher risk of caesarean section (RR 3.3, CI 2.55-4.27, $p<0.001$). They were also more likely to have preterm delivery than the UKOSS controls (RR 7.32, CI 5.81-9.20, $p<0.001$) or ONS controls (RR 6.86, CI 5.81-8.10, $p<0.001$), and had a higher rate of stillbirth than the UKOSS controls (RR 11.65, CI 4.9-27.7, $p<0.001$) and ONS controls (RR 12.11, CI 6.42-22.87, $p<0.001$), and a 5 min Apgar recording below 7 (RR 35.71, CI 13.01-98.03, $p<0.001$) (Table 3).

Discussion

Main findings

The 4 year UKOSS cohort study of adrenal tumours in pregnancy provided an accurate estimate of the incidence of hormone-secreting adrenal tumours in pregnancy, and confirmed that they are associated with high rates of maternal morbidity. Women with each type of tumour had severe hypertension, at levels consistent with increased rates of cerebral hemorrhage and death. Indeed, the UK Confidential Enquiry into Maternal Deaths recommends active treatment of maternal systolic blood pressures $>150\text{mmHg}$. When the outcome data for the cases ascertained in this study were combined with those from all cases reported in the past 30 years, there were significantly increased rates of operative delivery, preterm labour and stillbirth.

The presenting symptoms of palpitations and headache in women with pheochromocytoma occurred at a similar frequency to other retrospective series [1, 5], although the proportion of women with documented hypertension was lower, likely reflecting the paroxysmal nature of clinical features in people with pheochromocytoma. In this series, women diagnosed during pregnancy had more severe hypertension than those in whom the diagnosis of pheochromocytoma had been made prior to pregnancy, indicating that outcomes are improved with adequate alpha blockade. One of the UKOSS cases had MEN2a, highlighting the relevance of screening for germline mutations.

There are currently no randomized clinical trials that provide evidence about the drugs of first choice in pregnancy, although the general consensus is that women should be treated initially with alpha-adrenoreceptor blockade, and no fetal harm has been reported following the use of phenoxybenzamine in pregnancy [29].

The rates of caesarean section in women with pheochromocytoma were significantly higher than controls. In a previous study, vaginal delivery had a higher maternal mortality (31%) than caesarean section (19%) [1]. Although there is no theoretical reason why a woman cannot undergo labour if she has adequate alpha-adrenoreceptor blockade it is recognized that women with pheochromocytoma in pregnancy are at high-risk of adverse outcomes, and this may have influenced decisions about the timing of delivery. The etiology of fetal death is likely to relate to impaired placental function secondary to vasoconstriction in addition to the metabolic insults associated with co-existing gestational diabetes mellitus and pre-eclampsia.

In primary aldosteronism cases the most common presenting features were headache and hypertension, with recorded blood pressures of up to 190/120. A range of anti-hypertensive medications were administered with methyldopa given most frequently.

One case in the UKOSS series was treated with amiloride and this woman had better blood pressure control in the third trimester than the other two cases with primary aldosteronism. She was also the only woman to have normokalemia in late pregnancy. A previous case report of primary aldosteronism in pregnancy managed with amiloride noted it was a safe and effective agent in the

non-surgical treatment of this disorder [30]. Therefore amiloride may be a worth investigating as an effective alternative agent to spironolactone as a potassium-sparing anti-hypertension agent for women with primary aldosteronism in pregnancy.

Women with primary aldosteronism during pregnancy were more likely to have a caesarean section (38.8%, 95% CI 23.14- 56.54). Maternal severe hypertension is likely to increase the risk of stillbirth, and electrolyte disturbances may also contribute.

There were two UKOSS cases of Cushing's syndrome, and both had severe hypertension. Although gestational diabetes mellitus was not diagnosed in the UKOSS cases, in a review of 140 cases of Cushing's syndrome in pregnancy 25% presented with diabetes mellitus [26]. Hypercortisolism in combination with hyperglycaemia increases the risk of having a miscarriage or a large-for-gestational-age or macrosomic infant [26].

The two most frequently used medications in the literature were metyrapone and ketoconazole [25, 26]. However, due to the small numbers of Cushing's syndrome cases in pregnancy, guidance is limited as to the optimal treatment regimen.

Women with Cushing's syndrome had an increased incidence of caesarean section, premature birth and stillbirth. Women with Cushing's syndrome should be assessed for their eligibility for adrenal surgery as a reduction in adverse maternal and neonatal outcomes has been reported following adrenalectomy during pregnancy [26].

Strengths and Limitations

The strength of this study is that all the UK obstetric units within the UK are included. The study was advertised through the already established robust UKOSS system and at the national British Endocrine Society conference. All UK Consultant Endocrinologists registered with the BES also received email and newsletter correspondence about the study, so it is likely that there was effective identification of cases.

The limitations are that the numbers are small and to draw statistically robust conclusions using the UKOSS data we would need to continue this prospective study for several years. As the number of cases recruited was small, we amalgamated our data with those obtained from previous reported studies. While this enabled us to study the impact of hormone-secreting tumours on the rate of adverse pregnancy outcomes, a limitation of this approach is that the outcomes of the UKOSS cases will have had less impact on the results than the outcomes reported in the larger number cases reported in previous studies. It is also possible that the current published literature has reporting bias with regard to the frequency of adverse outcomes.

Conclusions

Given that pheochromocytoma, primary aldosteronism and Cushing's syndrome are associated with an increased risk of preterm delivery and stillbirth, careful monitoring is mandatory along with the development of a detailed multidisciplinary treatment plan. The new information obtained from this study may also be beneficial for pre-pregnancy counselling for these women.

Acknowledgements

We would like to thank all UKOSS reporting clinicians who contributed to the study. It was funded by the charity Sparks and supported by National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London (CW, PS). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. PS is partly funded by Tommy's (Registered charity no. 1060508) and by CLAHRC South London (NIHR). CW is funded by the Wellcome Trust. We thank Leslie McMurtry for administrative support with this project.

Disclosure of interests

The authors have no interests to disclose. The ICMJE disclosure forms are available as online supporting information.

Contribution to authorship

KL, CW and MK devised the study. KL, CW, MK, MKD, PS and DMcC contributed to study design. GQ, KR and KL performed initial analysis of data. PS provided statistical advice. All authors reviewed the results. GQ wrote the first draft of the manuscript. All authors advised on subsequent drafts of the manuscript.

Details of ethics approval

The study was approved by the Riverside Ethics Committee, London in 2009 (09/H0706/78).

Funding

The study was funded by Sparks, grant reference number 09IMP01.

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Table Legends

Table 1: Pregnancy outcome data for the UKOSS pheochromocytoma cases as well as those identified in the literature

Table 2: Pregnancy outcome data for the UKOSS primary aldosteronism cases as well as those identified in the literature

Table 3: Pregnancy outcome data for the UKOSS Cushing's syndrome cases as well as those identified in the literature

Figure Legend

Figure 1: Flow chart showing the ascertainment of cases of adrenal tumour in pregnancy.

Online Supporting Information

Table S1: Demographic characteristics of women with adrenal tumours in pregnancy identified by the UKOSS system compared to UKOSS controls.

Table S2: Medication administered to the UKOSS pheochromocytoma cases and to those identified in the literature

Table S3: Medication administered to the UKOSS primary aldosteronism cases and to those identified in the literature

Table S4: The medication administered to the UKOSS adrenal Cushing's syndrome cases and to those identified in the literature

Table 1: Pregnancy outcome data for the UKOSS pheochromocytoma cases as well as those identified in the literature

	All cases*	UKOSS controls (n= 2250)	RR/MD ¹	P value ¹	ONS controls (n= 698,512)	RR/MD ²	P value ²
Vaginal delivery	28/114 (24.6%) (16.9- 33.5)	1703/2228 (76.4%) (74.6- 78.2)	0.32 (0.23- 0.44)	<0.001	**	.	.
Caesarean section	86/114 (75.4%) (66.5- 83.0)	525/2228 (23.3%) (21.6- 25.1)	3.2 (2.81- 3.64)	<0.001	**	.	.
Mean gestational age at delivery (weeks)	32.5	39.6	MD 7.1	.	**	.	.
Preterm delivery	59/106 (55.6%) (45.6- 65.3)	144 (6.4%) (5.4- 7.5)	8.7 (6.9- 10.9)	<0.001	47657 (6.8%) (6.7- 6.8)	8.2 (6.9- 9.7)	<0.001
Stillbirth	15/119 (12.6%) (7.2- 19.9)	11 (0.5%) (0.2- 0.8)	25.8 (12.1- 54.9)	<0.001	3284 (0.47%) (0.4- 0.5)	26.8 (16.7- 43.0)	<0.001

The combined data were compared to UKOSS controls¹ and ONS controls². * Combined data from UKOSS cases and those previously reported, RR = relative risk, MD = mean difference, Denominator numbers vary depending upon whether the relevant information was reported in the case series/case reports, ** data not available, (.) comparison not possible.

Table 2: Pregnancy outcome of UKOSS primary aldosteronism cases as well as those identified in the literature

	All cases* (n=37)	UKOSS controls (n=2250)	RR/MD ¹	P value ¹	ONS controls (n= 698,512)	RR/MD ²	P value ²
Vaginal delivery	8/36 (22.2%) (10.12- 39.15)	1703/2228 (76.4%)	0.29 (0.15- 0.54)	<0.001	**	.	.
Caesarean section	14/36 (38.8%) (23.14- 56.54)	525/2228 (23.6%) (21.8- 25.4)	1.6 (1.08- 2.5)	<0.001	**	.	.
Mean gestational age at delivery (weeks)	36	39.6	MD 3.6	.	**	.	.
Preterm delivery <37 weeks	18/35 (51.4%) (33.9- 66.6)	144 (6.4%) (5.4- 7.5)	8.03 (5.6- 11.5)	<0.001	47657 (6.8%) (6.7- 6.8)	7.5 (5.4- 10.4)	<0.001
Stillbirth	2/35 (5.7%) (0.7- 19.2)	11 (0.5%) (0.2- 0.8)	11.68 (2.7- 50.8)	0.016	3284 (0.47%) (0.4- 0.5)	12.2 (3.2- 46.7)	0.012

The combined cases were compared to the UKOSS controls¹ and ONS controls², * Combined data from UKOSS cases and were previously reported, RR = relative risk, MD = mean difference, Denominator numbers vary depending upon whether the relevant information was reported in the case series/case reports, ** data not available, (.) comparison not possible.

Table 3: Outcome data for the UKOSS adrenal Cushing's syndrome cases as well as those identified in the literature

	All cases* (n=158)	UKOSS controls (n=2250)	RR/MD ¹	P value ¹	ONS controls (n= 698,512)	RR/MD ²	P value ²
Vaginal delivery	4/16 (25%) (7.2- 52.3)	1703/2228 (76.4%) (74.6- 78.2)	0.32 (0.14- 0.76)	<0.001	**	.	.
Caesarean section	14/18 (77.7%) (52.3- 93.5)	525/2228 (23.3%) (21.8- 25.3)	3.30 (2.55- 4.27)	<0.001	**	.	.
Mean gestational age at delivery (weeks)	34.5	39.6	MD 5.1	.	*	.	.
Stillbirth	9/158 (5.6%) (2.6- 10.5)	11 (0.5%) (0.2- 0.8)	11.65 (4.9- 27.7)	<0.001	3284 (0.47%) (0.45- 0.48)	12.11 (6.42- 22.87)	<0.001

The combined cases were compared to the UKOSS controls¹ and ONS controls², * Combined data from UKOSS cases and were previously reported, RR = relative risk, MD = mean difference, Denominator numbers vary depending upon whether the relevant information was reported in the case series/case reports, ** data not available, (.) comparison not possible

Figure 1. Flow chart showing the ascertainment of cases of adrenal tumour in pregnancy and control groups. *ONS controls were from the same years the study cases were recruited (2011 to 2015) **UKOSS controls were recruited separately prior to 2011.

