

Obstetric outcomes in women with prolactinomas from a culturally diverse population: a matched cohort study

Minh V Le

Royal Melbourne Hospital

Sarah A L Price

Royal Melbourne Hospital

Christopher J Yates

Royal Melbourne Hospital

Lauren Di-Salvo

Royal Melbourne Hospital

James King

Royal Melbourne Hospital

Yi Zhao

Royal Melbourne Hospital

Angeline Shen

Angeline.Shen@mh.org.au

Royal Melbourne Hospital

Research Article

Keywords: Prolactinoma, pituitary, cabergoline, bromocriptine, pregnancy, obstetric

Posted Date: September 19th, 2025

DOI: <https://doi.org/10.21203/rs.3.rs-7583113/v1>

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Prolactinomas are the most common type of pituitary adenomas in women of reproductive age. Data on obstetric outcomes in these women remain inconsistent, particularly in those exposed to dopamine agonists (DAs) during pregnancy. Most studies have been conducted in European and American populations, while data for other populations remain limited. We studied the prevalence of adverse obstetric outcomes in women with prolactinomas in the culturally diverse population of Australia.

Methods

This was a retrospective study of women with prolactinomas, treated at a metropolitan tertiary hospital and a co-located tertiary maternity centre in Melbourne, between 2021 and 2023. Controls were identified using a birth registry from the maternity hospital, matched for age, body mass index, parity, birth country and socio-economic status. Wilcoxon and Pearson's Chi-squared tests were used for statistical analyses.

Results

65 pregnancies from 28 women were included, 29% of whom had macroprolactinomas. Most women were born in Oceania, Asia, and Africa. DAs were used at the time of conception in 51 pregnancies: 30 with cabergoline and 19 with bromocriptine. Medical therapies were continued in 9 women with macroprolactinomas, following shared medical decision-making. Symptomatic prolactinoma growth was observed in 2 pregnancies, neither required surgical management. The risks of adverse maternal (gestational diabetes mellitus, hypertension, and obstetric haemorrhage) and foetal outcomes (preterm delivery and congenital anomalies) in women with prolactinoma were comparable to those in the 260 control pregnancies.

Conclusion

Compared to matched controls, women with prolactinomas, with or without DA exposure, did not

INTRODUCTION

Prolactinomas are the most common type of pituitary adenomas, accounting for approximately 50% of all pituitary tumours(1). The incidence is higher in women, particularly those of reproductive age. The prevalence of macroprolactinomas (≥ 1 cm in maximal diameter) among women with prolactinomas is estimated to be 10–20%. Prolactinomas cause hyperprolactinaemia and secondary hypogonadism via suppression of gonadotropin-releasing hormone (GnRH), leading to anovulatory menstrual cycles and

sub-fertility(2). Medical treatment with dopamine agonists (DAs) normalises the menstrual cycle and restores fertility, making pregnancy possible in over 90% women(3).

When a woman with a prolactinoma becomes pregnant, special consideration must be given to the effects of DA on early foetal development(4). Bromocriptine (BRM) has been shown to cross the placenta in human studies, while the data for cabergoline (CAB) is less clear (5). Current international guidelines from the Pituitary Society and the European Society of Endocrinology suggest that DAs should be discontinued upon confirmation of the pregnancy to reduce foetal drug exposure, with the exception of large macroprolactinomas(1, 6). Conversely, the rise in prolactin following DA cessation in pregnancy may have adverse effects on underlying tumour growth and maternal cardiovascular risk, including peripartum cardiomyopathy(7, 8).

A recent systematic review and meta-analysis demonstrated a low incidence of adverse obstetric outcomes in women with prolactinomas during pregnancy(9). However, most studies included in the review contained heterogenous cohorts, lacked control groups and did not account for possible confounders affecting pregnancy outcomes. Therefore, the effects of prolactinomas on pregnancy outcomes could not be reliably assessed. In addition, most studies were conducted in European and American populations, while data from other regions are lacking, which limit their generalisability. We therefore performed a retrospective matched cohort study to assess the prevalence of adverse obstetric outcomes in women with prolactinomas, compared to controls in the culturally diverse population of Australia.

MATERIALS AND METHODS

Study design and cohort

This was a retrospective matched cohort study of women with prolactinomas, who were reviewed at a metropolitan tertiary referral hospital with expertise in pituitary disease and/or a co-located tertiary maternity hospital in Melbourne, Australia, between January 2021 and December 2023. The primary aim of the study was to assess the obstetric outcomes of women with prolactinoma, compared to matched controls. The effects of DA exposure during pregnancy on maternal and foetal outcomes were sub-analysed as an exploratory outcome. The study was approved by the Royal Melbourne Hospital Human Research Ethics Committees (HREC/16/MH/132 2016.069).

The study included women aged over 18 years who became pregnant following a diagnosis of prolactinoma, with all subsequent pregnancies recorded. Prolactinoma was defined as the presence of persistent hyperprolactinaemia, in addition to radiological evidence of a pituitary tumour on neuroimaging. Most of the women received obstetric care at the co-located maternity hospital.

Controls were identified in the maternity hospital birth registry as mothers with no pre-existing medical conditions, during the same study period. The controls were then matched to each pregnancy in the

prolactinoma cohort, in a 1:4 ratio, for all 5 baseline characteristics which could influence obstetric outcomes as follows(10, 11, 12, 13, 14):

1. Age: categorised into either (i) Advanced maternal age (≥ 35 years at time of conception) or (ii) Non-advanced maternal age (< 35 years at time of conception)
2. Pre-pregnancy body mass index (BMI): categorised into either (i) Underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), (ii) Normal ($\text{BMI} 18.5\text{--}24.9 \text{ kg/m}^2$), (iii) Overweight ($\text{BMI} 25.0\text{--}29.9 \text{ kg/m}^2$) and (iv) Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$)
3. Parity status: categorised into either (i) Nulliparity (women who had never given birth) or (ii) Primiparity and Multiparity (women who had given birth once or more)
4. Country of birth: categorised into continents of birth (Asia, Africa, Europe, North America and South America)
5. Socio-Economic Status (SES): categorised into quintiles of the socio-economic indexes of areas (SEIFA), provided by the Australian Bureau of Statistics using reported residential address postcodes(15). Lower socio-economic indexes indicate more disadvantaged areas.

Data collection

Demographic, clinical and obstetric data for women with prolactinomas were collected independently via electronic medical records by two investigators, to ensure data accuracy. For women who delivered outside the Study Precinct, data were collected based on available correspondence and medical records. Prolactin (PRL) levels were expressed as fold above the upper limit of normal range (ULN), to account for differences in laboratory assays and reference ranges. Pre-conception PRL levels were defined as PRL measured within 6 months prior to conception dates. Macroprolactinoma was defined as prolactinoma whose maximal dimension was 10mm or greater, while microprolactinomas were those less than 10mm in size(1). Dopamine agonists used included cabergoline (CAB), bromocriptine (BRM) or quinagolide.

In this study, preterm birth was defined as birth of a baby prior to 37 weeks' gestation, while extreme preterm birth referred to those born prior to 28 weeks' gestation. Miscarriage was defined as pregnancy loss before 20 weeks' gestation. Stillbirth was defined as foetal death from 20 weeks of gestation to labour and/or birth. Neonatal mortality referred to the death of a baby within 28 days of birth(16). Postpartum haemorrhage (PPH) was defined as blood loss of greater than 500mL for normal vaginal delivery, or greater than 1000ml for Caesarean section (CS). Antepartum haemorrhage (APH) was defined as any bleeding from the genital tract, occurring after 24 weeks gestation and prior to the birth of the baby. Obstetric haemorrhage referred to either APH or PPH. Gestational diabetes mellitus (GDM) was diagnosed according to the 2014 Australasian Diabetes in Pregnancy Society (ADIPS) diagnostic criteria (fasting, 1-hour and 2-hour plasma glucose levels ≥ 5.1 , 10.0 and 8.5 mmol/L respectively on 75g oral glucose tolerance tests)(17). As per the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) Hypertension in Pregnancy Guidelines, gestational hypertension was defined as new onset hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on

repeated measurements) after 20 weeks' gestation. Pre-eclampsia was defined as gestational hypertension in the presence of new onset organ involvement (renal, liver, haematological, neurological, pulmonary or placental dysfunction)(18). Lastly, newborn respiratory distress syndrome was diagnosed clinically by treating physicians where either oxygen therapy or resuscitation ventilation methods (intermittent positive pressure ventilation or continuous positive airway pressure) were required. Transient tachypnoea of newborn was excluded from this definition.

Pregnancy outcomes for the control group were collected based on reported International Classification of Diseases 10th Revision (ICD-10) codes, linked to each delivery using the maternity hospital de-identified birth registry.

Statistical Analyses

Statistical analyses were performed using R, version 4.2.1(19). All hypotheses were tested at a two-tailed 0.05 level of significance. Wilcoxon and Pearson's Chi-squared tests (for continuous and categorical data respectively) were performed to compare the incidence of adverse obstetric outcomes in women with prolactinomas and matched controls. Given the matched cohort study design, statistical tests were not further adjusted for confounders.

Sub-analyses were performed within the prolactinoma group, to assess if the use of medical therapy in pregnancy was associated with adverse pregnancy outcomes. Fisher's exact tests were used given low frequencies of adverse obstetric outcomes.

RESULTS

Baseline characteristics of women with prolactinomas and matched controls

The analysis included 65 pregnancies from 28 women with prolactinomas. These pregnancies were matched in a 1:4 ratio, to 260 pregnancies in the control group, for age, BMI, parity, birth country and SES. The baseline characteristics for both prolactinoma and control groups are shown in Table 1.

Table 1
Baseline maternal characteristics of pregnancies with and without prolactinomas

	Prolactinoma (n = 65)	Control (n = 260)	p-values*
Age, years, median (IQR)	34 (31–36)	34 (30–36)	0.201
Advanced maternal age (≥ 35 years), n (%)	25 (38%)	100 (38%)	1.000
Pre-pregnancy BMI, kg/m ² , median (IQR)	25 (22–29)	25 (23–29)	0.982
Normal weight (BMI 18.5–24), n (%)	28 (43%)	112 (43%)	1.000
Overweight and obesity (BMI ≥ 25), n (%)	37 (57%)	148 (57%)	1.000
SEIFA decile, median (IQR)	6 (5–8)	6 (5–8)	0.528
Gravidity, median (IQR)	2 (1–3)	2 (1–3)	0.209
Parity, median (IQR)	1 (0–1)	1 (0–2)	0.735
Continent of birth			
Oceania	35 (54%)	140 (54%)	1.000
Asia	21 (32%)	84 (32%)	1.000
Africa	6 (9%)	24 (9%)	1.000
North America	2 (3%)	8 (3%)	1.000
South America	1 (2%)	4 (2%)	1.000
Europe	0 (0%)	0 (0%)	1.000
IQR: inter-quartile range			
BMI: body mass index			

SEIFA: socio-economic indexes of areas. Lower indexes indicate more disadvantaged areas

* p-values were calculated using either Wilcoxon or Pearson's Chi-squared tests

Pituitary Magnetic Resonance Imaging (MRI) data were available in medical records for 21 (75%) women at time of prolactinoma diagnosis: 13 (46%) microprolactinomas and 8 (29%) macroprolactinomas. Prior to conception, 25 (89%) women received medical therapies with DA and 4 (14%) required further surgical intervention. The indications for surgery included DA resistance, DA-induced cerebrospinal fluid leak, optic chiasm compression and apoplexy.

Median time from initial prolactinoma diagnoses to first conceptions was 3 years (inter-quartile range [IQR] 2–5). During the preconception period, MRI pituitary data were available in 52 pregnancies, 35/52

(67%) had microprolactinomas. Pre-conception PRL levels were available in 41 pregnancies with a median of 1.1 (IQR 0.7–1.7) fold above ULN. Fifty-one (78%) women were taking DA therapy in the pre-conception period: 30 (59%) with CAB, 19 (37%) with BRM and 2 (4%) with quinagolide. DAs were withdrawn in most pregnancies, except for 9 women with macroprolactinomas (5 with CAB and 4 with BRM), following shared medical decision-making between the women and their treating obstetric endocrine specialists. In one case, DA was ceased at time of pregnancy confirmation and restarted in third trimester due to onset of compressive symptoms.

Maternal and neonatal outcomes in pregnancies with and without prolactinomas

Of the 65 pregnancies in women with prolactinomas, spontaneous conception occurred in 60 (92%). Assisted reproductive technology (ART) was required in 5 (8%) pregnancies in the prolactinoma group, compared to 14 (5%) in matched controls ($p = 0.503$). For the women with prolactinomas who required ART, 1 had polycystic ovary syndrome, 1 had thalassaemia trait and 1 was of advanced maternal age (> 35 years old) at time of conception for both pregnancies. No contributing factor for infertility was identified for the other 2 women.

Out of 65 total pregnancies in the prolactinoma cohort, there were 53 (82%) live births (including 52 singleton and 1 twin pregnancies), 11 (17%) miscarriages (from 5 different women, 4 out of 5 had at least two miscarriages) and one (1%) stillbirth. Miscarriage data was not available for matched controls as they were identified from a registry with live births only. The prevalences of maternal and neonatal complications for pregnancies progressing to live births, from women with and without prolactinomas are outlined in Table 2.

Table 2
Maternal and neonatal outcomes in pregnancies progressing to live births from women with and without prolactinoma

	Prolactinoma (n = 53)	Control (n = 260)	p-values*
Maternal outcomes and complications			
Caesarean section (CS) delivery, n (%)	17 (32%)	109 (42%)	0.183
Elective CS, n (%)	12 (23%)	58 (22%)	0.958
Emergency CS, n (%)	5 (9.4%)	51 (20%)	0.078
Gestational diabetes mellitus, n (%)	13 (25%)	43 (17%)	0.167
Gestational hypertension, n (%)	5 (7.5%)	10 (3.8%)	0.083
Pre-eclampsia, n (%)	3 (5.7%)	4 (1.5%)	0.064
Hypertension without pre-eclampsia, n (%)	2 (3.8%)	6 (2.3%)	0.534
Obstetric haemorrhage, n (%)	10 (19%)	79 (30%)	0.078
Antepartum haemorrhage, n (%)	2 (3.8%)	17 (6.5%)	0.632
Postpartum haemorrhage, n (%)	9 (17%)	70 (27%)	0.114
Neonatal outcomes and complications			
Preterm birth, n (%)	6 (11%)	26 (10%)	0.806
Extreme preterm birth, n (%)	1 (1.9%)	2 (0.8%)	0.457
Multiple births, n (%)	1 (1.9%)	12 (4.6%)	0.354
Congenital anomalies, n (%)	3 (5.6%)	9 (3.5%)	0.465
Newborn respiratory distress syndrome, n (%)	2 (3.7%)	9 (3.5%)	0.930
* p-values were calculated using either Wilcoxon or Pearson's Chi-squared tests			

Symptomatic prolactinoma growth was observed in 2 (3%) pregnancies, from 2 women. One primiparous woman with a macroprolactinoma (11mm), discontinued her CAB at pregnancy confirmation. She then developed mild headache at 16 weeks' gestation. A pituitary MRI performed the following week showed prolactinoma growth to 17mm without optic chiasm compression. She was managed conservatively until 31 weeks' gestation, when BRM was started due to worsening headache and visual symptoms. Due to poor response, her therapy was subsequently changed to CAB with good effects. The second woman was multiparous and had a microprolactinoma (7mm) at baseline. Her CAB was ceased after pregnancy confirmation. At 36 weeks' gestation, she experienced headache without visual changes. MRI showed prolactinoma enlargement to 19mm, contacting the optic chiasm. Formal visual field testing however

was normal. She pursued conservative management with weekly visual field tests. Her symptoms remained stable until the elective CS delivery. Despite symptomatic prolactinoma growth, apoplexy and other obstetric complications were not observed in either case.

Associations between DA exposure in pregnancy and obstetric outcomes

We performed sub-analyses of women with prolactinomas, to determine if DA exposure in pregnancy was associated with obstetric complications. Of the 51 pregnancies conceived on DAs, 11 (22%) resulted in miscarriages, including 3 (33%) in the 9 pregnancies where DAs were maintained. Among pregnancies progressing to live births, the associations between gestational DA exposure and maternal and neonatal complications were summarised in Table 3.

Table 3
Associations between gestation DA exposure and maternal and neonatal complications

Maternal and neonatal complications	DA exposure in early gestation (prior to pregnancy confirmation)			DA exposure in late gestation (after pregnancy confirmation)		
	Yes (n = 40)	No (n = 13)	p-values*	Yes (n = 7^)	No (n = 46)	p-values*
Gestational hypertension	3 (7.5%)	2 (15%)	0.586	1 (14%)	4 (8.7%)	0.522
Gestational diabetes mellitus	10 (25%)	3 (23%)	1.000	0 (0.0%)	13 (28%)	0.173
Obstetric haemorrhage	9 (23%)	1 (7.7%)	0.419	3 (43%)	7 (15%)	0.114
Pre-term birth	4 (10%)	2 (15%)	0.627	1 (14%)	5 (11%)	1.000
Congenital anomalies	1 (2.5%)	2 (15%)	0.145	0 (0.0%)	3 (6.5%)	1.000
Newborn respiratory distress syndrome	2 (5.0%)	0 (0.0%)	1.000	1 (14%)	1 (2.2%)	0.249

^6 with continued DA use after pregnancy confirmation and 1 with DA restarted in third trimester due to symptomatic prolactinoma growth

*p-values were calculated using Fischer’s exact tests, comparing the frequencies of specified complications between pregnancies with and without DA exposure

DISCUSSION

In this study, women with treated prolactinomas experienced similar rates of adverse obstetric outcomes as matched controls during pregnancy. Our study cohort was unique with the majority of women born in Oceania, Asia and Africa, and a high proportion (29%) of macroprolactinomas. Median

maternal age at conception was 34 years, compared to 31 years in the general Australian population(16). The difference could be partially attributed to the subfertility period prior to prolactinoma diagnosis and the need for adequate management of the condition. Most women had well-controlled hyperprolactinaemia prior to conception (median PRL level of 1.1, IQR 0.7–1.7, folds above ULN). In the literature, the risk of symptomatic prolactinoma growth in pregnancy was estimated to be 2.4% for microprolactinomas and 21% for macroadenomas(20). In our study, only two women (one with microadenoma and one with macroadenoma) experienced compressive symptoms due to tumour growth. Neither case was complicated by apoplexy. Both women had DA withdrawn at conception and re-introduction of DA led to good symptoms control in one woman while the other only required close clinical surveillance. This is consistent with previous studies where medical therapies are generally adequate in managing tumour re-growth in pregnancy, while surgery is reserved for those with apoplexy(9). The lower rate of symptomatic tumour re-growth of macroprolactinomas in our cohort (12.5%) could be explained by the ongoing use of DAs in 9 pregnancies.

Numerous studies have reported an association between hyperprolactinaemia and metabolic complications (21, 22, 23, 24, 25). In vitro, PRL has been shown to exert vasoconstrictive and pro-angiogenic effects on endothelial cells, leading to arterial stiffness and hypertension (26, 27, 28, 29). In addition, higher serum PRL levels have been associated with an increased incidence of hypertension(30). In our study, the prevalence of pre-eclampsia appeared to be higher in women with prolactinoma (5.7%) compared to matched control (1.5%), however this difference did not reach statistical significance ($p = 0.064$). As PRL level during pregnancy was not routinely measured in our patient cohort, the association between hyperprolactinaemia and pre-eclampsia risk could not be reliably assessed.

A complex interplay underlies the effects of hyperprolactinaemia on glucose homeostasis. In vivo, PRL signalling pathway appeared to play an important role in pancreatic β -cell proliferation and insulin secretion(31). On the other hand, some studies reported hyperprolactinaemia to be associated with hyperinsulinaemia, insulin resistance and increased GDM risk in pregnancy(32, 33, 34). In our cohort, the prevalence of GDM was slightly higher in women with prolactinoma (25%) than control (17%), however this finding was statistically non-significant ($p = 0.167$). The prevalence of GDM amongst our control was comparable to the Australian incidence of GDM of around 18%(16).

Other obstetric outcomes measured in the study included the spontaneous abortion rate of 17% in the prolactinoma cohort, similar to that reported in Australia (19%) and worldwide (15.3%) (35, 36). CS delivery occurred in 32% women with prolactinomas, compared 38% in the general population and 42% in the control group(16).

Regarding neonatal outcomes, in our cohort 11% of births among women with prolactinomas were preterm. This rate was comparable to that observed in matched controls (10%) and the general population (8.2–11%) (16, 37). The risk of perinatal mortality was very low across both groups, similar to the 2% frequency reported in the meta-analysis(9). No statistical significant difference was observed in

the rates of congenital anomalies in babies born to women with and without prolactinomas (5.6% and 3.5% respectively, $p = 0.465$), comparable to that of 3% in the Australian population (16). The risk of respiratory distress syndrome was similar between the two groups (3.7% vs 3.5%, $p = 0.930$).

Our study adds to the safety data for DA use in pregnancy. At least 78% of the studied pregnancies were conceived on DA therapies, most commonly with CAB. This is different from the reported data in the systematic analysis, where BRM was used in the majority of pregnancies(9), which could be explained by the publication years. Traditionally, BRM was the preferred DA therapy in pregnancy due to its shorter half-life and larger pregnancy safety database(4, 9). Over the past decade, CAB has emerged as the preferred therapy due to better efficacy, tolerability, and safety profile(1, 38), resulting in accumulating evidence supporting its use during pregnancy(9, 38, 39, 40, 41). Most observational studies did not identify increased maternal or foetal risks associated with short-term DA exposure (less than 10 weeks of gestation)(9), although some raised potential concern. In a study of 183 French women with DA use in pregnancy (30.6% beyond first trimester), increased risks of pregnancy loss and preterm birth were reported(40). However, the rate of birth defects and birth weights were comparable between the two groups. In contrast, a 12-year observational study reported a possibly higher incidence of birth defects, predominantly musculoskeletal in nature, in 329 pregnancies conceived on CAB (9% vs 6% in the general population)(39). Notably, 15% were exposed to DAs beyond two months' gestation. Current international guidelines, including those of the Pituitary Society and the European Society of Endocrinology, recommend the discontinuation of DA upon confirmation of pregnancy(1, 4, 6). In our study, reassuringly we observed no increased risks of preterm births nor congenital anomalies in pregnancies with DA exposure at conception or in late pregnancy.

This study has several limitations. Firstly, the rarity of prolactinoma limited the size of the study cohort. Women included in the study were selected from two tertiary referral centres, which may be subject to selection bias for those at greater risk. While medical chart reviews were retrospectively reviewed by two investigators to ensure data accuracy, some information was not consistently available for all participants, including gestational and postpartum PRL level and pituitary size, breastfeeding duration, neonatal birth weight and long-term health outcomes. This limits further analyses for their potential associations. Due to the de-identification of each birth in the registry, information on past obstetric history was unavailable, representing a potential confounder. As ethnicity data were unavailable in the database, country of birth was used for matching instead. Finally, since the registry used to derive the control group included only live births, direct comparison of birth rates with women with prolactinomas is limited.

CONCLUSION

In summary, women with prolactinomas in our culturally diverse study cohort experienced similar rates of adverse obstetric outcomes, compared to matched controls. Despite the common use at conception, DA therapy was not associated with increased maternal or short-term foetal risks. Symptomatic prolactinoma growth was uncommon following DA discontinuation in pregnancy. Future prospective

studies with larger study cohort are required to investigate the effects of hyperprolactinaemia and gestational DA exposure on obstetric and metabolic outcomes.

Declarations

Nil conflict of interest to declare

AUTHOR CONTRIBUTIONS

AS and SP conceptualised and designed the study. Material preparation, data collection and analysis were performed by ML and LD. The first draft of the manuscript was written by ML and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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