

1 **Macroprolactinomas and Nonfunctioning Pituitary** 2 **Adenomas and Pregnancy Outcomes**

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24
25 ***Abbreviated Title:*** Pituitary Tumors in Pregnancy

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44

45 Précis:

46 Macroprolactinoma and nonfunctioning pituitary adenoma can present in pregnancy with expansion

47 and apoplexy, but typically respond to medical management with good pregnancy outcomes.

48

49 **Abstract**

50

51 **Objective**

52 To examine the monitoring, management, and outcomes of pituitary tumors in pregnancy.

53 **Methods**

54 A national, prospective, observational, population-based case series study was conducted in all UK
55 consultant-led obstetric units over 3 years using the UK Obstetric Surveillance System. In order to
56 evaluate rates of adverse pregnancy outcomes, women with a macroprolactinoma (≥ 10 mm) or non-
57 functioning pituitary adenoma, diagnosed before or during pregnancy, were compared to 2
58 comparison groups: 1) a UKOSS cohort with singleton (n=2205) or twin (n=27) pregnancy and 2)
59 data from the Office of National Statistics (n=2,703,102). Main outcome measures were the
60 incidence, management, and frequency of adverse maternal and offspring outcomes of pituitary
61 tumors in pregnancy.

62 **Results**

63 There were 71 confirmed cases of pituitary tumors in pregnancy (49 macrolactinoma, 16 non-
64 functioning adenomas, 3 acromegaly, 3 Cushing's disease). The women with pituitary tumors were 4
65 years older than comparison women ($P < 0.001$). None of the 9 women treated with surgery or
66 radiotherapy prior to pregnancy had symptomatic tumor expansion. This occurred in 6 out of 40
67 women with macroprolactinomas and 1 out of 7 non-functioning adenomas diagnosed before
68 conception, and in 3 out of 5 women with non-functioning adenomas diagnosed in pregnancy. Two
69 women had pituitary apoplexy, both of whom also had symptoms of expansion of tumor or
70 surrounding pituitary tissue. To within the level of accuracy possible, there was no evidence that
71 pituitary tumors were associated with adverse pregnancy outcomes (pregnancy-induced hypertension,
72 preeclampsia, preterm labor, stillbirth). Women with non-functioning adenomas were more likely to
73 have cesarean section compared to controls (RR 2.06, CI 1.26-3.36, $p = 0.035$).

74

75 **Conclusions**

76 The majority of women with macroprolactinomas and non-functioning adenomas have good
77 pregnancy outcomes. Non-functioning pituitary adenomas occur more commonly in pregnancy than
78 previously thought, and can present *de novo* with symptoms of pituitary expansion in pregnancy.

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82 Introduction

83 The majority of pituitary tumors in pregnant women are microprolactinomas (diameter < 10mm).

84 Macroprolactinomas (diameter \geq 10mm) are less common, affecting approximately 24% of pregnant
85 women with prolactinoma [1] and the precise incidence of these tumors in pregnancy is unknown.

86 Other pituitary tumors occur more rarely in pregnant women and may be functioning (producing
87 growth hormone, adrenocorticotrophic hormone or thyroid stimulating hormone), or nonfunctioning
88 pituitary adenomas.

89 Pregnant women with microprolactinomas typically have uncomplicated pregnancies with no
90 symptoms of tumor enlargement [1]. Among all prolactinomas, about 46% enlarge during pregnancy
91 [2], while symptomatic enlargement occurs less frequently. Approximately 30% of
92 macroprolactinomas undergo symptomatic enlargement while only 3% of the more common
93 microprolactinomas do so. If women with macroprolactinomas are treated prenatally with surgery or
94 radiation, their risk of tumor enlargement is markedly reduced [3].

95 Symptoms consistent with enlargement are reported in 5 of 9 cases of nonfunctioning pituitary
96 adenoma reported in the literature [4-7]. We identified 3 reported women with thyrotrophinomas [8-
97 10]; 2 of whom had gestational tumor enlargement. Three retrospective series described 72
98 pregnancies in 58 women with acromegaly. Maternal complications included type 2 diabetes,
99 gestational diabetes mellitus, pregnancy-induced hypertension and pre-eclampsia and 8% had
100 symptomatic enlargement [11, 12]. Combined data from 136 pregnancies in 122 women with
101 Cushing's disease demonstrated a high rate of adverse outcomes, including preterm labor (43%),
102 intrauterine growth restriction (21%), stillbirth (6%), pre-eclampsia (14%), diabetes or impaired
103 glucose tolerance (25%) [13].

104 The aim of this study was to describe the incidence, characteristics, management and outcomes of a
105 UK national case series of pregnant women with pituitary tumors.

106

108

109 **Materials and Methods**

110 A national, prospective observational, population-based case series study was undertaken over 3 years
111 (March 2010 to February 2013) using the UK Obstetric Surveillance System (UKOSS). UKOSS is a
112 research platform with reporting clinicians in all UK consultant-led maternity units, designed to study
113 rare complications of pregnancy on a national basis. UKOSS utilizes a prospective monthly case
114 collection scheme that includes all 202 consultant-led obstetric units in the UK. Women are not
115 contacted directly and no personally identifiable information is collected. As all women with pituitary
116 tumors should have consultant-led care, we anticipate that the study is likely to have covered all
117 women with pituitary tumors within the entire UK birth cohort. The study was approved by the
118 Riverside Ethics Committee, London (reference number 09/H0706/78).

119 Exposed women were defined as those with macroprolactinomas ($\geq 10\text{mm}$), nonfunctioning pituitary
120 adenomas, Cushing's disease, acromegaly or thyrotrophinomas diagnosed before or during pregnancy.
121 As the UKOSS system is limited to the study of rare diseases (incidence < 1 in 2000 deliveries),
122 women with microprolactinoma ($< 10\text{mm}$ diameter) were excluded from the study.

123 Women who met the criteria for the study were identified by the obstetrician or endocrinologist
124 responsible for their care. On reporting a woman with a pituitary tumor, the clinician was asked to
125 complete a data collection form. Anonymized data were collected about pituitary tumor diagnosis,
126 monitoring and management before pregnancy and antenatally, as well as maternal demographics,
127 obstetric and medical history, delivery and perinatal outcomes. Thirty eight women were excluded
128 (Figure 1) if they did not meet the entry criteria ($n=16$) or a data collection form was reported in error,
129 duplicated or notes could not be found ($n=22$). Two comparison groups were used. The first
130 comparison group included women in an established UKOSS database with an uncomplicated
131 singleton ($n=2205$) or twin ($n=27$) pregnancy. The UKOSS comparison group comprised pregnant
132 women from whom data had previously been collected between February 2005 and February 2006.
133 They included the two women delivering in the same hospital before UKOSS cases with the

134 conditions under study at that time (antenatal pulmonary embolism, eclampsia or peripartum
135 hysterectomy). They did not have the conditions being studied for UKOSS and were not matched for
136 gestational week. Data were collected retrospectively by the UKOSS investigators from their medical
137 charts on any complications of pregnancy they experienced. These data were collected in an identical
138 manner to the data on exposed women through specific data collection forms completed by clinical
139 staff; when forms were returned with invalid or out of range responses, clinicians were contacted and
140 asked to correct the information. The control women did not have any known pituitary pathology at
141 the time they were identified. These data were collected 5 years prior to commencement of the
142 UKOSS Pituitary Study. Information from the Office of National Statistics in England for the years of
143 the study was used for a second comparison group to calculate incidence rates of each tumor in
144 pregnancy. The Office of National Statistics database is based on statutory birth and death
145 registrations and includes the information recorded on birth and death certificates; no further
146 validation of these data takes place. For the Office of National Statistics data we could not separate
147 singleton and multiple pregnancies and this should be taken into account in pregnancy outcome
148 comparisons.

149 The study was advertised at the UK Society for Endocrinology Annual Conference and all
150 UK endocrinologists were contacted via email and by post to ask them to inform their local
151 UKOSS team of any pregnant women with pituitary tumors during the study period. No
152 additional cases were identified. The main outcome measures were the incidence, management,
153 and frequency of adverse maternal and offspring outcomes of pituitary tumors in pregnancy.

154

155 Statistical analysis was performed using Stata version 12.1 [14]. P values were considered significant
156 if ≤ 0.05 . Women with multiple pregnancies were included in comparisons of sociodemographic data,
157 and to calculate the incidence of pituitary tumors in the UK, but women with multiple pregnancies
158 were excluded from the UKOSS control group for pregnancy outcome comparisons, as this group has
159 an increased risk of both maternal and neonatal adverse outcomes. For Office of National Statistics

160 control data it was not possible to remove multiple pregnancies from the dataset. Incidence rates were
161 estimated with 95% CI. Adjustment for variables such as maternal age or occupation was not possible
162 for comparison of adverse pregnancy outcomes due to small numbers ($n < 8$ for all outcomes).
163 Presence or absence of tumor expansion was compared between different disease groups using
164 Fisher's exact test. For categorical data, unadjusted risk ratios (RR) [15] were used with Fisher's exact
165 p values (more appropriate for small sample sizes), and risk differences (RD). For continuous data,
166 mean differences and t-tests were calculated [16]. No woman included in the analysis had data
167 included from repeat pregnancies.

168

169 **Results**

170 During the 3 year study period there were 71 confirmed cases of the pituitary tumors included in this
171 study in pregnant women (Figure 1). There were 2,703,102 maternities (defined as women giving
172 birth to one or more live born or stillborn babies after 24 weeks' gestation) in the UK in the same
173 study period (from March 2010 to February 2013). The estimated incidence of each of the tumors in
174 pregnant women is shown in Table 1. As the majority of women identified had macroprolactinomas
175 and non-functioning pituitary tumors the principal focus of the study relates to these cases. There
176 were 3 cases of Cushing's disease, and 3 of acromegaly that were not included in subsequent analysis.
177 Only one of these 6 women had a normal delivery at term, the other 5 pregnancies resulted in either
178 surgical termination, ectopic pregnancy, or unexplained stillbirth.

179 Affected women were more likely to be older than UKOSS controls (Mean difference 4.06, CI 2.76 to
180 5.36, $p < 0.001$) (Table 2). There were no differences in ethnic group or BMI.

181 The presenting symptoms differed between women with macroprolactinoma and nonfunctioning
182 pituitary adenoma (Figure 2). Ninety eight percent (48/49) of macroprolactinomas and 75% (12/16) of
183 nonfunctioning pituitary adenomas were identified prior to pregnancy. Women with a
184 macroprolactinoma were more likely to present with symptoms of hormone excess such as

185 amenorrhoea (RR 5.06 CI 1.36-18.8, $p < 0.001$) and galactorrhoea (RR 2.45 CI 0.63-9.6, $p = 0.20$). In
186 contrast, women with nonfunctioning pituitary adenoma were more likely to present with clinical
187 features consistent with tumor mass expansion such as visual symptoms (RR 4.59, CI 1.48-14.3, $p =$
188 0.011).

189 There were 10 cases with tumor expansion in pregnancy; 6 had a macroprolactinoma and 4 a
190 nonfunctioning pituitary adenoma (Table 3). Apart from previous treatment with surgery,
191 radiotherapy or both, there were no significant factors in the demographic or previous obstetric
192 features to predict tumor expansion. Of the 60 women in whom a macroprolactinoma or
193 nonfunctioning pituitary adenoma was diagnosed prior to pregnancy, 9 had undergone surgery,
194 radiotherapy or both prior to pregnancy. None of this group had tumor expansion during pregnancy.
195 Of the remaining 51 patients who did not have surgery or radiotherapy prior to pregnancy 7 (13.7%)
196 had tumor expansion, 6 of whom had symptoms (Table 3). All the macroprolactinoma cases with
197 symptomatic expansion were diagnosed prior to pregnancy, while only 1 of the 4 cases of
198 nonfunctioning pituitary adenoma with symptoms of tumor expansion was diagnosed pre-pregnancy.

199 There was no significant difference in the size of the macroprolactinoma prior to conception in those
200 who did or did not have symptomatic tumor expansion (mean diameter 13.8 mm compared to 13.0
201 mm, respectively). The symptoms reported in association with tumor expansion included headache,
202 visual impairment and neurological impairment (Table 3).

203 In the entire case series, 17 women had symptoms (11 out of 49 macroprolactinomas and 6 out of 16
204 nonfunctioning pituitary adenomas) suggestive of tumor expansion (headache, visual field changes or
205 specific neurological symptoms as described in Table 3). The majority (80%, CI 51.9-96) of the cases
206 with symptoms had further investigation with formal visual field testing. A larger proportion of
207 women with macroprolactinomas (75.5%; CI 61.1-87) had formal visual field tests performed during
208 pregnancy than women with nonfunctioning pituitary adenoma (56.3%; CI 29.9-80) (RR 1.34, CI
209 0.85-2.13, $p = 0.21$). There was no difference in the proportion of women with macroprolactinoma or
210 nonfunctioning pituitary adenoma that had impaired visual fields.

211 Of the 60 women diagnosed prior to pregnancy, 46 out of 48 (95.9%, CI 86.0-99.5) with a
212 macroprolactinoma and none of the women with a nonfunctioning pituitary adenoma received
213 medical treatment before they conceived (Table 4). Cabergoline was the most likely dopaminergic
214 drug to be prescribed to those with macroprolactinoma prior to pregnancy. It was prescribed to 32
215 women (65.3%, CI 50.4-78.3) compared to bromocriptine 10 (20.4%, CI 10.2-34.3) or quinagolide 4
216 (8.2%, CI 2.3-19.6). Nineteen women stopped taking cabergoline before the end of the first trimester
217 as did 5 women treated with bromocriptine. Eighteen women with a macroprolactinoma continued
218 medication during the first trimester of pregnancy.

219 A larger proportion of women with macroprolactinoma had dopamine agonists prescribed during
220 pregnancy (47%, CI 32-62), compared to only 12.5% of those with nonfunctioning pituitary adenoma
221 (CI 1.6-38), (RR 3.76, CI 0.99-14.2, $p = 0.018$). Only 6 of the 49 women with a macroprolactinoma
222 took dopamine agonists throughout the entire pregnancy; 1 was treated with bromocriptine and 5 took
223 cabergoline. Seven women (5 with macroprolactinoma and 2 with nonfunctioning pituitary adenoma)
224 started taking dopamine agonists *de novo* in pregnancy. Of the 2 women with nonfunctioning pituitary
225 adenoma, one started taking cabergoline in the 2nd trimester and one in the 3rd trimester.

226 Of the 15 women with symptoms suggestive of tumor enlargement, 6 (40%, CI 16.3-67.7) were
227 prescribed dopamine agonists in the first trimester.

228 The pregnancy outcome data are only presented for singleton pregnancies due to the known increased
229 risk of adverse outcomes with multiple pregnancies [17]. Overall women with macroprolactinoma or
230 nonfunctioning pituitary adenoma in pregnancy did not have increased rates of adverse outcomes
231 (preterm birth, pregnancy-induced hypertension, pre-eclampsia or stillbirth) compared to controls
232 (Table 5).

233 Women with nonfunctioning pituitary adenoma had significantly more cesarean deliveries (50%)
234 than both UKOSS (23%) (RR 2.14, CI 1.31-3.52, $p = 0.032$) and Office of National Statistics
235 controls, i.e. those from the national comparison group (24%) (RR 2.06, CI 1.26-3.36, $p = 0.035$). In
236 contrast, women with macroprolactinoma were no more likely to have cesarean deliveries (27%)

237 compared to UKOSS controls (RR 1.14, CI 0.71-1.82, $p = 0.61$) or ONS controls (23% vs 24%) (RR
238 1.09, CI 0.68-1.74, $p = 0.74$). Women with macroprolactinoma or nonfunctioning pituitary adenoma
239 were more likely to have induction of labor than Office of National Statistics controls (37% and 44 %
240 respectively vs 20% of controls) (RR 1.95, CI 1.44 – 2.66 $p < 0.001$).

241 Of the 10 women who had tumor expansion in pregnancy, 4 had spontaneous vaginal
242 deliveries, one had an induction of labor and vaginal delivery, and 5 had cesarean
243 deliveries. Of these 5 women, only 2 cesarean deliveries were for symptoms associated with
244 raised intracranial pressure: 1 was due to worsening vision, diabetes insipidus and pre-
245 eclampsia, and another woman had pituitary apoplexy. The other cesarean deliveries were
246 performed as a consequence of failed induction, and maternal request following previous
247 cesarean delivery..

248 The numbers were too small in the exposed group of pregnant women to be able to make a
249 robust statement about the risk of birth defects.

250

251

252 **Discussion**

253 This large prospective UK case series study of macroprolactinomas and nonfunctioning pituitary
254 adenomas in pregnant women has provided valuable insights into the presentation, course and
255 management of these tumors. One advantage of a case series drawn from a national cohort of known
256 size is that it provides a more accurate estimate of the incidence of these rare tumors in pregnancy.
257 Nonfunctioning pituitary adenoma is the second most frequently occurring pituitary macroadenoma in
258 the non-pregnant population and therefore it is surprising that so few cases in pregnancy have been
259 documented. In our study women with pituitary macroadenomas in pregnancy were likely to be older
260 than control women.

261 The pituitary gland normally increases in size in pregnancy as a likely consequence of estrogen-
262 stimulated hyperplasia and hypertrophy of lactotroph cells [18, 19]. This prospective UK study
263 identified a lower rate of symptomatic macroprolactinoma expansion during pregnancy than has
264 previously been reported [3]. This may be because 94% (46 out of 49) of women with a
265 macroprolactinoma took a dopamine agonist prior to pregnancy, and 39% (18 out of 46) continued it
266 during the first trimester. The preferred dopamine agonist was cabergoline. The relatively high
267 proportion of women that continued dopamine agonists is similar to the findings of a study that
268 questioned endocrinologists about how they would manage these cases; 82% stated that they would
269 continue treatment in women with large macroprolactinomas [20]. Many endocrinologists continue
270 dopamine agonists in women with large macroprolactinomas, consistent with guidelines of the
271 Pituitary Society [21] and the Endocrine Society [22] (summarised in Box 2). However the British
272 Medicine and Healthcare Products Advisory Authority guidance in 2008 recommended stopping
273 cabergoline 1 month prior to pregnancy due to concern about cardiac fibrosis [23]. Thus, current
274 practice may reflect the fact that most clinicians are likely to be more concerned about the risks of
275 tumor enlargement than unsubstantiated theoretical risks of cardiac fibrosis. It is encouraging that this

276 prospective study demonstrated no cases of symptomatic macroprolactinoma enlargement in women
277 previously treated with surgery or radiotherapy, consistent with previous reports [3].

278

279 The Pituitary Society guidance on management of macroprolactinomas in pregnancy recommends
280 close surveillance if dopamine agonists have been stopped [21], and The Endocrine Society
281 recommends that for women with a macroprolactinoma who have not undergone pituitary surgery, “it
282 is prudent to undertake more frequent clinical examination and formal visual field testing” [22]. The
283 Society’s guidance has never been prospectively evaluated. In our study 75% of women with
284 macroprolactinomas and 56% (9 out of 16) with nonfunctioning pituitary adenoma had a formal
285 visual field test performed at least once during the pregnancy. However, only 33% of women with
286 macroprolactinoma had visual fields monitored in each trimester. It is possible that some cases of
287 tumor expansion might have been identified prior to onset of symptoms if surveillance had been
288 performed more regularly.

289 There were two UKOSS cases of pituitary apoplexy. One had a macroprolactinoma and the other
290 nonfunctioning pituitary adenoma, and both were diagnosed as having pituitary tumors prior to
291 pregnancy. Both cases were managed conservatively with good outcomes. This is a rare, serious
292 complication of pituitary adenoma in pregnancy and to date only 15 cases have been reported in the
293 literature (PubMed search, keywords: pregnancy, pituitary, tumor, non-functioning,
294 macroprolactinoma, acromegaly, Cushing, TSHoma, apoplexy, cabergoline, bromocriptine,
295 quinagolide, pegvisomont, somatostatin analogue, octreotide, lanreotide; dates: 1985-2015) [6]. Most
296 cases were not diagnosed as having a pituitary tumor until they presented with apoplexy in pregnancy.
297 Box 1 summarises the symptoms of pituitary apoplexy and of pituitary tumor expansion in pregnant
298 women reported in the literature and in the current study.

299

300

301 There was no increase in the rate of congenital malformations associated with dopamine agonist use
302 in the first trimester. Although this is consistent with the current literature [2, 24, 25], the current

303 study was not powered to detect a difference. Similarly, women with macroprolactinoma or
304 nonfunctioning pituitary adenoma in pregnancy did not have increased rates of preterm labor,
305 hypertensive disease, pre-eclampsia or fetal loss.

306 Potential limitations of this study include the fact that microprolactinomas were not included.
307 Unfortunately this was not possible as they were too common to include in a UKOSS study of rare
308 disorders of pregnancy. It would have been valuable to establish whether the findings in
309 macroprolactinomas can be generalized to all prolactinomas. Some cases may have been missed if
310 they were managed by neurologists or neurosurgeons, and a future study could benefit from also
311 writing to these specialists to ensure all UK cases were identified.

312 In summary, the majority of women with macroprolactinoma and nonfunctioning pituitary adenoma
313 have good pregnancy outcomes, although pituitary apoplexy occurred in one woman with each type of
314 tumor. This study demonstrates that nonfunctioning pituitary adenoma occurs more commonly in
315 pregnancy than previously thought, and that this group of tumors can present *de novo* with symptoms
316 of expansion. Ergot-containing dopamine agonists, particularly cabergoline, were the treatment of
317 choice most frequently used for symptomatic expansion of pituitary tumors, and the majority of
318 women with symptoms suggestive of tumor expansion can be successfully treated without surgery. A
319 significant number of clinicians elect to continue or restart dopaminergic therapy during pregnancy in
320 women with macroprolactinomas, consistent with national guidelines.

321

322

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373 **Table 1: Incidence of Pituitary Tumors in Pregnant women in the UK**

Tumor Type	Number of pregnancies identified in UKOSS study	Incidence in pregnancy-cases per 100,000 maternities (95% CI)
Macroprolactinoma	49	1.80 (1.30-2.40)
Non-functioning pituitary adenoma	16	0.59 (0.34-0.96)
Acromegaly	3	0.11 (0.02-0.32)
Cushing's disease	3 ¹	0.11 (0.02-0.32)
Thyrotropin secreting pituitary adenoma	0	0.00 (0.00-0.13)

374

375 ¹One woman with Cushing's disease had 2 pregnancies within the UKOSS study time span.

376 * Denotes not possible to determine

377

378 Table 2. Sociodemographic characteristics of women with rare pituitary tumors in pregnancy and healthy controls.

379

	Macroprolactinoma N=49	Nonfunctioning Pituitary Adenoma N=16	UKOSS control N=2250
Age			
Mean (SD)	33.6 (5.2)	31.6 (5.0)	29.1 (6.1)
< 30 no. (%) (95% CI)	11 (22.4) (11.8-36.6)	5 (31.3) (11.0-58.7)	1133 (50.4) (48.3-52.4)
30-35	17 (34.7) (21.7-49.6)	6 (37.5) (15.2-64.6)	620 (27.5) (25.7-29.5)
>35	21 (42.9) (28.8-57.8)	5 (31.3) (11.0-58.7)	497 (22.1) (20.4-23.9)
Ethnic group no. (%) (95% CI)			
White	36 (73.5) (58.9-85.1)	15 (93.8) (69.8-99.8)	1793/2172 (82.6) (80.9-84.1)
Black	6 (12.2) (4.6-2.5)	0	115/2172 (5.3) (4.4-6.3)
Asian	5 (10.2) (3.4-22.2)	0	195/2172 (9.0) (7.8-10.3)
Not known	2 (4.1) (0.5-14.0)	1 (6.3) (0.16-30.2)	44/2172 (2.0) (1.4-2.6)
Mixed	0	0	25/2172 (1.2) (0.75-1.7)
Non white	11 (22.4) (11.8-36.6)	0	335/2172 (15.4) (13.9-17.0)
BMI			
Mean (SD)	27.3(6.8)	25.2(5.9)	25.7 (5.5)
<18 no. (%) (95% CI)	0	0	30 (1.3) (0.90-1.9)
18-24.9	22 (44.9) (30.7-59.8)	8 (50) (24.7-75.3)	1089 (48.4) (46.3-50.5)
25-29.9	9 (18.4) (8.8-32.0)	3 (18.8) (4.05-45.6)	543 (24.1) (22.4-26.0)
30-34.9	11 (22.4) (11.8-36.6)	2 (12.5) (1.6-38.3)	228 (10.1) (8.9-11.5)
>35	7 (14.3) (5.9-27.2)	3 (18.8) (4.05-45.6)	360 (16) (14.5-17.6)

380 **Table 3: Clinical details of cases that underwent tumor expansion in pregnancy**

Diagnosis Type	Pre-Pregnancy				Pregnancy						
	Medication	Length of time on medication prior to pregnancy (months)	Reduced visual fields	Trimester of tumor expansion	Increase in size (cm)	Extension beyond sella turcica	Visual field testing			Presenting symptoms	Management (trimester)
						1 st trimester	2 nd trimester	3 rd trimester			
MP	No	36	NK	2 nd	0.3	NK	2	2	NP	Clinical notes indicate likely visual defect	Cabergoline (2 and 3) Bromocriptine (2)
MP	Bromocriptine	2	Yes	1 st	1.4	Yes	3	3	3	6 th nerve palsy Left 3 rd , 4 th and 6 th nerve palsy	Bromocriptine (1) Cabergoline (2)
MP	Cabergoline	5	No	2 nd	0.8	No	1	NP	NP	Headache	Cabergoline (1, 2, 3)
MP	Cabergoline	48	No	3 rd	0.0	Yes	1	2	3	Deterioration in visual fields ⁺	Cabergoline (1, 2, 3)
MP	Cabergoline	12	No	2 nd	0.7	No	1	1	1	Headache Haemorrhage into tumor on MRI	Dexamethasone (2)
Macroprolactinoma	Cabergoline Levothyroxine	2	NK	3 rd	1.2	NK	3	NP	NP	Blurred Vision	Cabergoline (1) Bromocriptine (3)
Nonfunctioning pituitary adenoma	NA	DP	---	3 rd	NA	No	NP	NP	NP	Focal neurology	No
Nonfunctioning pituitary adenoma	No	48	Yes	2 nd	NK	No	2	2	2	Headache Pituitary apoplexy	Cabergoline (2)
Nonfunctioning	NA	DP	---	2 nd	NA	NK	NP	NP	NP	Visual loss	Surgery

pituitary adenoma											
Nonfunctioning pituitary adenoma	NA	DP	---	3 rd	NA	Yes	1	1	1	Absence episodes	Cabergoline (3)

NA: not applicable; NK: information not known; DP: diagnosed in pregnancy; NP: not performed

* Diagnosed during pregnancy

*Visual fields improved following cabergoline treatment

Visual field assessment; 1: normal; 2: abnormal; 3: worsening of defect

	Macroprolactinoma N=49	Macroprolactinoma that expanded N=6	Nonfunctioning pituitary adenomaN=16
<u>Women prescribed dopamine agonist</u>	46 (95.9, CI 86.0-99.5)	5 (83.3, CI 35.8-99.6)	2 (12.5, CI 1.6-38.3)
<u>Cabergoline</u>			
Pre pregnancy	32 (65.3, CI 50.4-78.3)	4 (66.7, CI 22.3-95.7)	0 (0.0, CI 0.0-21.0)
1 st trimester	13 (26.5, CI 14.9-41.1)	3 (20.4, CI 11.8-88.2)	0 (0.0, CI 0.0-21.0)
2 nd trimester	9 (18.4, CI 8.8-32.0)	4 (66.7, CI 22.3-95.7)	1 (6.3, CI 0.16-30.2)
3 rd trimester	7 (14.3, CI 5.9-27.2)	3 (20.4, CI 11.8-88.2)	1 (6.3, CI 0.16-30.2)
<u>Bromocriptine</u>			
Pre pregnancy	10 (20.4, CI 10.2-34.3)	1 (16.7, CI 0.42-64.1)	0 (0.0, CI 0.0-21.0)
1 st trimester	5(10.2, CI 3.4-22.2)	1 (16.7, CI 0.42-64.1)	0 (0.0, CI 0.0-21.0)
2 nd trimester	4 (8.2, CI 2.3-19.6)	1 (16.7, CI 0.42-64.1)	0 (0.0, CI 0.0-21.0)
3 rd trimester	3 (6.1, CI 1.3-16.9)	1 (16.7, CI 0.42-64.1)	0 (0.0, CI 0.0-21.0)
<u>Quinagolide</u>			
Pre pregnancy	4 (8.2, CI 2.3-19.6)	0 (0.0, CI 0.0-46.0)	0 (0.0, CI 0.0-21.0)
1 st trimester	2 (4.1, CI 0.50-14.0)	0 (0.0, CI 0.0-46.0)	0 (0.0, CI 0.0-21.0)
2 nd trimester	0 (0.0%, CI 0-7.3)	0 (0.0, CI 0.0-46.0)	0 (0.0, CI 0.0-21.0)
3 rd trimester	0 (0.0%, CI 0-7.3)	0 (0.0, CI 0.0-46.0)	0 (0.0, CI 0.0-21.0)

Table 4: Dopamine agonist prescription in pregnancy

Table 5: Pregnancy Outcomes

	Macroprolactinoma N=47	Nonfunctioning pituitary adenomaN=16	RR ¹	P value	UKOSS control N=2205	RR ²	ONS**	RR ³
Prematurity (<37 weeks) no. (%) (95% CI)	2/46 (4.3) (0.53-14.8)	2 (12.5) (1.6-38.3)	0.35 (0.053-2.27)	0.27	144/2200 (6.5) (5.5-7.7)	0.99 (0.38-2.58)	151,082/2,144,019 (7.05) (7.01-7.08) ⁴	0.92 (0.35-2.36)
Pregnancy induced Hypertension no. (%) (95% CI)	4/47 (8.5) (2.36-20.4)	1 (6.3) (0.16-301.2)	1.36 (0.16-11.3)	1.00	*	---	90,038/2,008,386 (4.48) (4.45-4.51)	1.77 (0.76-4.10)
Pre- eclampsia no. (%) (95% CI)	2/47 (4.3) (0.52-14.5)	0/15 (0) (0-0.22)	NC	1.00	*	---	*	---
Stillborn no. (%) (95% CI)	0/44 (0) (0-0.08)	1 (6.3) (0.16-30.2)	NC	0.27	11/2205 (0.50) (0.25-0.89)	4.01 (0.53-30.5)	11,083/2,176,752 (0.509) (0.50-0.52)	3.22 (0.46-22.5)

* These data were not available for comparison. However, pre-eclampsia is believed to affect 2-8% pregnant women in the UK [26])

** Data only available including multiple pregnancies. Comparisons may be affected

NC = Data could not be calculated

¹ Comparison between macroprolactinoma and Nonfunctioning pituitary adenomawith 95% CI

² Comparison between UKOSS controls and those with macroprolactinoma or Nonfunctioning pituitary adenomawith 95% CI

³ Comparison between ONS controls and those with macroprolactinoma or Nonfunctioning pituitary adenomawith 95% CI

⁴ ONS data was obtained from 2009, 2010 and 2011 statistics

Box 1: Presenting symptoms of pituitary apoplexy and tumour expansion in pregnant women**Symptoms of pituitary apoplexy:**

Headache
 Visual disturbance
 Ophthalmoplegia
 Nausea and vomiting
 Altered consciousness

Symptoms of pituitary tumor expansion:

Headache
 Visual disturbance
 Ophthalmoplegia
 Altered consciousness
 Diabetes insipidus

Box 2: Management of macroprolactinoma in pregnancy**Endocrine Society guideline:**

Continue dopaminergic therapy in pregnancy in selected patients based upon:

- Proximity to the optic chiasm
- Whether they have had previous surgery or radiotherapy

Close surveillance including regular clinical review and formal visual field testing

If symptoms of tumour expansion therapeutic options include:

- Reinstitution of dopamine agonist therapy
- Surgical debulking
- If the pregnancy is near term, deliver is an option prior to neurosurgical intervention

Pituitary Society guideline:

Due to the 20-30% risk of symptomatic expansion, options are either to:

- Continue dopamine agonist throughout pregnancy
- Ensure close surveillance if dopamine agonists are stopped in early pregnancy

Recommended management if symptomatic tumour expansion occurs:

- Assess using MRI
- Restart dopamine agonist if the tumour has grown significantly
- If no response to reinstatement of dopamine agonist therapy, consider delivery or surgery