Clinical Features and Surgical Management of Pituitary Adenoma During Pregnancy: Case Series and Literature Review

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Research Article

Keywords: Pituitary adenoma, pregnancy, surgery, surgical indication, surgical timing

Posted Date: January 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1247050/v1

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Abstract

Purpose

Although conservative treatment was recommended for pregnant patients with pituitary adenomas (PAs), surgical treatment is occasionally necessary for those with acute symptoms. However, surgical intervention among these patients is poorly studied.

Methods

Six patients with PAs who underwent surgical treatment during pregnancy at Peking Union Medical College Hospital between January 1990 and June 2021 and another 35 pregnant patients profiled in the literature were included.

Results

All the 41 enrolled patients (mean age 29.8 ± 5.3 years) had acute symptoms including visual field defects, severe headaches, or vision loss requiring emergency pituitary surgeries. Mean tumor diameter was 2.16 ± 0.9 cm, and 92.6% were macroadenomas. PA apoplexies were found in 23 patients. The average gestation time at surgery was 25.1 ± 7.1 weeks; 55.9% of these patients underwent surgery in the second trimester of pregnancy. Multidisciplinary team was involved from before surgery to after delivery. Except one patient underwent an induced abortion, and one fetus died due to a nuchal cord, thirty-nine patients delivered successfully, and 37 of fetuses were healthy till the last follow-up. One fetus died of congenital diaphragmatic hernia, and another had a low Apgar score after a cesarean section but survived.

Conclusion

PA surgery for pregnant patients with PAs is effective and safe during the second and third trimesters. Pregnant patients requiring emergency PA surgery need multidisciplinary evaluation and healthcare management. Cooperation of neurosurgery, endocrinology, obstetrics, anesthesiology, and neonatology is necessary for a successful surgical intervention for pregnant patients with PAs.

Introduction

Pituitary adenoma (PA) is the second most common primary brain tumor, accounting for 15–17% of brain tumors and a quarter of benign brain tumors [1]. Although PAs can occur at any age, those pregnant patients have unique characteristics. Pregnancy can cause the enlargement of pre-existing PAs which may compress the anterior pituitary gland contributing to some acute symptoms such as severe headache and visual defect, thus affecting maternal health and fetal development [2]. In addition, hormone-secreting PAs may also lead to high-hormone states such as ACTH and TSH hypersecretion resulting in poor prognoses [1, 3].

During pregnancy, some PAs can be controlled by conservative treatment. For example, patients with prolactinomas can orally take dopamine agonists (DAs) [1, 4–6]. Although there is no evidence that somatostatin analogue (SSA) is safe for the fetus during pregnancy, SSA is effective in reducing tumor size, growth hormone (GH) and insulin-like growth factor 1 (IGF1) levels in acromegaly[7, 8]. However, some pregnant patients with acute compression...
symptoms such as visual defects and severe headache, as well as non-prolactinoma patients with pathologically high hormone levels during pregnancy may accept surgical treatment in clinical practice, if the problem cannot be solved by conservative treatment or potential side effects rule out pharmacological treatment. These patients pose a challenge to neurosurgeons in terms of surgical timing, surgical indications, anesthesia risk, and perioperative treatment. At present, few case reports on the surgical treatment of pregnant PA patients are available, and adequate knowledge and experience regarding this surgical intervention are lacking.

The pituitary specialty at the Peking Union Medical College Hospital (PUMCH) has a long history [9], and the Neurosurgery Department of PUMCH is the founding unit of the China Pituitary Adenoma Specialist Council and the China Pituitary Disease Registry Network. The endocrinology department at PUMCH is known as a leader in endocrinology [10]. We summarized the clinical presentation, imaging features, surgical indications, perioperative management, and other vital considerations of six pregnant patients with PAs surgically treated at our hospital, as well as 35 similar patients reported in the literature. Our goal was to make some suggestions to physicians in neurosurgery, endocrinology, obstetrics/gynecology, ophthalmology, and other related specialties.

Materials And Methods

Patient enrollment at PUMCH

Six pregnant patients with PAs admitted to the neurosurgery department of PUMCH between January 1990 and June 2021 were retrospectively analyzed. All patients underwent surgery for PAs during pregnancy. The data collected included clinical symptoms, imaging features, perioperative treatment, pathological classification, and postoperative follow-up. All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Ethics Committee of Peking Union Medical College Hospital at the Chinese Academy of Medical Sciences & Peking Union Medical College and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Additional cases from the literature and data extraction

We performed a literature search using PubMed to identify relevant literatures published between January 1990 and June 2021. The search was limited to literatures written in English, and we included them only when sufficient data were available. Our search used the MeSH terms “pituitary adenoma,” “pregnancy,” and “surgery.” Citation indices were used to expand the search for relevant literatures.

After reading and reviewing relevant literatures, only patients with PAs who underwent surgery during pregnancy were included. Patients treated with conservative treatment alone, as well as treatment of pathological non-PA, were excluded.

Patients with duplicate reports due to multiple articles published by the same clinical center at different times were manually removed. Based on the above criteria, 30 literatures were screened, resulting in the inclusion of a further 35 patients.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 22.0, SPSS, Inc., Chicago, IL, USA). Measurement data conforming to a normal distribution were represented by $\bar{x} \pm s$. 

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Enumeration data were expressed as percentages or ratios. Paired-sample $t$-tests were used for preoperative and postoperative comparisons. Statistical significance was set at $P < 0.05$.

**Results**

**Clinical characteristics**

Forty-one patients with PAs who underwent surgery during pregnancy were included. A summary of their clinical characteristics was provided in Table 1, which included six cases from our center and 35 cases from the PubMed database. Except for three patients without an exact age, the age of the remaining 38 patients ranged from 21 to 41, with a mean age of 29.7 ± 5.3.
| Data source                     | Case | Age (Y) | Gender | Clinical Symptoms | Headache | Vision Loss | Visual Field | OP | DI | HT | Cushing Syndrome | Acromegaly |
|-------------------------------|------|---------|--------|-------------------|----------|-------------|--------------|----|----|----|-------------------|-------------|
| Peking Union Medical College Hospital | 1    | 29      | F      |                   | No       | Bi          | BTH           | No | No | No | No                | No          |
|                               | 2    | 36      | F      | Yes               | No       | No          | No            | No | No | No | No                | No          |
|                               | 3    | 34      | F      | No                | No       | No          | BTH           | Yes| Yes| No | No                | No          |
|                               | 4    | 32      | F      | No                | No       | No          | No            | No | Yes| No | No                | No          |
|                               | 5    | 37      | F      | Yes               | No       | No          | No            | No | No | No | No                | No          |
|                               | 6    | 28      | F      | Yes               | No       | No          | No            | No | No | No | No                | No          |
| Jallad et al[15]             | 7    | 25      | F      | Yes               | No       | No          | BTH           | No | No | No | No                | No          |
|                               | 8    | 27      | F      | Yes               | No       | No          | BTH           | No | No | No | No                | No          |
|                               | 9    | 27      | F      | Yes               | No       | No          | BTH           | No | No | No | No                | Yes         |
| Chaiamnuay et al[16]         | 10   | 39      | F      | Yes               | No       | No          | UTH           | No | No | Yes| No                | No          |
| Guven et al[17]              | 11   | 32      | F      | No                | Bi       | No          | BTH           | No | No | No | No                | Yes         |
| Zhong et al[37]              | 12   | 29      | F      | No                | Bi       | No          | No            | No | No | No | No                | No          |
| Jemel et al[18]              | 13   | 35      | F      | Yes               | No       | No          | BTH           | No | No | No | No                | No          |
|                               | 14   | 30      | F      | Yes               | Bi       | No          | BTH           | No | No | No | No                | No          |
| Xia et al[19]                | 15   | 25      | F      | Yes               | Bi       | No          | BTH           | No | No | No | No                | No          |
| Yamaguchi et al[20]          | 16   | 35      | F      | Yes               | Bi       | No          | UTH           | No | No | No | No                | No          |
| Tandon et al[21]             | 17   | 27      | F      | Yes               | Mo       | No          | BTH           | No | No | No | No                | No          |
| Parihar et al[35]            | 18   | 22      | F      | Yes               | Bi       | No          | No            | No | No | No | No                | No          |
| Gondim et al[22]             | 19   | 29      | F      | Yes               | Mo       | No          | UTH           | Yes| No | No | No                | No          |
| Witek et al[23]              | 20   | 25      | F      | Yes               | Bi       | No          | BTH           | No | No | No | No                | No          |
| Kita et al[24]               | 21   | 26      | F      | Yes               | No       | No          | BTH           | No | No | No | No                | No          |

**Abbreviations:**

Bi, binocular; BTH, bitemporal hemianopsia; DI, diabetes insipidus; F, female; HPRL, hyperprolactinemia; HT, hyperthyroidism; Mo, monocular; OP, oculomotor paralysis; PA, pituitary adenoma; UTH, unilateral temporal hemianopia; Y, year.
| Data source          | Case | Age (Y) | Gender | Clinical Symptoms | Headache | Vision Loss | Visual Field | OP | DI | HT | Cushing Syndrome | Acromegaly |
|----------------------|------|---------|--------|-------------------|----------|-------------|--------------|----|----|----|------------------|------------|
| Nossek et al[25]     | 22   | 29      | F      |                   | No       | Bi          | No           | No | No | No | No               | No         |
|                      | 23   | 34      | F      |                   | No       | No          | BTH          | No | No | No | No               | No         |
| Iuliano et al[26]    | 24   | 28      | F      | Yes               | No       | No          | No           | No | No | No | No               | No         |
|                      | 25   | 35      | F      | Yes               | Mo       | UTH         | Yes          | No | No | No | No               | No         |
| Hayes et al[27]      | 26   | 41      | F      | Yes               | No       | BTH         | No           | No | No | No | No               | No         |
| Boronat et al[51]    | 27   | 26      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
|Abbassy et al[36]     | 28   | 38      | F      | Yes               | No       | No          | No           | No | No | No | Yes              | No         |
| Coyne et al[52]      | 29   | 22      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
| Pinette et al[53]    | 30   | 33      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
| Ross et al[54]       | 31   | 24      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
| Mellor et al[50]     | 32   | 40      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
| Karaca et al[14]     | 33   | —       | F      | No                | No       | No          | No           | Yes| No | No | No               | Yes        |
| Jolly et al[55]      | 34   | 30      | F      | No                | No       | No          | No           | No | No | No | Yes              | No         |
| Galvao et al[28]     | 35   | —       | F      | Yes               | Bi       | BTH         | No           | No | No | No | No               | No         |
| Abid et al[29]       | 36   | 25      | F      | Yes               | Bi       | BTH         | No           | No | No | No | No               | No         |
| Barraud et al[30]    | 37   | —       | F      | Yes               | No       | BTH         | No           | No | No | No | No               | No         |
| Freeman et al[31]    | 38   | 22      | F      | Yes               | Mo       | BTH         | No           | Yes| No | No | No               | No         |
| Lunardi et al[32]    | 39   | 21      | F      | Yes               | Bi       | BTH         | No           | No | No | No | Yes              | No         |
| Oguz et al[33]       | 40   | 26      | F      | Yes               | No       | UTH         | No           | No | No | No | No               | No         |

Abbreviations:

Bi, binocular; BTH, bitemporal hemianopsia; DI, diabetes insipidus; F, female; HPRL, hyperprolactinemia; HT, hyperthyroidism; Mo, monocular; OP, oculomotor paralysis; PA, pituitary adenoma; UTH, unilateral temporal hemianopia; Y, year.
| Data source | Case | Age (Y) | Gender | Clinical Symptoms | Headache | Vision Loss | Visual Field | OP | DI | HT | Cushing Syndrome | Acromegaly |
|-------------|------|---------|--------|-------------------|---------|-------------|--------------|----|----|----|-----------------|------------|
| O’Neal et al[34] | 41   | 27      | F      |                   | No      | No          | No           | No | No | No | No              | No         |

Abbreviations:
Bi, binocular; BTH, bitemporal hemianopsia; DI, diabetes insipidus; F, female; HPRL, hyperprolactinemia; HT, hyperthyroidism; Mo, monococular; OP, oculomotor paralysis; PA, pituitary adenoma; UTH, unilateral temporal hemianopia; Y, year.

The clinical presentations of the 41 patients were as follows: visual field defects in 28 cases (68.3%) (bitemporal hemianopsia in 23 cases, unilateral temporal hemianopsia in five cases; Fig. 1), headaches in 27 cases (65.9%), vision loss in 20 cases (48.8%) (15 cases binocular, five cases monocular), Cushing diseases in seven cases (17.1%), acromegaly in six cases (14.6%), oculomotor paralysis in four cases (9.8%), diabetes insipidus in two cases (4.9%) and hyperthyroidism in two cases (4.9%).

Image data

The image data of 41 patients were shown in Online Resource Table 1, comprising magnetic resonance imaging (MRI) in 37 cases (90.2%) and contrast-enhanced MRI in four cases (9.8%). The tumor size in 27 patients whose data was available ranged from 0.4 to 4.0 cm, average 2.1 ± 0.9 cm. Pituitary microadenomas were found in two patients (7.4%, 2/27), and 25 patients (92.6%, 25/27) were pituitary macroadenomas.

Twenty-seven patients underwent T1-weighted imaging (T1WI), comprising hypointensity in three cases (11.1%, 3/27), isointensity in 10 cases (37.0%, 10/27), isointensity and hypointensity in one case (3.7%, 1/27), isointensity and hyperintensity in eight cases (29.6%, 8/27), as well as hyperintensity in five cases (18.5%, 5/27). Three types of T1WI for cases with pituitary apoplexy were shown in Figure 2. None of these patients had hypointensity on T1WI.

Ten patients had T2-weighted imaging, including hypointensity in one case (10%, 1/10), hyperintensity in four cases (40%, 4/10), as well as isointensity and hyperintensity in five cases (50%, 5/10). Three of four patients who underwent contrast-enhanced MRI (75%, 3/4) showed no enhancement, and one case (25%, 1/4) showed inhomogeneous enhancement.

The Knosp classification was reported in 20 patients among whom five cases (25%, 5/20) were invasive (Knosp classification III or IV), and 15 cases (75%, 15/20) were non-invasive. Five patients were in the highest unilateral
Knosp classification IV (25%, 5/20). Two patients (10%, 2/20) were in Knosp classification II. Nine patients (45%, 9/20) were in Knosp classification I, and four patients were in Knosp classification 0 (20%, 4/20).

**Hormone levels**

Changes in hormone levels in the 41 patients were shown in Online Resource Table 2. Complete hormone monitoring was performed in 8 of 13 patients with prolactinoma. Prolactin levels decreased after operation, and the difference was statistically significant (P < 0.05).
Table 2
Treatment and follow-up outcomes of patients who underwent the surgery during pregnancy.

| Data source                      | Ca | Treatment          | Pathology | Follow up |
|----------------------------------|----|--------------------|-----------|-----------|
|                                   | Pre| Post               | Medical therapy | Operation | Delivery | M | I |
| Peking Union Medical College Hospital | 1  | Bromocriptine     | No        | 12th W TSS | 40th W CS | NF PA | ER | H |
|                                   | 2  | No                 | No        | 32nd W TSS | Full term CS | NF PA | ER | H |
|                                   | 3  | No                 | No        | 22nd W TSS | 38th W CS | NF PA | ER | H |
|                                   | 4  | Sandostatin        | No        | 26th W TSS | 38th W CS | TSH PA | ER | H |
|                                   | 5  | Bromocriptine      | No        | 35th W TSS | 35th W CS | PRL PA | ER | H |
|                                   | 6  | Prednisone         | Prednisone| 30th W TSS | 39th W CS | NF PA | ER | H |
| Jallad et al[15]                 | 7  | No                 | No        | 3rd Mon TSS | 38th W CS | GH PA | ER | H |
|                                   | 8  | No                 | No        | 4th Mon TSS | 16th W A | GH PA | EC | A |
|                                   | 9  | Cabergoline        | No        | 4th Mon TSS | 39th W CS | GH PA | ER | H |
| Chaiamnuay et al[16]             | 10 | Propylthiouracil   | No        | 27th W TSS | 39th W CS | TSH PA | ER | H |
|                                   |    | Bromocriptine      |           |            |            |        |     |   |
| Guven et al[17]                  | 11 | No                 | Octreotide| 34th W TSS | 34th W CS | GH PA | EC | H |
| Zhong et al[37]                  | 12 | No                 | Cortisone | 22nd W TSS | 40th W VD | NF PA | ER | H |
|                                   |    | Thyroxine          |           |            |            |        |     |   |

Abbreviations: A, abortion; CS, cesarean section; D, death; DDAVP, 1-desamino-8-D-arginine vasopressin; EC, endocrine control; ER, endocrine remission; W, week; H, healthy; I, infant; LAS, low apgar score; M, maternal; Mon, month; Post, postoperatively; Pre, preoperatively; R, recurrence; TSS, transsphenoidal surgery; VD, vaginal delivery.
| Data source          | Case | Treatment                     | Pathology   | Follow up |
|----------------------|------|-------------------------------|-------------|-----------|
| Jemel et al[18]      | 13   | Cabergoline, Hydrocortisone   | 22nd W TSS | 37th W VD | ER H      |
|                      | 14   | Corticosteroids               | 24th W TSS | 38th W VD | ER H      |
| Xia et al[19]        | 15   | No                            | 24th W TSS | 38th W CS | PRL PA    |
| Yamaguchi et al[20]  | 16   | Methylprednisolone            | 36th W TSS | 37th W CS | ER H      |
| Tandon et al[21]     | 17   | Bromocriptine, Desmopressin  | 36th W TSS | 37th W CS | PRL PA    |
| Parihar et al[35]    | 18   | No                            | 20th W TSS | Full term VD | PRL PA |
| Gondim et al[22]     | 19   | Bromocriptine, Thyroxine, Hydrocortisone | 32nd W TSS | 39th W VD | EC H      |
| Witek et al[23]      | 20   | Bromocriptine, Hydrocortisone | 20th W TSS | 38th W CS | PRL PA    |
| Kita et al[24]       | 21   | DDAVP                         | 27th W TSS | 40th W VD | NF PA     |
| Nossek et al[25]     | 22   | No                            | 33rd W TSS | 35th W CS | ER LAS    |
|                      | 23   | No                            | 31st W TSS | 40th W VD | PA ER H   |
| Iuliano et al[26]    | 24   | Bromocriptine, Dexamethasone  | 30th W TSS | 39th W CS | ER H      |
|                      | 25   | Bromocriptine, Dexamethasone, Levothyroxine, Hydrocortisone | 33rd W TSS | 39th W CS | NF PA ER H |

Abbreviations: A, abortion; CS, cesarean section; D, death; DDAVP, 1-desamino-8-D-arginine vasopressin; EC, endocrine control; ER, endocrine remission; W, week; H, healthy; I, infant; LAS, low apgar score; M, maternal; Mon, month; Post, postoperatively; Pre, preoperatively; R, recurrence; TSS, transsphenoidal surgery; VD, vaginal delivery.
| Data source          | Case | Treatment               | Pathology | Follow up |
|----------------------|------|-------------------------|-----------|-----------|
| Hayes et al[27]      | 26   | Corticosteroids         | No        | 18th W TSS | Full term VD | PRL PA | ER | H |
| Boronat et al[51]    | 27   | Alpha-metildopa         | Metrapone | 16th W TSS | 34th W VD | ACTH PA | R | H |
| Abbassy et al[36]    | 28   | No                      | Hydrocortisone Desmopressin | 18th W TSS | 39th W VD | ACTH PA | ER | H |
| Coyne et al[52]      | 29   | No                      | Hydrocortisone Desmopressin | 14th W TSS | 38th W VD | ACTH PA | ER | H |
| Pinette et al[53]    | 30   | No                      | Atenolol  | 16th W TSS | –         | ACTH PA | ER | D |
| Ross et al[54]       | 31   | No                      | Dexamethasone | 18th W TSS | 37th W CS | ACTH PA | ER | H |
| Mellor et al[50]     | 32   | No                      | Hydrocortisone Mid-trimester TSS | 34th W CS | ACTH PA | ER | H |
| Karaca et al[14]     | 33   | No                      | No        | 11th W TSS | 39th W CS | GH PA | ER | H |
| Jolly et al[55]      | 34   | No                      | Hydrocortisone Metformin Labetalol Nifedipine | 23rd W TSS | 38th W CS | ACTH PA | ER | D |
| Galvao et al[28]     | 35   | No                      | No        | 2nd trimester TSS | – | PRL PA | ER | H |
| Abid et al[29]       | 36   | Bromocriptine Lisuride hydrogen | 27th W TSS | 39th W VD | PRL PA | ER | H |
| Barraud et al[30]    | 37   | Bromocriptine No        | 3rd Mon TSS | –         | PRL PA | ER | H |
| Freeman et al[31]    | 38   | DDAVP Hydrocortisone Thyroxine | 32nd W TSS | 39th W VD | PRL PA | ER | H |

Abbreviations: A, abortion; CS, cesarean section; D, death; DDAVP, 1-desamino-8-D-arginine vasopressin; EC, endocrine control; ER, endocrine remission; W, week; H, healthy; I, infant; LAS, low apgar score; M, maternal; Mon, month; Post, postoperatively; Pre, preoperatively; R, recurrence; TSS, transsphenoidal surgery; VD, vaginal delivery.
GH levels in four patients with complete hormone monitoring decreased postoperatively, although without statistically significance (P = 0.085). One patient (Case 11) had higher IGF1 on the second day after surgery, however the IGF1 level returned to normal after six months. The IGF1 difference in the other three patients was not statistically significant (P = 0.115).

Adrenocorticotropic hormone (ACTH) levels of the three patients completing hormone monitoring increased preoperatively and sharply decreased postoperatively. The difference was statistically significant (P < 0.05). However, among two patients with decreased thyroid-stimulating hormone (TSH) levels postoperatively, the difference was not statistically significant (P = 0.308).

### Perioperative conservative treatment

Perioperative conservative treatment for the 41 patients were shown in Table 2. Twenty-two patients did not receive conservative treatment. Seven patients were treated with bromocriptine alone, including six cases of prolactinoma and one case of nonfunctioning PA. One GH secreting PA was treated with cabergoline alone. Four patients (three cases of nonfunctioning PAs and one without pathological classification) were treated with a combination of dopamine agonist (DA) and glucocorticoid, and two patients were treated with glucocorticoid alone. One TSH secreting PA was treated with bromocriptine and propylthiouracil, and another such patient was treated with somatostatin. One nonfunctioning PA was treated with thyroxine and glucocorticoid. One ACTH secreting PA patient received alpha-methyldopa for hypertension, and one prolactinoma patient received 1-des amino-8-D-arginine vasopressin desmopressin for diabetes insipidus. Postoperatively, 30 patients received conservative treatment, comprising 13 cases of glucocorticoid treatment, seven cases of thyroxine treatment, five cases of arginine-vasopressin treatment and five cases of desmopressin treatment.

### Operations and pathological classifications

All 41 patients underwent transsphenoidal surgery under general anesthesia, and none accepted craniotomy. With the exception of seven patients who did not report their specific gestation, the surgical gestations of the other 34 patients ranged from 11 to 36 weeks, average 25.1 ± 7.1, including two cases in the first trimester (gestation <14
weeks; 5.9%, 2/34), 19 cases in the second trimester (14 weeks ≤ gestation < 28 weeks; 55.9%, 19/34), and 13 cases in the third trimester (gestation ≥ 28 weeks; 38.2%, 13/34).

Except for three cases without pathologic classifications in PubMed, there were 13 cases of prolactinoma (34.2%, 13/38), 10 cases of nonfunctioning PAs (26.3%, 10/38), seven cases of ACTH secreting PAs (18.4%, 7/38), six cases of GH secreting PAs (15.8%, 6/38), and two cases of TSH secreting PAs (5.3%, 2/38).

**Follow-up information**

Except for 10 nonfunctioning PAs, 26 patients (63.4%) were in endocrine remission. Four patients (9.8%) were in endocrine control, and one patient (2.4%) relapsed. In terms of pregnancy outcomes, one patient underwent an induced abortion at 16 weeks, and one fetus died due to a nuchal cord at 33 weeks of gestation. The remaining 39 patients delivered 37 healthy fetuses successfully. One fetus died of a congenital diaphragmatic hernia within 36 hours after cesarean section at 38 weeks of gestation, and one fetus survived with a low Apgar score after cesarean section at 35 weeks of gestation. Except two patients for whom the specific methodology was not reported, 22 patients underwent cesarean section (59.5%, 22/37) and 15 chose vaginal delivery (40.5%, 15/37).

Delivery gestation was not reported in 6 of the 39 patients; of the remaining 33, gestation ranged from 34 to 40 weeks, averaging 37.8 ± 1.7. Premature delivery (28 weeks ≤ gestation < 37 weeks) occurred in five cases (15.2%, 5/33) and full-term delivery (37 weeks ≤ gestation < 42 weeks) in 28 cases (84.8%, 28/33).

**Discussion**

During pregnancy, physicians may face many challenges when diagnosing and treating PAs. Although conservative treatment is recommended for some pregnant patients with PAs, such as prolactinoma, some patients may accept surgery due to visual defects, severe headaches, and high hormone secretion levels which cannot be alleviated after conservative treatment [7, 11–14]. We summarized the data of 41 patients with PAs who underwent surgery during pregnancy. To our knowledge, this is the most comprehensive report related to the surgery in pregnant patients with PAs.

**Clinical characteristics**

Here, the three most common clinical symptoms of these patients were visual field defects (68.3%) [15–34], headaches (65.9%) [15, 16, 18–24, 26–36], and vision loss (48.8%) [17–23, 25, 26, 28, 29, 31, 32, 35, 37]. Previous studies showed that the two most common clinical symptoms of PA patients with apoplexy during pregnancy were headaches and visual impairment [18, 33], which is similar to our study.

The pituitary gland and pre-existing PAs may enlarge during pregnancy [2, 38], and the risk is greater in patients with macroadenomas than in those with microadenomas [1]. This observation was confirmed here. In prolactinomas, the most common type of PAs, the risk of symptomatic tumor enlargement during pregnancy was 27.9% in patients with macroadenomas and only 2.2% in patients with microadenomas [39].

**Conservative treatment during pregnancy**

Conservative treatment during pregnancy mainly includes treatment of PAs and supplementation to hormone deficiency. DAs have been recommended for prolactinomas [1], and GH secreting PAs may be treated with SSAs [1, 7]. Although there is no evidence that SSAs increase the risk of fetal malformation [6, 40–42], discontinuation of all medication except DAs during pregnancy is recommended to ensure fetal health to the maximum extent possible [7,
Resumption is recommended only when symptoms leading to poor prognoses such as visual defects or severe headaches occur. In some patients with prolactinomas, symptoms can be controlled by DAs; however, in cases without significant remission, clinicians should consider surgical treatment as soon as possible, following a multidisciplinary evaluation [8, 11, 43]. Additionally, to ensure maternal health and fetal development, hormone deficiencies such as glucocorticoid or thyroxine should be supplemented in time [44].

**Indications for surgery during pregnancy**

Patients with macroadenomas have a higher risk of symptomatic progression during pregnancy [1]. However, the size of PA is not the criterion. The severity of visual defects and headaches should be used as surgical indications for PAs during pregnancy [11, 12]. Some microadenomas are also associated with adverse effects on maternal and fetal health due to high hormone levels [45]. Based on our results, the surgical indications during pregnancy are summarized as follows:

**Visual defects**

PAs are more likely to compress the optic chiasm during pregnancy than outside of pregnancy, leading to visual defects [2]. When conservative treatment cannot relieve visual impairment, clinicians should conduct a multidisciplinary evaluation to balance visual defects with pregnancy safety and decide whether to treat surgically as soon as possible. Although the recovery rate of visual field can be as high as 80% [46] or even 95.7% [47], the severity and duration of visual impairment are essential factors for postoperative visual prognosis, and irreversible adverse effects caused by severe visual impairment during pregnancy should be avoided [47].

**Severe headache**

Sudden, severe headache is the most common symptom of PAs with apoplexy, primarily due to the enlargement of PAs during pregnancy, increased pressure on the sella turcica, and dural pressure [44]. Headache is often accompanied by nausea, vomiting, eye muscle paralysis, and impairment of consciousness. Because severe headache can induce contractions, the surgery is indicated if the multidisciplinary evaluation considers that the headache is due to mass effect and that pain medication would affect fetal health [48].

**Hormonal abnormalities**

ACTH secreting PAs and TSH secreting PAs can cause ovulation disorders in women of reproductive age [49]. This type of patient should be treated before pregnancy as early as possible. Nevertheless, a few patients have unintended pregnancies after diagnosis [36, 50, 51] or are diagnosed during pregnancy [52–55]. High hormone secretion during pregnancy, such as ACTH and TSH hypersecretion, is closely related to several complications and poor prognoses [45, 49]. Surgical treatment in appropriate timing is the most effective method for reducing hormone levels in such patients [11, 16, 43].

**Operative timing during pregnancy**

The timing of transsphenoidal surgery depends on the potential risks and benefits, including maternal symptoms, fetal safety, and gestational weeks, which is the most critical indicator. The spontaneous abortion rate in the first trimester is approximately 12% versus only 5% in the second and third trimesters [12]. The overall malformation incidence in pregnancy is 2%, compared with 3.9% in the first trimester, and the incidence of neural tube defects and preterm delivery is highest in the third trimester [56]. In our study, most patients also underwent surgery in the
second trimester [16, 18, 19, 23, 24, 27, 29, 33, 35–37, 51–55]. Therefore, the second trimester is the best time for PA surgery [11–13, 57, 58].

For patients in the first trimester, the surgery should be postponed to the second trimester to the extent possible [13, 14]. For patients in the third trimester, considering that fetal survival can reach 90% after 27 weeks of gestation, Lynch et al. [59] recommended delaying surgery to 30 weeks of gestation if possible. In comparison, Priddy et al. [13] suggested that induced labor or cesarean section should be delayed until 34 weeks of gestation, if possible, followed by surgical treatment. However, among the 13 patients in this study who underwent surgeries in the third trimester, 12 patients and fetuses were healthy; one fetus survived with a low Apgar score, but the mother was healthy [17, 20–22, 25, 26, 31, 34]. In this regard, we suggest that the balance of symptom severity and gestational weeks should be considered in the third trimester, when glucocorticoids can be administered to promote fetal lung maturation. If symptoms do not worsen significantly, a cesarean section should be performed first. However, surgical treatment should then be performed promptly if symptoms progress significantly (Fig. 3).

**Precautions for surgery during pregnancy**

**Before the surgery**

A professional multidisciplinary team should be established to conduct individualized evaluations prior to surgery for pregnant patients with PAs indicated for surgical treatment. The team should include neurosurgeons, endocrinologists, obstetricians, gynecologists, pediatricians, and anesthesiologists [19, 58]. MRI must be acquired before the surgery. Although fetal toxicity of gadolinium is not established, MRI without gadolinium enhancement is preferred and is sufficient to make a definitive diagnosis and plan the surgery. Given the teratogenicity of X-rays, computed tomography should be avoided [60].

Preoperative ophthalmic examination is also essential, including examinations of visual acuity, visual field, fundus, retinal nerve fiber layer, and optical coherence tomography of the ganglion cell complex [11]. The ophthalmic examination can roughly predict the postoperative recovery rates for visual impairment [47]. The possible visual sequelae include severe visual impairment, severe visual-field defects, and severe degeneration of the retinal nerve fiber layer/ganglion cell complex [11].

Preoperative fetal ultrasonography should be performed routinely to evaluate fetal health. Continuous fetal heart rate monitoring is feasible under the proper conditions [11]. The endocrine examination can assess pituitary function, and, if necessary, relevant deficient hormones should be supplemented. Preoperative operations such as enemas that can induce contractions should be avoided. After evaluation, patients and their families should be fully informed of the risks and benefits of surgery. And written informed consent should be obtained after weighing the advantages and disadvantages and making a careful choice.

**During the surgery**

Inhaled anesthetics can reduce uterine tension, increase bleeding risk and cerebral perfusion pressure in a concentration-dependent manner [61]. Total intravenous anesthesia, which is preferred during pregnancy, does not affect uterine tension and can constrict the cerebrovascular system and maintain cerebral perfusion pressure [62]. FDA Class B drugs such as propofol are recommended. However, Class C drugs, which have potential risks but can be used given sufficient expected benefit, should be carefully used after weighing the pros and cons [57].
Intraoperative reduction of cardiac return can lead to severe complications such as hypotension, placental insufficiency, and cerebral insufficiency. Therefore, surgeons should lower the left side of the patient below the right side to avoid compression of the inferior vena cava [11, 12]. Although there is no optimal cerebral perfusion pressure target, it seems reasonable to control the mean arterial pressure 20% above the baseline [12]. During surgery, the use of diuretics and anticonvulsants should be avoided. If necessary, contractions should be suppressed to protect the fetus [11].

**After the surgery**

Fetal heart rate variation is an essential indicator of fetal health and can indicate fetal distress; therefore, continuous fetal heart rate monitoring should be performed after the surgery [12]. If postoperative reactions such as nausea, vomiting, and headache occur, Class B drugs such as pethidine can be used for symptomatic treatment. Routine ophthalmic examinations should be conducted postoperatively to evaluate visual defect recovery. If no significant improvement is observed, differential diagnoses with other diseases leading to visual impairment, such as optic neuritis, should be considered [20]. Hormone stoss therapy, neurotrophic drugs, and other treatments can also be administered.

**Conclusions**

The surgical treatment and perioperative management of PAs during pregnancy is complex. And the surgical indications and timing issues must be well understood and carefully considered with the cooperation of neurosurgery, endocrinology, obstetrics, anesthesiology, neonatology, and other related specialties. In the second and third trimesters, transsphenoidal surgery is a safe and effective approach for emergency treatment during pregnancy after evaluation by a multi-disciplinary team. Additionally, for patients with irregular menstrual cycles, pituitary screening is necessary. Women of reproductive age who have been diagnosed with PAs should follow the advice of their endocrinologists and neurosurgeons before pregnancy.

**Declarations**

**Data availability**

All data generated or analyzed here are included in this article or in public repositories.

The supplementary files are available at https://doi.org/10.6084/m9.figshare.16817914.

**Funding**

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

**Author contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xinyu Jia, Xiaopeng Guo, Mingjie Luo, Yong Yao, Wei Lian and Bing Xing. The first draft of the
manuscript was written by Xinyu Jia and Xiaopeng Guo, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Preoperative visual field of Case6

Postoperative visual field of Case6

Figure 1
Shown is a comparison of the preoperative and postoperative visual fields for Case 6. Preoperative visual field examination shows bitemporal hemianopsia, which is more severe in the left eye. Three days after surgery, examination reveals a partial temporal visual field defect in the left eye and a standard visual field in the right eye.

Figure 2

Three typical images of PA apoplexy are shown. Sagittal T1WI shows isointensity and hyperintensity with a visible liquid level (Fig. 2a, Case 15) or mixed, mainly hyperintensity (Fig 2b, Case 40). Coronal T1WI of another PA apoplexy shows isointensity (Fig 2c, Case 5).
Figure 3
Flow diagram of treatment procedures for PAs during pregnancy

Supplementary Files
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